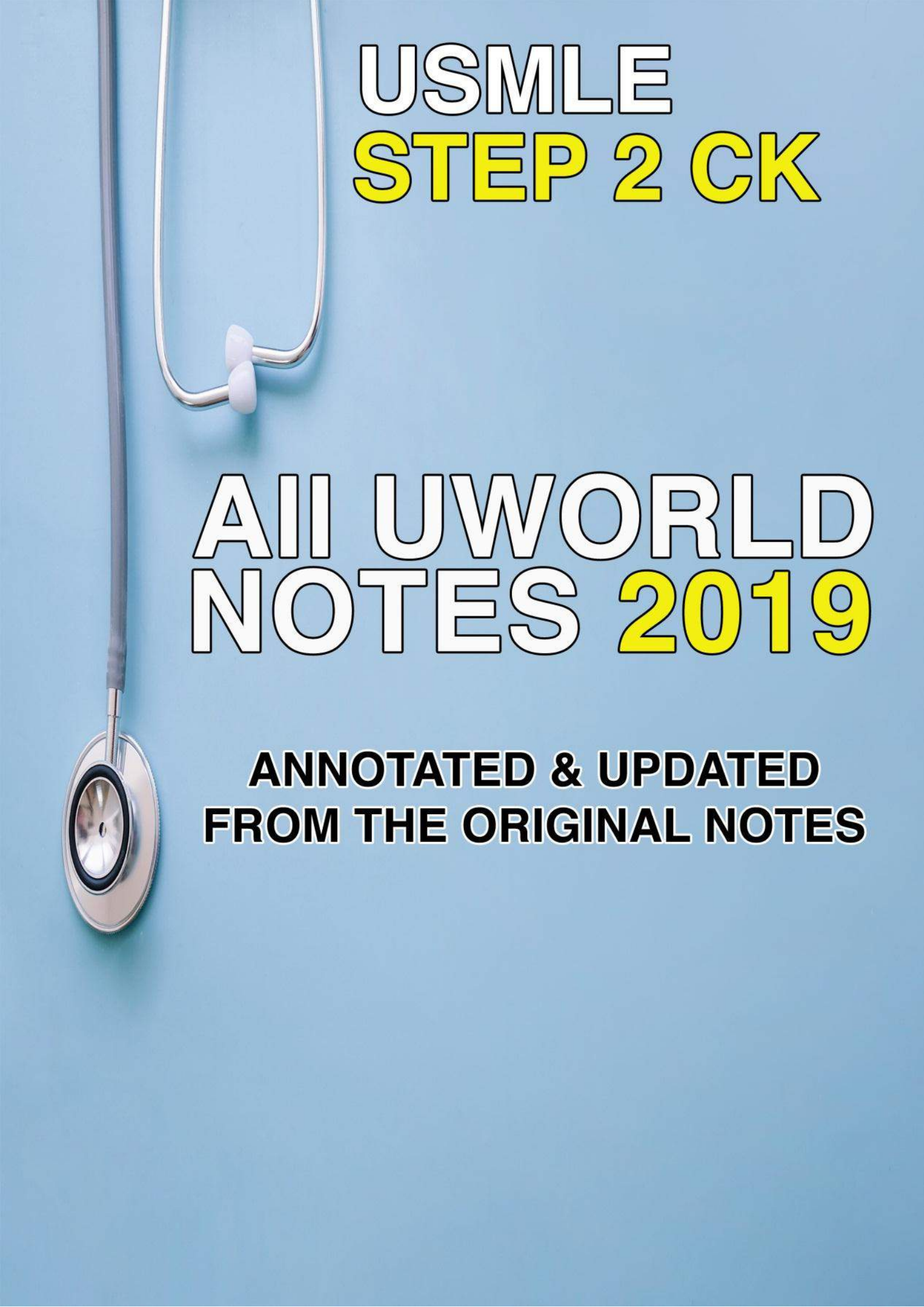


USMLE STEP 2 CK

All UWORLD NOTES 2019

ANNOTATED & UPDATED FROM THE ORIGINAL NOTES

منتدى افريقيا سات

www.afriqa-sat.com

م.عبدالعزيز الضاوي

للمراسلة على موقع فكونتاكتي

www.vk.com/aldawi_sat

للمراسلة على الفيس بوك

www.facebook.com/abdelaziz.dawi

رابط قناتي على يوتيوب

www.youtube.com/AldawiSat

This Summary is a work of students who were in your shoes once; they shared it to help you & everybody in this journey.

Taking Uworld notes is the most soul consuming thing in step 2 ck preparation, so we hope these notes are the best aid for your journey that will soon come to an end.

Hope you achieve your goal in the exam.

Just pray for us in our journey to the "You matched" email.

This message is from the guy who updated the notes, I don't own these notes; all the credit goes to original creator, as he did a massive work that made our lives easy.

Contents

BACTERIOLOGY

ACUTE BACTERIAL RHINOSINUSITIS

Diagnostic features of acute bacterial rhinosinusitis

- *Persistent* symptoms ≥ 10 days without improvement

OR

- *Severe* symptoms, fever ≥ 39 C (102 F), purulent nasal discharge, or face pain ≥ 3 days

OR

- *Worsening* symptoms ≥ 5 days after initially improving viral upper respiratory infection

- **Most common predisposing factor**: viral upper resp. tract infection
- **Most common organisms:** Streptococcus pneumoniae (~30%), non-typeable Haemophilus influenzae (~30%), and Moraxella catarrhalis (~10%)
- Symptoms can last 10-30 days without improvement
- **Dx:** usually clinical. CT scan can be used to evaluate complications as orbital cellulitis, intracranial extension. Findings of sinusitis: sinus opacification, mucosal thickening and/or air fluid levels
- **Rx:** due to ↑ beta-lactamase resistance, **amoxicillin-clavulanic acid** (DOC) for acute sinusitis
- Pseudomonas aeruginosa is common in nosocomial sinusitis, especially in immunocompromised patients with nasal tubes or catheters
- S. aureus may be a cause of chronic sinusitis (> 12wks) but not a cause of acute

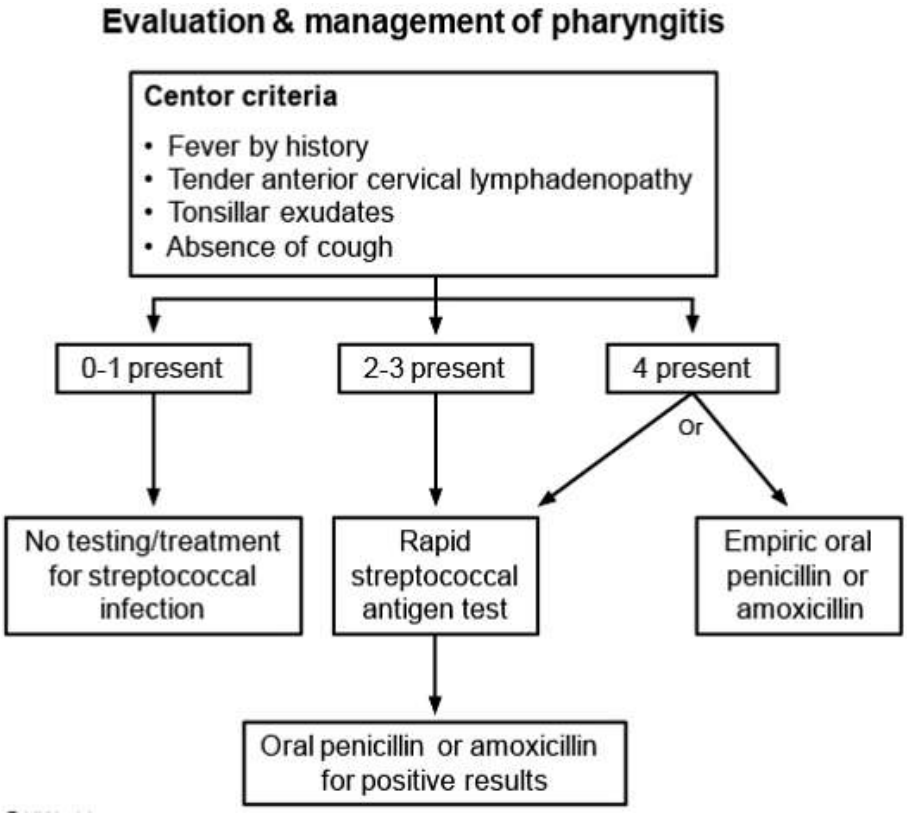
UPPER RESPIRATORY TRACT ILLNESSES

Distinguishing features of common upper respiratory illnesses			
	Viral upper respiratory syndrome	**Influenza**	**Streptococcal pharyngitis**
Onset of symptoms	Slow, stepwise, migratory, or evolving	Abrupt & often dramatic	Variable
Upper respiratory symptoms	Rhinorrhea, coryza, sneezing, mild pharyngitis	Usually mild	Predominantly pharyngeal symptoms
Systemic symptoms	Usually mild	Prominent with possible high fever, myalgias, headache	Variable with possible fever & myalgias
Examination findings	Nasal edema with normal or slightly erythematous pharynx	Variable but often unremarkable	Pharyngeal erythema, tonsillar hypertrophy & exudates, tender cervical lymph nodes

STREPTOCOCCAL PHAYNGITIS

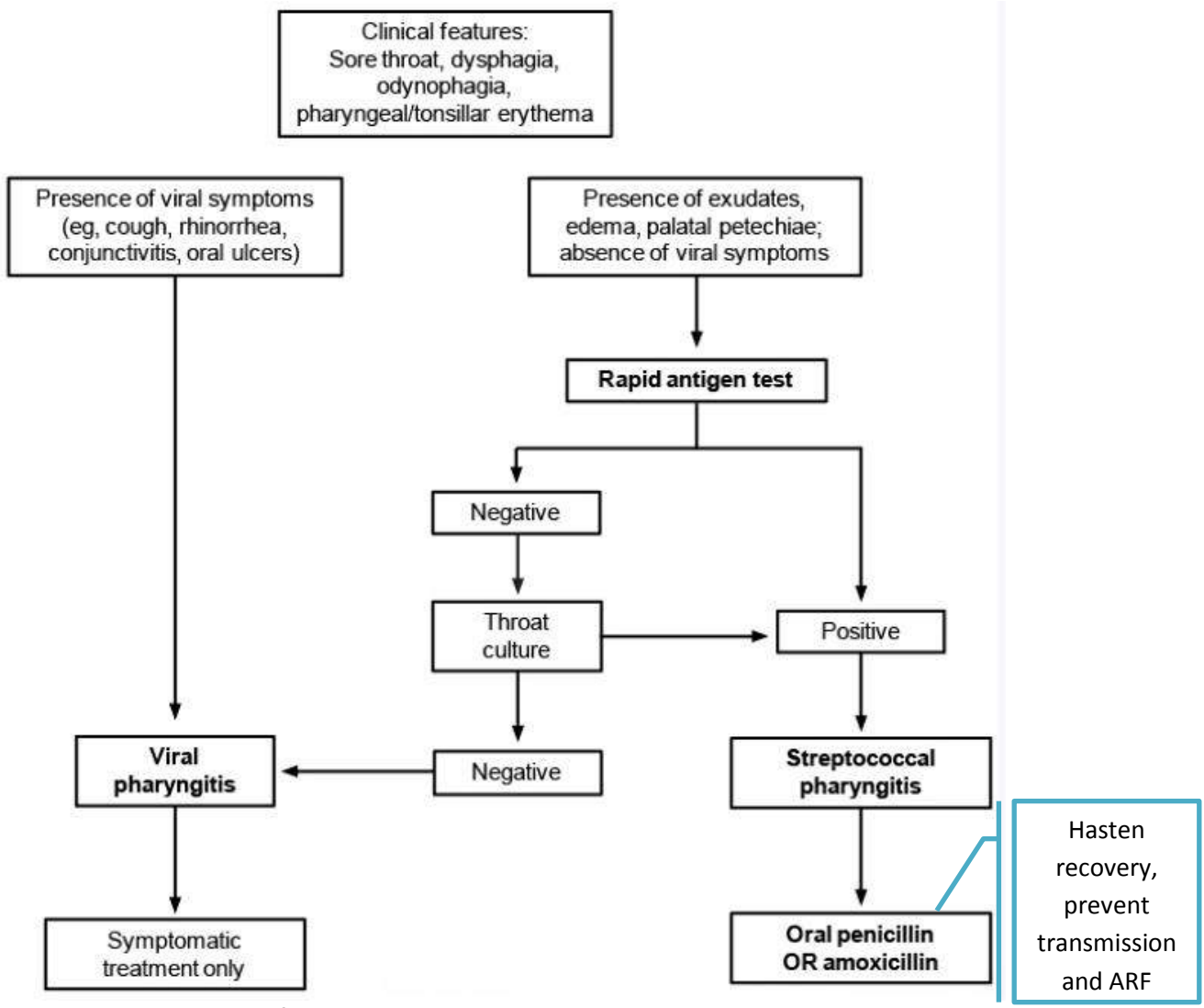
- **Rapid testing for streptococcal pharyngitis** is most helpful in patients with moderate to high likelihood or exposure to confirmed cases. Testing should be considered for patients with >/=2 Centor criteria (tonsillar exudates, tender anterior cervical adenopathy, fever, and absence of cough)

EVALUATION AND MANAGEMENT OF PHARYNGITIS IN ADULTS



EVALUATION AND MANAGEMENT OF PHARYNGITIS IN CHILDREN

- Can be viral or bacterial
- **Bacterial pharyngitis** in children and adolescents (5-15 yrs)—most commonly due to group A streptococcus
- C/F, prediction rules and scoring system do not reliably differentiate bacterial and viral in this age group except when obvious viral manifestations are present→ confirm bacterial pharyngitis prior to treatment to avoid unnecessary antibiotics for viral
- Approach of pharyngitis is different in children and adults due to ↑ risk of viral in children and ↓ risk of rheumatic fever in adults
- Centor criteria is not reliable in this age



- Macrolides reserved for penicillin allergic pts
- ASO titers peak 1 month after infection and not helpful in determining acute pharyngitis

INFLUENZA

- **Influenza** has 3 antigenic types: A, B and C. A and B cause most significant disease and C cause minor disease.
- Usually self-limiting within 3-10 days.
- Rapid "point-of-care" testing can confirm an influenza diagnosis. Indicated in high-risk children in whom treatment would be indicated (e.g., age <2, history of pulmonary/cardiac disease, need for hospitalization)
- Therapy is based on timing of clinical presentation.
  - Neuraminidase inhibitors (eg, oseltamivir, zanamivir) can decrease illness severity and duration by 2-3 days.
  - Amantadine and rimantadine are effective only against influenza A and are rarely used due to significant side effects.
  - Current guidelines recommend treating all confirmed or suspected influenza within 48 hours of symptom onset.
  - Treatment is also considered for patients presenting after >48 hours with symptoms that are not improving or who are at high risk for complications.
  - All others can receive symptomatic treatment (eg, rest, simple analgesics, cough suppressants) after the 48-hour window.

Adults at high risk for influenza complications

- Age >65
- Women who are pregnant & up to 2 weeks postpartum
- Underlying chronic medical illness (eg, chronic pulmonary, cardiovascular, renal, hepatic)
- Immunosuppression
- Morbid obesity
- Native Americans
- Nursing home or chronic care facility residents

- **Pneumonia** is the most common complication of influenza:
1. Secondary bacterial infx (e.g. strep pneumo).
2. direct viral attack (**influenza pneumonia).**

- Influenza pneumonia:
SOB, dry cough, leuckocytosis (<15,000/mm^3), hypoxia, CXR shows **bilateral, diffuse interstitial infiltrates**

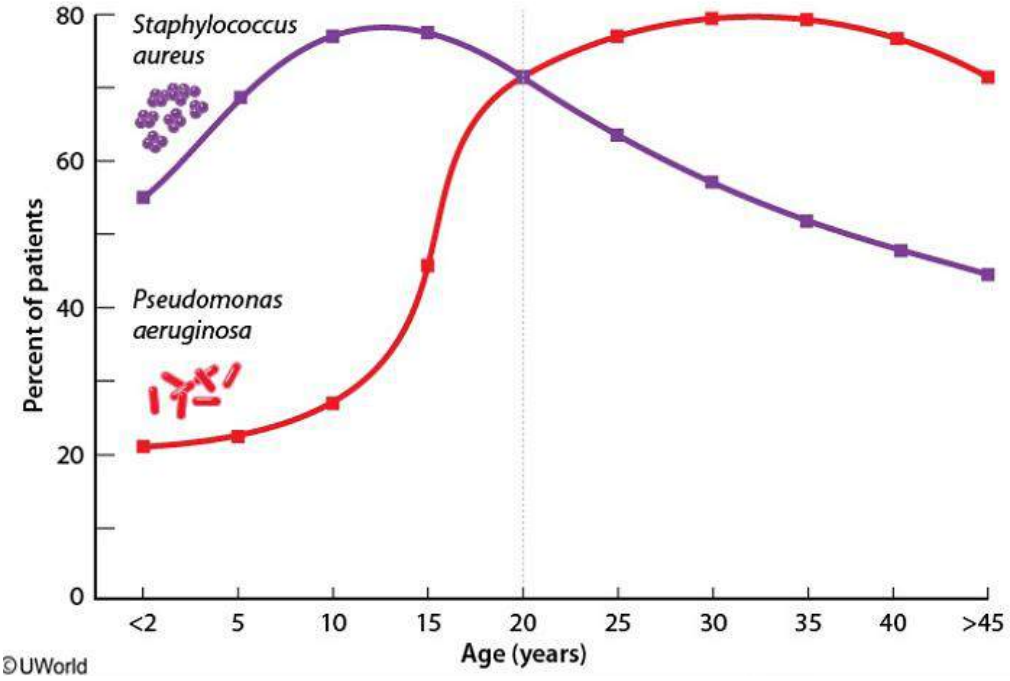
- Tx: Hospitalization + supplemental oxygen + antiviral (eg, oseltamivir).

The Centers for Disease Control and Prevention recommends against vaccinating patients with moderate to severe illness, with or without fever. Although some clinicians vaccinate patients with mild or resolving symptoms during their visit.

PNEUMONIA IN CYSTIC FIBROSIS

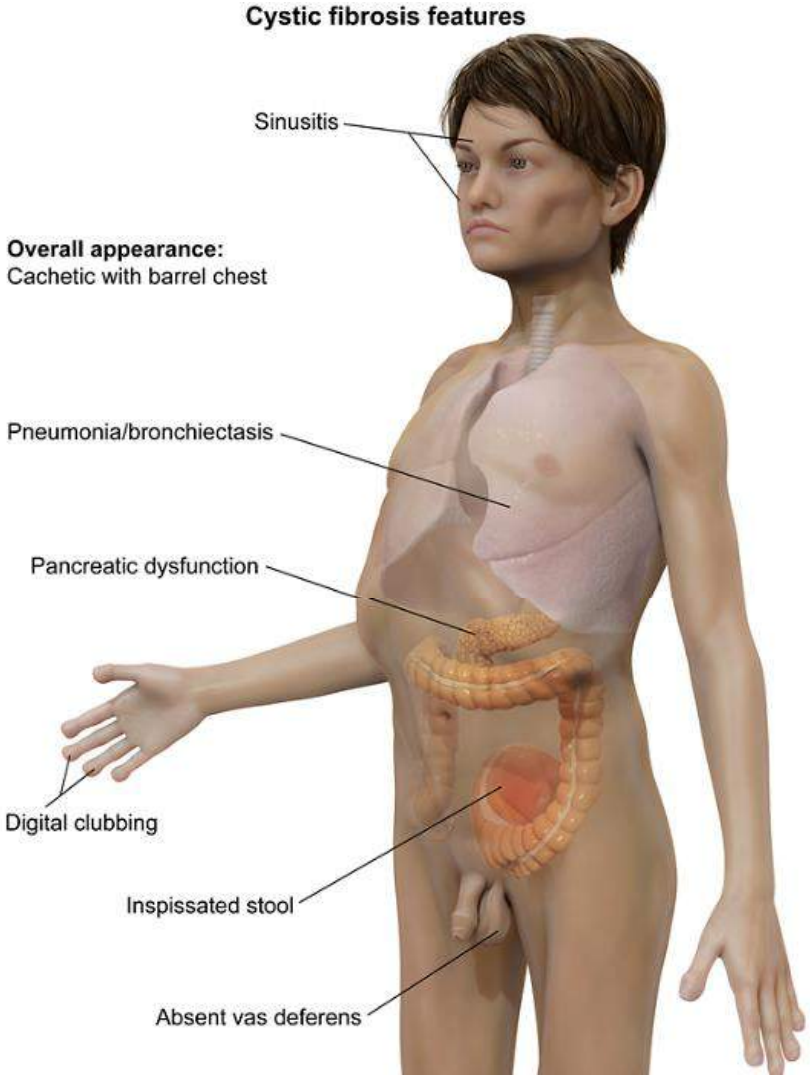
- CF leads to recurrent pneumonias→ irreversible bronchiectasis, chronic hypoxia, and progressive respiratory failure→ hyperinflation→ rib cage partially expanded "barrel chest" and clubbing

Rates of bacterial colonization in cystic fibrosis based on age



- **S. aureus— most common cause** of CF related pneumonia in **infants and young children**, colonization ↓ with age but remains significant source in > 50% adults.
  - CF children with acute pulmonary exacerbation (e.g. from influenza infection), presenting with hypoxia and respiratory distress→ S. aureus is common esp. in concurrent influenza→ give empiric anti-staphylococcal antibiotic and consider MRSA due to multiple hospitalization in these pts→ give **IV vancomycin**
  - Young children are unable to expectorate sputum from lower resp. tract for culture. Culture should be obtained from upper resp. tract secretions to isolate pathogen and refine antibiotic

    - If symptoms do not resolve despite antibiotic, bronchoscopy and brochoalveolar lavage may be considered to identify bacterial flora in lungs
- **Pseudomonas aeuroginosa—**can occur as early as infancy, **most common cause in adults**—cause precipitous ↓ in pulmonary function and ↑ed risk of death
    - Amikacin, ceftazidime, and ciprofloxacin are appropriate for empiric treatment of Pseudomonas aeruginosa
- **S. pneumonia—**common bacterial pathogen in children and most common cause of pneumonia in all pts
    - High dose amoxicillin is DOC for outpatient treatment of community acquired S.pneumoniae coverage (does not cover S. aureus)
- **Burkholderia cepacia complex**—several similar species that colonize a small percentage of patients with CF— associated with accelerated pulmonary decline and decreased survival



RETROPHARYNGEAL ABSCESS

- Most patients with RPA have pre-existing upper respiratory infection (eg, rhinorrhea and nasal congestion). RPA results from direct spread of bacterial infection from pharyngitis, tonsillitis, otitis media, or sinusitis.
- Usually **polymicrobial**, involving **Streptococcus pyogenes, Staphylococcus aureus, and anaerobes**.
- Most commonly in children age **6 months to 6 years**. Incidence ↓ after age 6 years due to a combination of retropharyngeal lymph node regression and fewer viral upper respiratory infections.

- **S/S:**
  - Combination of fever, odynophagia/dysphagia, drooling, neck stiffness, inability to extend neck, muffled voice, and trismus (inability to open the mouth completely)→ very concerning for infection of the larynx, pharynx, or deep neck space. Due to the proximity of the airway, spine, and major vascular structures, infections in this region are potentially life-threatening
- **X-ray:**
  - Normal lateral neck x-ray: prevertebral soft-tissue space should be narrower than the vertebral bodies.
  - Retropharyngeal abscess (RPA): Widened prevertebral space).
- In patients with no signs of respiratory compromise→ perform CT with contrast→ confirm the presence and size of the abscess.
- **Complications:** rare but potentially fatal— airway compromise, bacteremia, carotid artery rupture, and jugular venous thrombosis→ early dx and management necessary to prevent these

ACUTE RHEUMATIC FEVER

Acute rheumatic fever		
Epidemiology	• Peak incidence: Age 5-15 • Twice as common in girls	
Clinical features	**Major**	• **J**oints (migratory arthritis) • ♥ (Carditis) • **N**odules (subcutaneous) • **E**rythema marginatum • **S**ydenham chorea
	Minor	• Fever • Arthralgias • Elevated erythrocyte sedimentation rate/ C-reactive protein • Prolonged PR interval
Late sequelae	Mitral regurgitation/stenosis	
Prevention	Penicillin for **group A streptococcal** (*Streptococcus pyogenes*) pharyngitis	

- Group A streptococcal pharyngitis usually precedes the onset of rheumatic fever by 2-4 weeks.
- **Diagnostic criteria:** evidence of a preceding group A streptococcal infection along with 2 major criteria; or 1 major plus 2 minor criteria; or if either of Sydenham chorea or carditis are present

- **Supportive Laboratory findings:** positive streptococcal antigen test or elevated antistreptolysin O titer.
- **Management:**
  - **Pharyngitis—** often self-resolve but still give a 10 day course of oral penicillin to prevent ARF
  - **ARF—**even in the absence of active pharyngitis, treat ARF with **long-acting IM benzathine penicillin G** until adulthood→ eradicate bacterial carriage to prevent recurrent ARF and worsening rheumatic heart disease
  - **Severe chorea**—corticosteroids
  - **Pericarditis and arthritis**—NSAIDS

TOXIC SHOCK SYNDROME

Clinical features of toxic shock syndrome

- Fever usually >38.9 C (102 F)
- Hypotension with systolic BP ≤90 mm Hg
- Diffuse macular erythroderma
- Skin desquamation, including palms & soles, 1-2 weeks after illness onset
- Multisystem involvement (3 or more systems)
  - Gastrointestinal (vomiting &/or diarrhea)
  - Muscular (severe myalgias or elevated creatine kinase)
  - Mucous membrane hyperemia
  - Renal (BUN or serum creatinine >1-2x upper)
  - Hematologic (platelets <100,000/µL)
  - Liver (ALT, AST & total bilirubin >2x upper limit of normal)
  - Central nervous system (altered mentation without focal neurological signs)

ALT = alanine aminotransferase; **AST** = aspartate transaminase; **BP** = blood pressure; **BUN** = blood urea nitrogen.

- Caused by TSST-1 of S. aureus that acts as superantigen and cause T cell activation
- Almost 50% cases are related to menstruation (tampon use); remainder are non-menstrual
- Sx develop rapidly, median interval after the onset of menstruation/infection is 2-3 days.
- Leukocytosis may not be present but immature neutrophils are elevated. Thrombocytopenia, however, is common.
- Rx/ management: supportive (e.g. IV fluids), removal of foreign material from surgery and broad spectrum anti-staphylococcal antibiotics

NECROTIZING SURGICAL SITE INFECTION

- S/S:
  - Pain, edema, or erythema spreading beyond the surgical site
  - Systemic signs such as fever, hypotension, or tachycardia
  - Paresthesia or anesthesia at the edges of the wound
  - Purulent, cloudy-gray discharge (**"dishwater drainage"**)
  - Subcutaneous gas or crepitus
- More commonly in **patients with diabetes**
- Usually **polymicrobial.**
- Considered emergencies if they involve the fascial plane and develop into necrotizing fasciitis.

- **Most important step in management**: early **surgical exploration** to assess the extent of the process and debride necrotic tissues.
- **Adjunctive therapies**, including broad-spectrum antibiotics, adequate hydration, and tight glycemic control—imp but 2* to surgical exploration
- **Negative-pressure wound therapy** (i.e., vacuum-assisted wound closure) is a wound-dressing system that applies sub-atmospheric pressure to a wound to accelerate the healing process. It is reserved for healthy, granulating wounds. It is not used initially when the wound is infected or necrotic.
- Intravenous antibiotics alone are sufficient therapy for wound infections limited to cellulitis, but surgical debridement is required when the infection penetrates the deeper skin layers and adjacent tissue.

LYMPHADENITIS

- Cervical LAD is common in children
- **Lymphadenitis:** LN become large, tender and erythematous
- Multiple causes. Can be differentiated by acute (develop within days) and subacute/chronic (present over weeks to months), U/L or B/L

ACUTE CERVICAL ADENITIS IN CHILDREN

Acute cervical adenitis in children

Location	Pathogen	Additional features
Unilateral	*Staphylococcus aureus*, *Streptococcus pyogenes*	Pronounced erythema, tenderness
	Anaerobic bacteria (eg, *Prevotella buccae)*	Dental caries, periodontal disease
	Bartonella henselae	Papular nodular at site of cat scratch or bite
	Mycobacterium avium	Gradual onset, nontender
Bilateral	Adenovirus	Pharyngoconjunctivitis
	EBV/CMV	Mononucleosis

CMV = cytomegalovirus; **EBV** = Epstein-Barr virus.

- Usually occur in <5 yo, pt appears non-toxic. LN is tender, warm, erythematous, 3-6cm. usually affects submandibular nodes
- **Complications if left untreated:** can progress to induration and fluctuance, suppuration and abscess
- **Dx:** of acute lymphadenitis can be made clinically.
- **Empiric Rx of acute u/l LAD**: clindamycin (has activity against MRSA and S. pyogenes)

- **Tularemia**—caused by Francisella tularensis—zoonosis (rabbits, hamsters, or blood-sucking arthropods)→ acute, u/l cervical LAD, fever, chills, headache, and malaise
- **Peptostreptococcus**—anaerobic bacteria—acute, u/l lymphadenitis—seen in older children with h/o periodontal disease
- **Nontuberculous mycobacteria** (most commonly Mycobacterium avium-intracellulare)—cause of u/l subacute-chronic lymphadenopathy—usually less than 5 years old and present with firm, nontender LAD, usually less than 4cm in size. The skin over the lymph node often thins and develops a violaceous color. Fever and tenderness are unusual with this infection

LYME DISEASE

EARLY LOCALIZED DISEASE

- **Oral doxycyline** is the DOC for this condition in non-pregnant and pts >/= 8 yr old**. P**referred as concurrently treats Anaplasma phagocytophilum which is also spread by Ixodes tick
- **Oral amoxicillin** OR **cefuroxime** is given to pts <8 yrs, pregnant and lactating women. Rash and constitutional symptoms should resolve within 3 wks of treatment. Pregnant women should be reassured that Lyme dis. is not known to cause congenital dis.

EARLY DISSEMINATED AND LATE DISEASE

- Although **IV ceftriaxone** is also very effective in early disease but it is reserved for early disseminated and late disease—used for cardiac and neurologic manifestations of Lyme disease
- In case of facial nerve palsy which usually lasts <2mo, cornea may be at risk of dryness and abrasions due to poor eyelid closure. **Artificial tears** should be used during day in addition to ophthalmic ointments and **eyepatch** at night.

Stage	Clinical manifestations of Lyme disease
Early localized (days-1 month after tick bite)	• **Erythema migrans** (80% of patients) • Fatigue, malaise, lethargy • Mild headache & neck stiffness • Myalgias & arthralgias

Early disseminated (weeks-months after tick bite)	• **Carditis** (5% untreated patients)
	  ◦ Atrioventricular block, cardiomyopathy
	• **Neurologic** (15% untreated patients)
	  ◦ Unilateral or bilateral cranial nerve defects (usually VII), meningitis, encephalitis
	• **Muscular** (60% untreated patients): Migratory arthralgias
	• **Conjunctivitis** (10% untreated patients)
	• **Skin**: Multiple erythema migrans
	• Regional or generalized lymphadenopathy

Late or chronic (months-years after tick bite)	• **Muscular** (60% untreated patients): Arthritis • **Neurologic**: Encephalomyelitis, peripheral neuropathy

Help diagnose without labs—not painful but may burn or itch

FACTORS THAT MAKE LYME DISEASE LESS LIKELY

- Ixodes scapularis, the tick that carries Borrelia burgdorferi, is not commonly found in the southern United States.
- The majority (80%) of patients with early localized (primary) Lyme disease (within days of the tick bite) have the classic erythema migrans rash with or without constitutional symptoms. The absence of a rash and the presence of a high fever and hematologic and liver enzyme abnormalities make Lyme disease less likely.
- Finally, absence of any prominent neurologic (eg, encephalitis, cranial nerve palsy, radiculopathy) or cardiac (eg, heart block, pericarditis) manifestations of early disseminated (secondary) Lyme disease makes Lyme unlikely. These would more commonly occur several weeks to months after the initial tick bite.
- Serology is not recommended for early disease as it is very insensitive and usually negative. After the appearance of EM, IgM antibodies usually develop within 1-2 wks and IgG antibodies typically appear within 2-6 wks. Serology however should be performed in pts with signs of early disseminated or late disease.

HOW TO REMOVE TICK IF FOUND ATTACHED:

- CDC recommendations: if tick is found attached to body, grasp the tick with tweezers as close to body as possible and then remove the tick with steady upward pressure.
- If mouth parts break off and remain in the skin, they can be left alone as the infective body is no longer attached.
- Risk of developing Lyme dis. Is low if the tick remains attached for less than a month.
- Pts should be advised to seek medical attention if bull's eye rash (erythema migrans) develops over the next month.
- One dose of doxycycline should be administered if all the criteria (as below) of prophylaxis are met

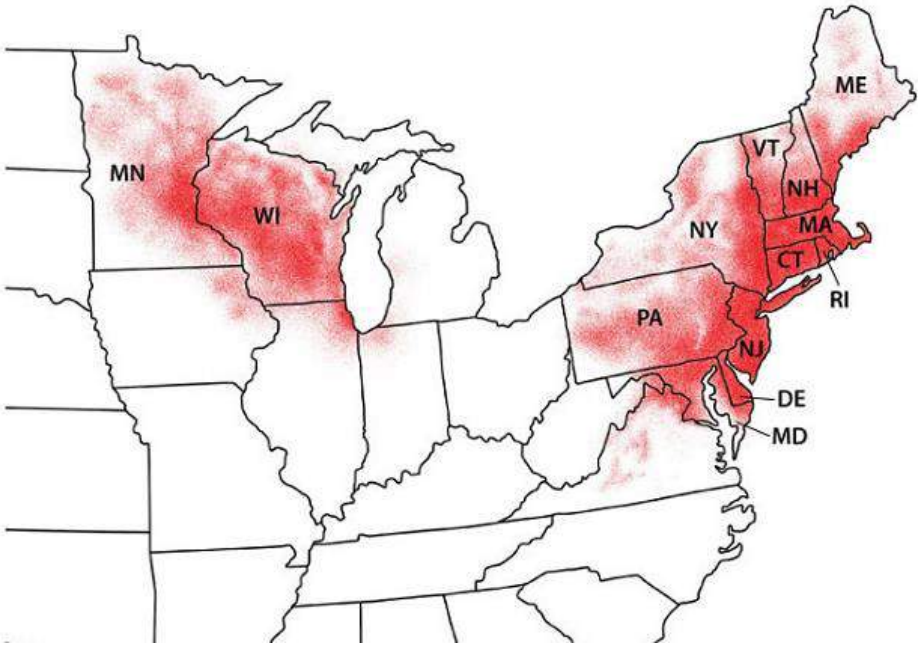
PREVENTION IN LYME ENDEMIC AREAS

- Wear long sleeved shirts and pants
- Application of insect repellents contain DEET should be applied on skin and permethrin on clothes
- Daily checking of entire body for ticks
- Bathing immediately after exposure to tick infested environments

PROPHYLAXIS CRITERIA OF LYME DISEASE

Prophylaxis criteria for Lyme disease (must meet all 5)
• Attached tick is an adult or nymphal *Ixodes scapularis* (deer tick) • Tick attached for ≥36 hours or engorged • Prophylaxis started within 72 hours of tick removal • Local *Borrelia burgdorferi* infection rate ≥20% (eg, New England area) • No contraindications to doxycycline (eg, age <8, pregnant, or lactating)

Lyme Disease: Endemic Areas in the United States



HEMOPHIILUS INFLUENZAE

- **Epiglottitis:** incidence has ↓es due to vaccination against Hib. Other bacteria can also cause this but Hib was the most common cause and still causes in unvaccinated children
  - **Abrupt onset** dysphagia, sore throat, fever and drooling
  - Airway obstruction is most dangerous potential complication
  - Signs of impending airway obstruction: restlessness, anxiety, impaired inspiration and a muffled "hot potato" voice
  - Keeping the neck extended provide some relief as it maximizes airway diameter
  - Mostly require nasotracheal intubation

Infectious epiglottitis	
Epidemiology	• ***Haemophilus influenzae*** • Risk reduced with *H influenzae* vaccination
Clinical	• **Rapidly progressive** & life-threatening • Fever, **sore throat**, drooling, muffled voice • **Airway obstruction** (stridor, dyspnea) • Pooled oropharynx secretions/laryngeotracheal tenderness
Diagnosis	• **Direct visualization** • Imaging
Treatment	• **Early artificial airway** (if needed) • Intravenous antibiotics (ceftriaxone plus vancomycin)

BORDETELLA PERTUSSIS

Pertussis in infants & children			
Clinical phases	**Catarrhal** (1-2 weeks)	**Paroxysmal** (2-6 weeks)	**Convalescent** (weeks to months)
	• Mild cough, rhinitis	• Coughing paroxysms with inspiratory "whoop" • Posttussive emesis • Apnea, cyanosis (infants)	• Symptoms resolve gradually
Diagnosis	• Pertussis culture or polymerase chain reaction • Lymphocyte-predominant leukocytosis		
Treatment	• Macrolides (eg, azithromycin, erythromycin, clarithromycin)		
Prevention	• Acellular pertussis vaccine		
Complications	• Pneumonia, weight loss, subconjunctival hemorrhages, pneumothorax, respiratory failure, death (infants)		

Pertussis treatment & post-exposure prophylaxis	
Age <1 month	Azithromycin x 5 days
Age ≥1 month	Azithromycin x 5 days OR Clarithromycin x 7 days OR Erythromycin x 14 days

- Total duration in untreated pt→ ~3mo
- Prior pertussis infection or vaccination can attenuate the course but **does not provide lifelong immunity**
- **Immunization:**
  - 5 doses of DTaP given between 2mo and 6 yrs:
    - **3 doses in infancy— 2, 4 and 6 mo**
    - **One 15-18mo**
    - **Last at 4-6 yrs**
  - TdaP booster given during adolescence (age 11-18 preferably 11-12 and in >/=19 if did not receive it earlier)
  - During each pregnancy
  - Subsequently vaccination with Td should be continued every 10 yrs to maintain immunization

- **Dx:** culture and/PCR from nasopharyngeal secretions with <1 mo of Sx. Sx >/=1 mo require **serology** to confirm diagnosis
- **Rx:** start antibiotic based on suspicion without waiting for test results—most effective in ↓ing symptoms severity in catarrhal stage. However, treatment should be given in the latter phases to prevent the spread of infection to individuals at risk for devastating complications (e.g., neonates, immunocompromised patients).
- Over-the-counter antitussive medications should be avoided due to lack of proven efficacy and risk of toxicity, especially in children age <6 years.
- **Prevention:** close contacts should be given antibiotics as above table despite immunization status and those with incomplete vaccination should also be given vaccination according to recommended immunization schedule (not needed when fully immunized)
  - Erythromycin use in neonates is associated with pyloric stenosis
  - Safety data for clarithromycin is not available for neonates
- Respiratory isolation is necessary only during the first 5 days of antibiotic therapy. Hospitalization is indicated in infants <3 months (due to high risk of apnea) or any patient with severe paroxysms that impair feeding or are complicated by pneumonia, seizures, or other comorbidities.

CONTRAINDICATIONS AND PRECAUTIONS TO DIPHTHERIA, TETAUS AND PERTUSSIS CONTAINING VACCINE

Contraindications & precautions to diphtheria-, tetanus-, &/or pertussis-containing immunizations

Vaccine component	Contraindications	Precautions
Diphtheria/ tetanus	• Anaphylaxis to vaccine ingredients	• Moderate or severe acute illness +/- fever • Guillain-Barré syndrome within 6 weeks of tetanus toxoid-containing vaccine • Arthus-type hypersensitivity reaction following diphtheria- or tetanus toxoid-containing vaccine

Pertussis	• Anaphylaxis to vaccine ingredients
	• Progressive neurologic disorder (eg, uncontrolled epilepsy, infantile spasms)
	• Encephalopathy within a week of previous vaccine dose
		• Moderate or severe acute illness +/- fever
		• Reactions to previous doses:
		  • Seizure within 3 days
		  • Temperature ≥40.5 C (105 F) within 2 days
		  • Hypotonic-hyporesponsive episode within 2 days
		  • Inconsolable, persistent crying within 2 days

- H/o or family history of febrile seizure is not a contraindication to DTaP
- Generally safe vaccine, some may experience erythema/swelling at injection site or fever

- The benefit of DTaP vaccination, especially in the setting of pertussis outbreak, outweighs the unlikely risk of significant side effects
- Infants with progressive neurologic disorders should also avoid pertussis immunization to prevent confusion about causality until treatment is established and the condition has stabilized
- Only contraindication for avoidance of all vaccine components→ immediate anaphylactic reaction following DTaP vaccination

TUBERCULOSIS (TB)

PPD SKIN TEST INTERPRETATION:

PPD/TST induration	Patients to treat
≥5 mm	• HIV-positive patients • Recent contacts of known TB case • Nodular or fibrotic changes on chest x-ray consistent with previously healed TB • Organ transplant recipients and other immunosuppressed patients
≥10 mm	• Recent immigrants (<5 years) from TB-endemic areas • Injection drug users • Residents and employees of high-risk settings (eg, prisons, nursing homes, hospitals, homeless shelters) • Mycobacteriology lab personnel • Higher risk for reactivation TB (eg, diabetes, prolonged corticosteroid therapy, leukemia, end-stage renal disease, chronic malabsorption syndromes) • Children <4 years of age, or those exposed to adults in high-risk categories
≥15 mm	• All of the above plus healthy individuals

United States guidelines use a cutoff value of 15 mm as a positive response in healthy individuals with a low likelihood of TB infection; Canadian guidelines use a cutoff value of 10 mm. This is due to a high likelihood of exposure to non-tuberculous mycobacteria in several parts of the southern United States, which would increase the false-positive response if lower cutoff values are used.

Treatment options for latent tuberculosis infection
• **Isoniazid and rifapentine weekly for 3 months** under direct observation (not recommended in HIV patients) • Isoniazid monotherapy for 6–9 months • Rifampin for 4 months • Isoniazid & rifampin for 4 months *Pyridoxine is added to prevent neuropathies in patients who are taking isoniazid & have the following conditions: diabetes, uremia, alcoholism, malnutrition, HIV, pregnancy & epilepsy

A treatment option for active pulmonary tuberculosis is the combination of 4 drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) for 8 weeks (2 months). This is then followed by a continuation phase of combined therapy with isoniazid and rifampin for an additional 4 months (total of 6 months).

INFECTIVE ENDOCARDITIS

Infective endocarditis – modified Duke criteria	
Diagnostic criteria for IE	**Major criteria** • Blood culture positive for typical microorganism (eg, *Streptococcus viridans*, *Staphylococcus aureus*, *Enterococcus*) • Echocardiogram showing valvular vegetation **Minor criteria** • Predisposing cardiac lesion • Intravenous drug use • Temperature >38 C • Embolic phenomena • Immunologic phenomena (eg, glomerulonephritis) • Positive blood culture not meeting above criteria **Definite IE** 2 major **OR** 1 major + 3 minor criteria **Possible IE** 1 major + 1 minor **OR** 3 minor criteria
Clinical findings (frequency)	• Fever (>90%) • Heart murmur (85%) • Petechiae (≤50%) • Subungual splinter hemorrhages (<50%) • Osler nodes, Janeway lesions (<50%) • Neurologic phenomena (embolic) (≤40%) • Splenomegaly (≤30%) • Roth spots (retinal hemorrhage) (<5%)

Mitral valve disease, usually **mitral valve prolapse** with coexisting **mitral regurgitation**, is the most common valvular abnormality detected in patients with infective endocarditis.

- The aortic valve is the second most common cardiac valve involved in IE

The diagnosis of IE is based on the combination of clinical presentation, laboratory studies (blood cultures), and results of cardiac imaging studies with the use of modified Duke criteria.

The most appropriate next step is to obtain serial blood cultures when IE is suspected. It is recommended that a minimum of 3 blood cultures be obtained from separate venipuncture sites (not from a vascular catheter) over a specified period prior to initiating antibiotic therapy. In patients with acute illness, all 3 blood cultures should be obtained over a 1-hour period before beginning empiric antibiotic therapy. Patients with stable subacute illness (eg, general malaise with no fever) should have blood cultures obtained over several hours, and antibiotic therapy can be delayed until the blood culture results become available. Patients with suspected IE should have appropriate blood cultures drawn prior to cardiac imaging studies.

Overview of endocarditis

Overview of endocarditis	
Risk factors	• Poor dentition • Cardiac causes (eg, congenital heart disease, valvular abnormalities/repair) • Intravascular catheters (eg, hemodialysis catheters) • Intravenous drug use
Physical examination	• Skin: Osler's nodes, subungual hemorrhages, Janeway lesions, petechiae • Ocular: Roth's spots • Cardiac: Heart murmurs • Gastrointestinal: Splenomegaly • Neurologic: Symptoms related to stroke, meningitis, or brain abscess
Laboratory/ imaging testing	• Positive blood cultures • ↑ White blood cells or normal (subacute endocarditis) • Hematuria/proteinuria (glomerulonephritis) • Septic emboli • Transesophageal echocardiogram is the gold standard for diagnosis (100% specific)
Treatment	• Initial treatment is vancomycin • Subsequent treatment based on cultures

Complications of infective endocarditis	
Cardiac	• Valvular insufficiency – common cause of death • Perivalvular abscess • Conduction abnormalities • Mycotic aneurysm
Neurologic	• Embolic stroke • Cerebral hemorrhage • Brain abscess • Acute encephalopathy or meningoencephalitis
Renal	• Renal infarction • Glomerulonephritis • Drug-induced acute interstitial nephritis from therapy
Musculoskeletal	• Vertebral osteomyelitis • Septic arthritis • Musculoskeletal abscess

Infective endocarditis (IE) in intravenous drug users (IVDU)

• HIV infection increases IE risk in IVDU
• *Staphylococcus aureus* is the most common organism
• Tricuspid valve involvement (right-sided) more common than aortic valve
  ◦ Often lacks audible heart murmur
  ◦ Septic pulmonary emboli common
  ◦ Fewer peripheral IE manifestations (eg, splinter hemorrhages, Janeway lesions)
  ◦ Heart failure more common in aortic valve involvement, but rare with tricuspid valve disease

Empiric antibiotic therapy: it should be based on the condition of heart valves (prosthetic valves) and h/o IVDU. Empiric therapy in a native valve should cover methicillin susceptible and methicillin resistant staph, strep and enterococci. Vancomycin is most appropriate antibiotic for empiric therapy in these pts. due to its broad

spectrum antibiotic. Once the organism is identified in blood culture, antibiotics can be changed to most appropriate antibiotic.

MICROBIOLOGY OF INFECTIVE ENDOCARDITIS

Microorganism	Clinical association/predisposing conditions
Staphylococcus aureus	• Prosthetic valves • Intravascular catheters • Implanted devices (pacemakers, defibrillators) • Injection drug users
Viridans group streptococci	• Dental procedures (manipulation of gingival tissue or perforation of oral mucosa) • Procedures involving incision & biopsy of respiratory tract
Coagulase-negative staphylococci	• Intravascular catheters • Prosthetic valves • Pacemakers or defibrillators
Enterococci	• Nosocomial urinary tract infections
Streptococcus bovis (*S gallolyticus*)	• Colon carcinoma • Inflammatory bowel disease
Fungi	• Immunocompromised host • Chronic indwelling catheters • Prolonged antibiotic therapy

- Native valve = S viridans

- prosthetic valve = Staph **aureus** / epidermis

- Staphylococcal infection is the most common cause of **healthcare**-associated IE; streptococcal infection is a common cause of **community**-acquired IE.

- HACEK group of organisms, which includes
H*aemophilus aphrophilus,*
A*ggregatibacter actinomycetemcomitans*
C*ardiobacterium hominis,*
E *corrodens,* and
K*ingella kingae.*

- HACEK cause only a minority (3%) of cases of IE

- IE due to *E corrodens* is usually seen in the setting of **poor dentition** and/or periodontal infection

Clinical features of splenic abscess	
Risk factors	• Infection (eg, infective endocarditis) with hematogenous spread • Hemoglobinopathy (eg, sickle cell disease) • Immunosuppression (eg, HIV) • IV drug use • Trauma
Clinical presentation	• Classic triad of fever, leukocytosis & left upper-quadrant abdominal pain • Left-sided pleuritic chest pain with left pleural effusion commonly seen • Possible splenomegaly • Most commonly due to *Staphylococcus, Streptococcus* & *Salmonella* • Usually diagnosed by abdominal computed tomography scan
Treatment	• Combination of broad-spectrum antibiotics & splenectomy • Possible percutaneous drainage in poor surgical candidates

There is 10-20% incidence of splenic abscess or infarction with left-sided endocarditis possibly because of hematogenous seeding or septic emboli to spleen

EHRLICHIOSIS

Human monocytic ehrlichiosis	
Epidemiology	• Transmitted by tick vector (lone star tick) • Seen in southeastern & south central United States
Clinical manifestations	• Flu-like illness (high fever, headache, myalgias, chills) • Neurologic symptoms (confusion) • Rash is uncommon (<30% in adults) ("Rocky Mountain spotted fever without the spots")
Laboratory findings	• **Leukopenia & thrombocytopenia** • Elevated liver enzymes & lactate dehydrogenase
Diagnosis	• Intracytoplasmic **morulae** in monocytes • Polymerase chain reaction testing for *E chaffeensis/E ewingii*
Treatment	• Empiric **doxycycline** while awaiting confirmatory testing

- Ehrlichiosis—tick-borne infection caused by *Ehrlichia chaffeensis* and *E. ewingii.* These bacteria are carried by ticks, including the lone star tick *(Amblyomma americanum).* The principal reservoir is the **white tail deer**.
- C/F: acute febrile illness with malaise and altered mental status. Ehrlichiosis is not often associated with a rash (<30% in adults) and is described as **"Rocky Mountain spotted fever (RMSF) without the spots."** Neurologic symptoms may include confusion, mental status changes, clonus, and neck stiffness.
- **Laboratory studies** often show leukopenia and/or thrombocytopenia (hemolysis and jaundice are not common), along with elevated aminotransferases and lactate dehydrogenase.
- **Diagnosis—**often clinical, although definitive diagnosis can be made as mentioned in table

SEXUALLY TRANSMITTED DISEASES

Characteristics of ulcerative sexually transmitted diseases			
Disease	**Causative agent**	**Features of primary lesion**	**Initial lesion painful?**
Chancroid	*Haemophilus ducreyi*	• Multiple & deep ulcers • Base may have gray to yellow exudate • Organisms often clump in long parallel strands ("school of fish")	**Yes**
Genital herpes	Herpes simplex virus 1 & 2	• **Multiple**, small, grouped ulcers • Shallow with erythematous base • Multinucleated giant cells & intranuclear inclusions (Cowdry type A)	**Yes**
Granuloma inguinale (donovanosis)	*Klebsiella granulomatis*	• Extensive & progressive ulcerative lesions without lymphadenopathy • Base may have granulation-like tissue • Deeply staining gram-negative intracytoplasmic cysts (Donovan bodies)	No
Syphilis	*Treponema pallidum*	• Single, indurated, well-circumscribed ulcer • Clean base • Thin, delicate, corkscrew-shaped organisms on dark-field microscopy	No
Lymphogranuloma venereum	*Chlamydia trachomatis*	• Small & shallow ulcers • Large, painful, coalesced inguinal lymph nodes ("buboes") • Intracytoplasmic chlamydial inclusion bodies in epithelial cells & leukocytes	No

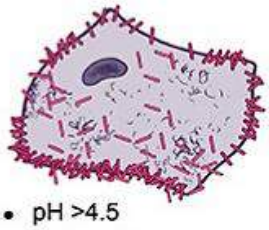
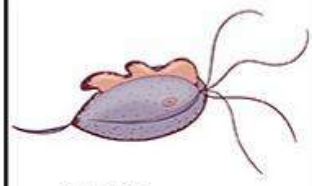
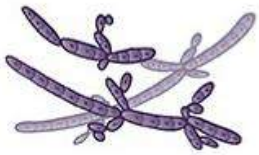
Infectious etiology for genital ulcers	
Painful	
Herpes simplex virus	• **Multiple** small, grouped ulcers with erythematous base • Shallow • Tender lymph nodes • Most common in United States • Recurrence is common
Haemophilus ducreyi (chancroid)	• Single or **multiple** deep ulcers, often with irregular/ragged border • Base may be friable and have gray/ yellow exudate • Matted lymph nodes (can suppurate/rupture)
Painless	
Treponema pallidum (syphilis)	• **Single**, indurated, well-circumscribed, painless ulcer (chancre) • Clean base • Nontender lymph nodes
Chlamydia trachomatis serovars L1-3 (LGV)	• Small and shallow ulcers (often absent) • Matted lymph nodes • Large, painful, fluctuant "buboes" • Sinus tracts
Klebsiella granulomatis (granuloma inguinale)	• Extensive and progressive (nodules → ulcers/beefy-appearing lesions with bleeding) • Base may have granulation-like tissue

Common sexually transmitted infections				
Diagnosis	**Chlamydial cervicitis**	**Gonorrheal cervicitis**	**Herpes simplex virus**	***Trichomonas vaginitis***
Clinical features	Mucopurulent discharge, erythematous/ friable cervix	Mucopurulent discharge, erythematous/ friable cervix	Mucocutaneous ulcers/ vesicles	Thin, green-yellow, or grayish frothy, malodorous discharge; "strawberry cervix"
Treatment	Azithromycin	Ceftriaxone	Acyclovir	Metronidazole

- Most common cause of mucopurulent cervicitis is **Chlamydia trachomatis**, followed by **N. gonorrhea**→ mostly asymptomatic, symptomatic pts have cervicitis and less commonly PID
  - Gram staining—specific but less sensitive in differentiating these two
  - NAAT (nucleic acid amplification test)—more sensitive and recommended to differentiate the two→ empiric treatment should not be delayed waiting for test results. If this test turns out to be positive for either of the two then treat for that specific organism as this is more sensitive and specific. But if less reliable tests like gram staining is being used and shows one organism, then treat for both.
  - Coinfection is common, treat both if laboratory tests not available

VAGINAL DISCHARGE

Differential diagnosis of vaginitis

Diagnosis	Bacterial vaginosis (*Gardnerella vaginalis*)	Trichomoniasis (*Trichomonas vaginalis*)	Candida vaginitis (*Candida albicans*)
Examination	 • Thin, off-white discharge with fishy odor • No inflammation	 • Thin, yellow-green, malodorous, frothy discharge • Vaginal inflammation	 • Thick, "cottage cheese" discharge • Vaginal inflammation
Laboratory findings	 • pH >4.5 • Clue cells • Positive whiff test (amine odor with KOH)	 • pH >4.5 • Motile trichomonads	 • Normal pH (3.8-4.5) • Pseudohyphae
Treatment	Metronidazole or clindamycin	Metronidazole; treat sexual partner	Fluconazole

KOH = potassium hydroxide.

Both oral and intravaginal fluconazole are equally effective- oral 1st line due to convenience

PHYSIOLOGIC LEUKORRHEA

- Copious white or yellow discharge, non-malodorous and no abnormality on physical exam
- No treatment needed
- Microscopic exam may show squamous cells and polymorphous leukocytes

BACTERIAL VAGINOSIS

- Dx is made when 3 of 4 Amsel criteria are met (all 4 points mentioned in table including exam n lab findings except inflammation constitute Amsel criteria):
    - "Clue cells" (vaginal epithelial cells with adherent coccobacilli) on wet mount
- Rx: oral metronidazole 500 mg twice a day for 7 days—treatment is same during pregnancy. Vaginal metronidazole and clindamycin are alternatives

TRICHOMONAS VAGINALIS

- Trichomonads are larger than WBCs but smaller than vaginal epithelial cells
- These organisms have 3-5 flagella
- Oral metronidazole and tinidazole—avoid alcohol as it can cause disulfiram-like reaction (flushing, N/V, hypotension)
- Treat partner without testing

- Sexual activity should be avoided until both partners have completed treatment→ to prevent reinfection

CONGENITAL INFECTIONS

Clinical findings of congenital infections	
All	• Intrauterine growth restriction • Hepatosplenomegaly • Jaundice • Blueberry muffin spots
Cytomegalovirus	• Periventricular calcifications
Toxoplasmosis	• Diffuse intracerebral calcifications • Severe chorioretinitis
Syphilis	• Rhinorrhea • Abnormal long-bone radiographs • Desquamating or bullous rash
Rubella	• Cataracts • Heart defects (eg, PDA)

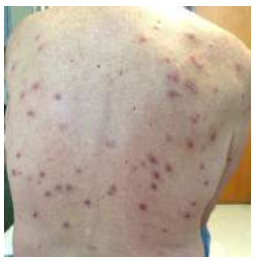
PDA = patent ductus arteriosus.

SYPHILIS

Stage	Clinical manifestations	Treatment	Penicillin-allergic
Primary syphilis	• Painless genital ulcer (chancre)	Penicillin G (IM) x 1 dose	Doxycycline x 14 days
Secondary syphilis	• Diffuse rash • Lymphadenopathy • Condyloma lata • Oral lesions • Hepatitis	Penicillin G (IM) x 1 dose	Doxycycline x 14 days
Latent syphilis	• Asymptomatic	Penicillin G (IM) x 3 doses	Doxycycline x 28 days
Tertiary syphilis	• Central nervous system: Tabes dorsalis, Argyll-Robertson pupil, dementia • Cardiovascular: Aortic aneurysms, aortic insufficiency • Cutaneous: Gummas	Penicillin G (IV) x 14 days	Ceftriaxone x 14 days
Pregnancy	• Intrapartum transmission & congenital disease	Penicillin (route/dose based on stage)	Desensitize & administer penicillin

- Pregnant pt with penicillin allergy→ perform penicillin skin test to evaluate for IgE mediated response→ positive→ desensitize→ IM penicillin
- B/l inguinal LAD and painless chancre in primary syphilis
- **Chancre** forms at the site of direct inoculation→ after 3-60 days of inoculation, **single papule** forms→ turns in to a **shallow, painless, non-exudative ulcer with indurated edges**
- Chancres—very infectious—30% transmission rate—resolve spontaneously in 6-8 wks (if untreated)—systemic spread results in continuous infection.

Syphilis manifestations	
Primary	• Painless genital ulcer (**chancre**)
Secondary	• **Diffuse rash** (palms & soles) • **Lymphadenopathy** (epitrochlear) • Condyloma lata • Grey mucous patches • Hepatitis
Latent	• **Asymptomatic**
Tertiary	• **CNS** (tabes dorsalis, dementia) • Cardiovascular (aortic aneurysm/insufficiency) • Cutaneous (gummas)



Syphilis - diagnostic serology	
Nontreponemal (RPR, VDRL)	• Antibody to cardiolipin-cholesterol-lecithin antigen • Quantitative (**titers**) • **Possible negative result in early infection** • Decrease in titers confirms treatment
Treponemal (FTA-ABS, TP-EIA)	• Antibody to treponemal antigens • Qualitative (**reactive/nonreactive**) • **Greater sensitivity in early infection** • Positive even after treatment

FTA-ABS = fluorescent treponemal antibody absorption; **RPR** = rapid plasma reagin; **TP-EIA** = *Treponema pallidum* enzyme immunoassay.

- Syphilis is diagnosed with a combination of nontreponemal and treponemal serologic testing.

- **Nontreponemal** tests have higher **false-negative** rates (20%-30%) in patients with primary syphilis.

- **FTA·ABS** has the highest diagnostic sensitivity (>97%) in patients with early primary syphilis.

- Either test can be used for screening but reconfirm positive test with test from opposite family
- Pt with **negative screening serology but strong clinical evidence** of primary syphilis (e.g. chancre)→ treat **empirically** with **intramuscular benzathine pencillin G (**↓ risk of transmission**)→ repeat non-treponemal serology** should be done **in 2-4 weeks to establish baseline titers**; a **4-fold titer decrease at 6-12 months confirm adequate treatment.**

CONGENITAL SYPHILIS

- Maternal dx of syphilis is made by serology—treatment prevents congenital syphilis in majority cases
- Children who do get syphilis→ penicillin is curative and prevents the development of late complications like frontal bossing, saddle nose, Hutchinson teeth
- Therefore, no infant should be discharged from nursery unless mother's serologic testing for syphilis is completed

NEISSERIA GONORRHEA

GONOCOCCAL CERVICITIS

Gonococcal cervicitis	
Clinical features	• Purulent or mucopurulent discharge • Friable cervix with easy bleeding (eg, intermenstrual or postcoital bleeding)
Diagnosis	Nucleic acid amplification testing
Empiric treatment	3rd-generation cephalosporin PLUS Azithromycin or doxycycline

- >50% infections are asymptomatic— 2nd most common cause of cervicitis—also major cause of urethritis and PID

DISSEMINATED GONOCOCCAL INFECTION

Disseminated gonococcal infection	
Clinical presentation	• Purulent arthritis without skin lesions **OR** Triad of: • Tenosynovitis (eg, wrist, ankles, fingers & knees) • Dermatitis (pustules, macules, papules & bullae) • Migratory asymmetric polyarthralgia without purulent arthritis
Diagnosis	• Blood cultures (2 sets) but may be negative • Synovial fluid analysis may show up to 50,000 cells/mm^3 • Urethral, cervical, pharyngeal or rectal cultures • Recommend HIV & syphilis screen • Recurrent DGI: check terminal complement activity
Treatment	• IV ceftriaxone 1 g/day for 7-14 days, switch to PO (cefixime) when clinically improved • Joint drainage for purulent arthritis • Empiric azithromycin (single 1-g dose) OR doxycycline for 7 days for concomitant chlamydial infection • Treat sexual partners

Tend to number from 2-10—may be dismissed as furuncles or pimples—painless

DGI = disseminated gonococcal infection; HIV = human immunodeficiency virus; IV = intravenous; PO = orally.

- H/O recent unprotected sex with a new partner is usually present while symptoms of symptomatic venereal dis. are most often absent
- Rash usually involves torso and extremities and can spare hands and feet. Fever and chills maybe present
- Culture is usually negative because of the fastidious growth of the organism and cultures have been found positive in <1/3 cases. However, organism can be recovered from genital site or mucosal lesions by nucleic acid amplification testing.
- Neisseria gonorrhea is the most common sexually transmitted disease causing septic arthritis.

CHLAMYDIA TRACHOMATIS

- Can cause: cervicitis, urethritis, vaginitis
- Asymptomatic in 50% men and 80% women
- Considering frequent absence of symptoms and ↑ risk of transmissibility→ CDC recommends annual screening. Criteria:
  - Sexually active women </=25 years
  - Sexually active women >25 if they have risk factors such as new or multiple sexual partners
- NAAT test is effective screening method
- Rx: single dose azithromycin or 7-day course of doxycycline for partners

PELVIC INFLAMMATORY DISEASE (PID)

- **Causative organisms:** Chlamydia, Neisseria and genital mycoplasmas
- **Criteria for diagnosis:**
  - Fever > 38*C

    - Leukocytosis
    - ↑ ESR
    - Purulent cervical discharge
    - Adnexal tenderness
    - Cervical motion tenderness
    - Lower abdominal tenderness
- Most common cause of infertility in women <30 with normal menstruation
- **Complications of untreated PID:**
    - Tubo-ovarian abscess
    - Abscess rupture
    - Pelvic peritonitis
    - Sepsis
- **Management:**
    - Managed promptly with empirical wide-spectrum antibiotics without waiting for culture results
    - **Regimens for hospitalized pts**: cefoxitin or cefotetan/doxycycline and clindamycin/gentamicin (all IV) Hospitalization and parenteral antibiotics are recommended for:
    1. High fever
    2. Failure to respond to oral antibiotics
    3. Pregnancy
    4. Inability to take oral antibiotics due to N/V
    5. Risk of non-compliance (teenage, women of low socioeconomic status)
        - In **non-hospitalized patients**: IM cefoxitin + oral probenecid and oral doxycycline, or IM ceftriaxone and oral doxycycline.

VULVOVAGINITIS IN PREPUBERTAL CHILDREN

- **Causes:** infections, congenital abnormalities, trauma, or dermatological conditions
- Nonspecific vulvovaginitis is responsible for 25 to 75% of cases due to the lack of labial development, unestrogenized thin mucosa, poor hygiene, bubble baths, shampoos, obesity and certain choices of clothing.
- **Pinworm:** causes nocturnal anal pruritis but can cause vulvovaginitis in prepubertal girls→ nocturnal itching and h/o contact with child with similar complains → perform scotch tape test→ treat empirically with mebendazole

NEONATAL CONJUNCTIVITIS

Type	Onset age	Findings	Treatment
Chemical	<24 hr	Mild conjunctival irritation/ injection & tearing after silver nitrate ophthalmic prophylaxis	Eye lubricant
Gonococcal	2-5 days	Marked eyelid swelling; profuse purulent discharge; corneal edema/ulceration	Intravenous or intramuscular ceftriaxone or cefotaxime
Chlamydial	5-14 days	Eyelid swelling; chemosis; watery, bloody, or mucopurulent eye discharge	Oral erythromycin

Cefotaxime preferred as ceftriaxone can cause kernicterus

Also treats pneumonia

- Diagnosis can be differentiated clinically based on clinical presentation and PE findings
- Most effective method to prevent gonococcal and chlamydia are screen, diagnose and treat infected mothers during pregnancy

CHEMICAL

- **Topical silver nitrate**: unlike topical erythromycin, it is effective prophylaxis against penicillinase producing N. gonorrhea. It is not available in US and is used in some countries. ↑ risk of chemical conjunctivitis

GONOCOCCAL

- Of the 3 most common causes, **gonococcal** is most destructive → can cause corneal ulceration, scarring, perforation and blindness.
- **Prophylaxis: Topical erythromycin ointment** 0.5% formulation is used as prophylaxis in 1-2 hours of vaginal delivery to prevent gonococcal conjunctivitis and other bacterial conjunctivitis. Given to all newborns regardless of screening results. Not effective for chlamydial conjunctivitis and nasal carriage.

Gonococcal conjunctivitis (ophthalmia neonatorum)	
Clinical presentation	• Copious exudates and eyelid swelling typically at age 2-5 days
Diagnosis	• Gram stain with Gram-negative intracellular diplococci • Positive culture on modified Thayer-Martin media
Treatment	• Hospitalization • One dose of ceftriaxone or cefotaxime

CHLAMYDIA

- Maternal infection may be asymptomatic and transferred during vaginal delivery
- Up to 50% exposed pts develop conjunctivitis and 30% develop pneumonia

- Untreated conjunctivitis can lead to corneal and conjunctival scarring
- Chlamydial pneumonia: presents at 4-12 wks with paroxysmal staccato cough
- **Oral erythromycin:** 1st line for both conjunctivitis and pneumonia. Although risk of pyloric stenosis ↑es with erythromycin use, still it is used as data on other macrolides is not available and benefits outweigh risks
- **Prevention:** all pregnant women should be tested on 1st prenatal visit. Repeat screening in high risk pts in 3rd trimester (age <25, multiple sexual partners). Treatment of maternal chlamydia is the best method of prevention

URINARY TRACT INFECTION (UTI)

URETHRITIS

- **C**hlamydia is culture negative.
- The diagnosis can be made with **nucleic acid amplification testing of a first-catch urine sample** without pre-cleaning the genital area.

Urethritis in men	
Etiology	• *Neisseria gonorrhoeae* (most common) • *Chlamydia trachomatis* • *Mycoplasma genitalium* • *Trichomonas* (rare)
Clinical features	• Dysuria • Discharge • Urgency • ↑Voiding frequency
Diagnosis	• Urinalysis • Gram stain & culture • **Nucleic acid amplification testing**
Treatment	• Azithromycin OR doxycycline • PLUS ceftriaxone if gonococcus suspected or not ruled out

Catheter-associated UTI
- prevented by
1. **Clean intermittent catheterization** (best)
2. Avoiding unnecessary catheter use and minimizing the duration of catheterization.

- Indwelling catheters (changed monthly)can be considered if patients or their caregivers cannot perform CIC but are associated with an increased risk of UTI, stricture, and bladder spasm

- Prophylactic antibiotics may increase the risk of development of resistant organisms and have not used, except when proven UTI has occured

STRUVITE STONES

- Caused by **Proteus mirabilis** → secretes urease → hydrolyzes urea to ammonia and CO2. Ammonia combines with hydrogen → form ammonium → decrease the free ion concentration and causes urine alkalinization (pH>7) → promote struvite stone formation (magnesium ammonia phosphate).
- ~~Struvite stones contain a mixture of bacteria, proteinaceous material and leukocytes~~
- ~~Stones become a permanent source of bacteria as bacteria grow within stone matrix~~
- Antibiotics are not sufficient to remove these stones and eradication needs removal of stones and its fragments (eradication if very difficult)
- Other urease producing bacteria: Klebsiella, Morganella morganii, Pseudomonas species, Providencia species, Staphylococcus and Pseudomonas species.
- Chronic indwelling catheters have increased risk of being colonized by bacteria and infection with urease producing organisms

PYELONEPHRITIS

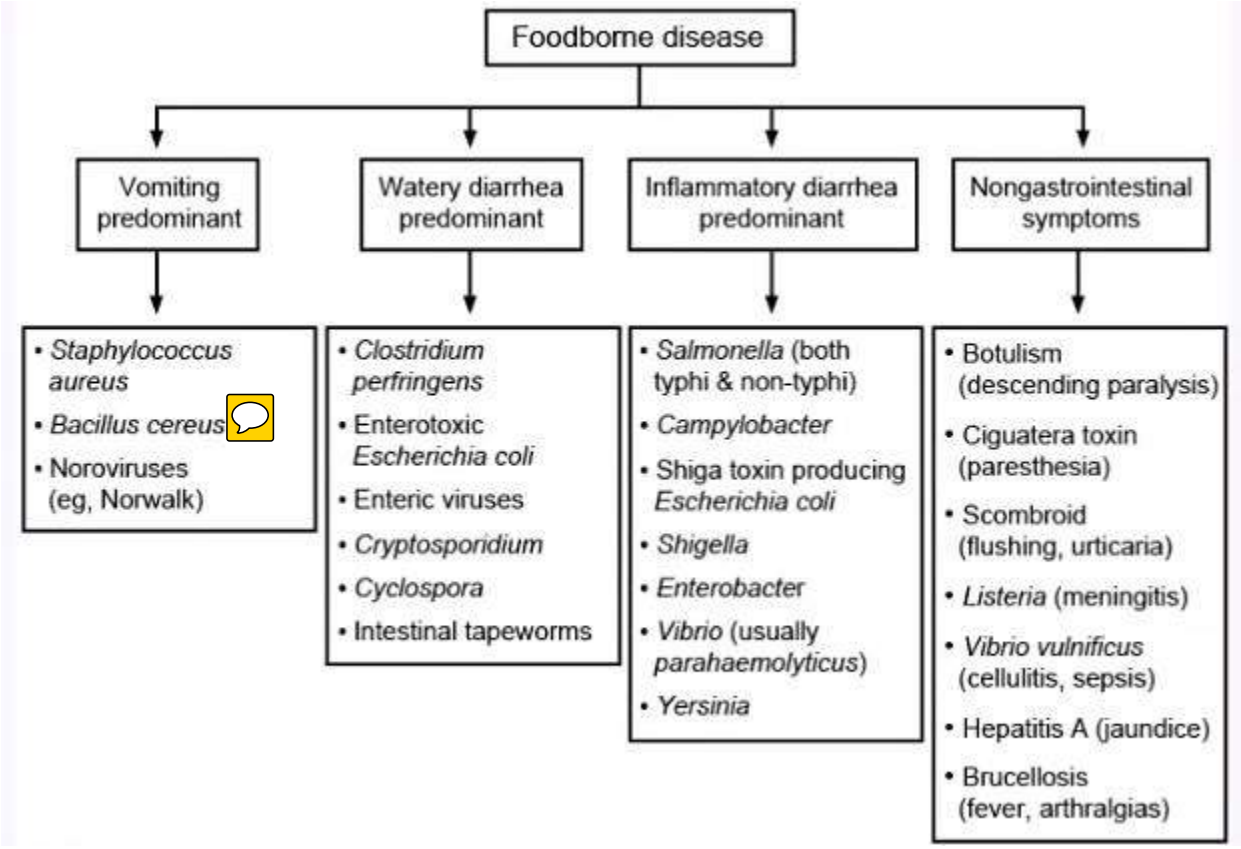
- **Patients with uncomplicated pyelonephritis** should have urine culture prior to empiric oral antibiotics against Gram-negative organisms (eg, fluoroquinolone).
- **Hypotensive patients:**
  1. Require hospitalization and blood cultures to determine the causative organism, evaluate for bacteremia, and check for drug-resistant organisms.
  2. Aggressive resuscitation with IV fluids and empiric IV antibiotics.
- Uncomplicated pyelonephritis does not require routine urological imaging (eg, CT of abdomen/pelvis), especially if the patient is improving clinically. Imaging is typically reserved for patients with persistent clinical symptoms despite 48-72 hours of therapy, history of nephrolithiasis, or unusual urinary findings (eg, gross hematuria, suspicion for urinary obstruction).
- **Complicated pyelonephritis:** involves progression of the initial pyelonephritis to renal corticomedullary abscess, perinephric abscess, emphysematous pyelonephritis, or papillary necrosis. Patients can develop sepsis with multiorgan failure, shock, and renal failure. Complicated pyelonephritis occurs more commonly in patients with conditions such as diabetes, kidney stones, immunosuppression, or other anatomic abnormalities of the urinary tract. These patients usually require imaging to evaluate for these complications, urological evaluation, and prompt therapy (medical/surgical).

Initial treatment of acute pyelonephritis in adults	
Uncomplicated infection	• Mild to moderate: Trimethoprim-sulfamethoxazole, fluoroquinolones (ciprofloxacin) (all usually oral) • Severe: Ceftriaxone, fluoroquinolones (ciprofloxacin, levofloxacin), trimethoprim-sulfamethoxazole (all usually intravenous)
Complicated infection	Indwelling urinary catheter, urinary obstruction or retention, recent urologic procedure or hospital-acquired infection, underlying renal impairment with azotemia, immunosuppression & comorbid diabetes. All are usually treated with hospitalization & intravenous antibiotics. • Mild to moderate: Ceftriaxone, cefepime, fluoroquinolones (ciprofloxacin, levofloxacin) • Severe: Ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, meropenem, imipenem, aztreonam (+/- gentamicin)
Pregnancy	Usually hospitalized for intravenous antibiotics • Ceftriaxone +/- gentamicin, aztreonam

- Diabetic pts are usually managed initially with IV antibiotics
- Unless there is a concurrent disorder affecting urinary tract that would impair clear the infection, most patients can be shifted to oral therapy **within 48-72 hours**
- Oral therapy options: fluoroquinolones and TMP-SMX, but treatment is based individually on the basis of culture and antibiotic sensitivity
- Oral antibiotics should be continued for treatment 10-14 days.

Most hospitalized patients can be transitioned to **culture-guided oral** antibiotics if symptoms are improved after 48 hours.

FOODBORNE DISEASE



Major pathologic mechanisms of foodborne illness		
Enterotoxin ingested	*Staphylococcus aureus* *Bacillus cereus*	• **Quick onset** (1-6 hours) • **Vomiting** predominant
Enterotoxin made in intestine	*Clostridium perfringens* ETEC/STEC *Vibrio cholerae*	• **Delayed** onset (>1 day) • Watery/bloody **diarrhea**
Bacterial epithelial invasion	*Campylobacter jejuni* Nontyphoidal salmonella *Listeria monocytogenes*	• Variable onset • Watery/bloody **diarrhea** • **Fever** • Systemic illness (*Listeria*)

ETEC = enterotoxigenic *Escherichia coli*; **S**TEC = Shiga toxin-producing *E coli*.

DIARRHEA

Bacterial causes of diarrhea	
Organism	**Features**
Bacillus cereus	• Diarrhea, abdominal cramping • Ingestion of preformed toxin in starchy foods such as **rice**
Staphylococcus aureus	• **Vomiting**, abdominal pain • Diarrhea not typical but may occur • Caused by preformed toxin with **rapid onset** of symptoms
Clostridium difficile	• Abdominal pain, watery diarrhea, possible fever • Bloody stools unusual • Associated with **antibiotic** exposure
Clostridium perfringens	• Brief illness with watery diarrhea, cramps & fever • Associated with undercooked or **unrefrigerated** food
Salmonella	• Watery diarrhea, fever, abdominal pain & vomiting • Associated with undercooked foods, especially **poultry & eggs** • Antibiotic treatment needed only for severe disease or immunocompromised patients
Vibrio vulnificus	• Vomiting, diarrhea & abdominal pain • Associated with raw or undercooked shellfish • May cause **invasive**, life-threatening disease in immunocompromised patients or those with liver disease
Escherichia coli	• Watery diarrhea, may be **bloody** if associated with enterohemorrhagic (Shiga-toxin producing) strain • Associated with undercooked beef or foods contaminated with bovine feces
Shigella	• **Bloody** diarrhea with fever & often bacteremia • Associated with contaminated food or water, especially during travel outside the United States
***Campylobacter* species**	• Abdominal pain, **bloody** diarrhea • Highest incidence in children & young adults • Associated with raw or undercooked meats

- Bloody diarrhea is most often caused by bacterial pathogens, specifically *Escherichia coli, Shigella,* and *Campylobacter.*
- *In E.coli* treatment is generally **supportive** ~ antibiotics are not helpful and may increase the risk of hemolytic uremic syndrome (EHEC).

TRAVELLER'S DIARRHEA

Differential diagnosis of travel-associated diarrhea	
Short-term illness	**Notable characteristics**
Rotavirus & norovirus	• Brief illness • Vomiting common
Enterotoxigenic *E coli* Enteropathogenic *E coli*	• Contaminated food & drinking water
Campylobacter	• Prominent abdominal pain • "Pseudoappendicitis" • Bloody diarrhea
Salmonella	• Frequent fever
Shigella	• Fever, bloody diarrhea & abdominal pain
Long-term illness (>2 weeks)	
Cryptosporidium *Cystoisospora* (formerly *Isospora*) Microsporidia species	• Chronic illness in immunosuppressed patients
Cyclospora	• May cause prolonged, relapsing infection
Giardia	• Common in wilderness & rural areas of United States • Asymptomatic patients may continue to shed organism for months

- These pathogens are prevalent worldwide but more in areas with poor sanitation and poor methods decontamination
- Stool examination usually show suspected protozoan pathogen but Cryptosporidia and Microsporidia may need special staining

C. DIFF COLITIS

Features of *Clostridium difficile* colitis	
Risk factors	• **Recent antibiotics** • **Hospitalization** • Advanced age • PPI

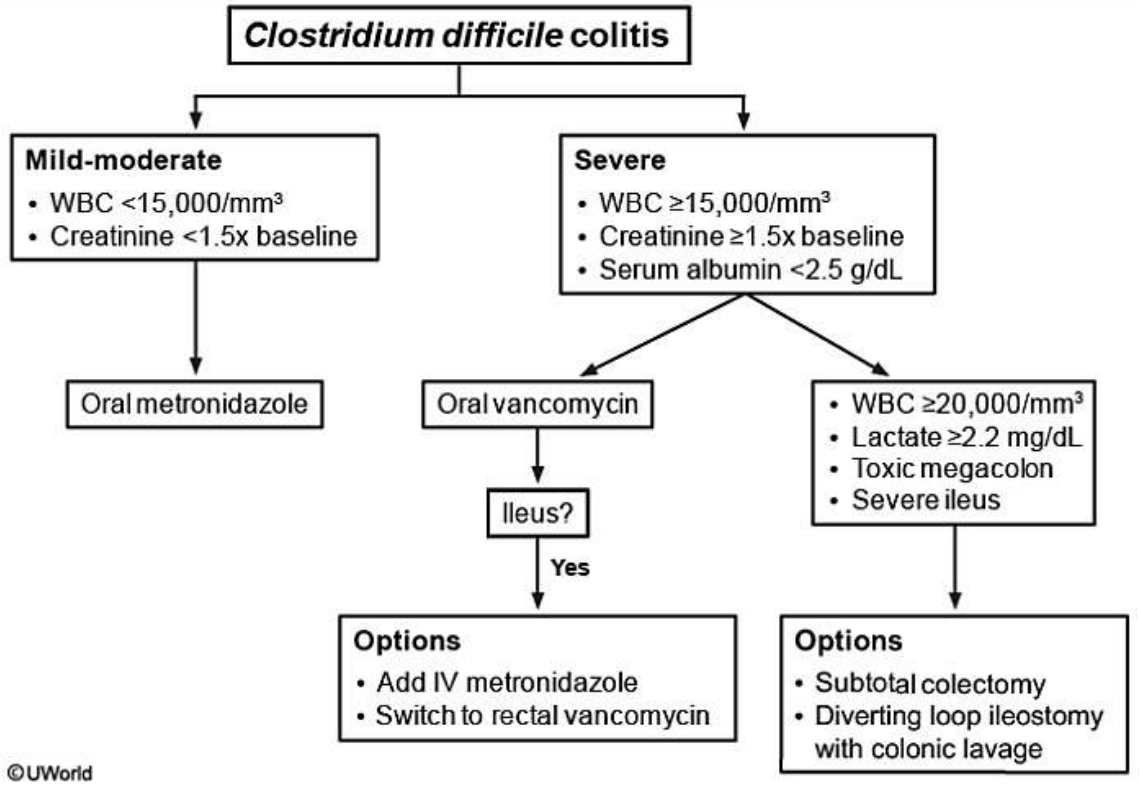
Pathogenesis	• **Intestinal overgrowth** of *C difficile* leads to toxin production:
	  ○ Enterotoxin A: Watery diarrhea
	  ○ **Cytotoxin B**: Colonic epithelial cell necrosis & fibrin deposition

Clinical presentation	• Fever, abdominal pain, watery diarrhea & **leukocytosis** ○ Ranges from mild watery diarrhea to fulminant colitis (**toxic megacolon**) • Characteristic white/yellow **pseudomembranes** on sigmoidoscopy
Diagnosis	• PCR detection of toxin genes in stool
Treatment	• Metronidazole or oral vancomycin

Or enzyme immunoassay

PCR = polymerase chain reaction; PPI = proton-pump inhibitor.

- Antibiotics most commonly associated with this include: fluoroquinolones, clindamycin, penicillin and cephalosporins
- Unexplained leukocytosis in hospitalized pt should also raise suspicion of C. diff. even without diarrhea
- If PCR or enzyme immunoassay turns out to be negative, then there is no need to repeat the test because of high sensitivity and specificity. Pts with negative tests may need sigmoidoscopy or colonoscopy with biopsy to document pseudomembranous colitis.
- Fidaxomicin is a bactericidal antibiotic usually reserved for recurrent colitis or as initial therapy for patients with severe colitis who cannot tolerate oral vancomycin



HEMOLYTIC UREMIC SYNDROME

- Caused by toxin released by E. coli
- Verotoxin invades and destroys colonic epithelial lining→abdominal pain and bloody diarrhea→ activation of coagulation system and red cell hemolysis→ jaundice
- More common in children 1-4 years
- Classic triad: uremia, thrombocytopenia and hemolytic anemia
- Investigations: CBC, blood smear, platelet count, urinalysis, BUN and creatinine
- Rx: generally supportive and plasmapheresis, dialysis if necessary and steroids. Antibiotics are not indicated

NEUTROPENIA

- **Neutropenia** is defined as absolute neutrophil count <1500/uL (severe neutropenia is <500/uL). Pt. with neutrophil count <1000 are at higher risk of developing bacterial infections due to less inflammatory response by neutrophils.
- Chemotherapy also disrupt mucosal and skin barrier leading to early bacterial entry into blood stream
- Gram –ve infections esp. Pseudomonal infections are more common. Gram +ve are also common and increasing in frequency.
- **Febrile neutropenia** is a medical emergency, and starting early empiric antibiotic therapy can avoid progression of infection to severe sepsis and life threatening complications.
- **Initial evaluation:** blood and urine culture, followed by IV broad spectrum antibiotics.
- Monotherapy with **anti-pseudomonal beta lactam antibiotic** (e.g. cefepime, meropenem, piperacillin-tazobactem) provide both Gram+ and –ve coverage and is recommended initially.
- ~~Ciprofloxacin has good coverage against Pseudomonas but does not cover anaerobes. It may be used in combination with beta-lactam/beta-lactamase agents (e.g. amoxicillin-clavulanic acid) for outpatient therapy in low risk neutropenic patients in outpatient setup.~~

- Vancomycin may be used if there is known infection with MRSA, catheter associated infection, skin/soft tissue infection, pneumonia or hemodynamic instability
- Antifungal therapy is recommended in high risk neutropenic pts with persistent fever after 4-7 days of initial therapy in whom a source of infection is not identified.

COMMON OROPHARYNGEAL LESIONS IN CHILDREN

Common oropharyngeal lesions in children	
Diagnosis	**Clinical features**
Aphthous stomatitis ("canker sores")	• Recurrent ulcers on **anterior** oral mucosa (lips, cheeks, mouth floor, ventrum of the tongue) • No fever or systemic symptoms
Herpangina	• Vesicles & ulcers on **posterior** oropharynx • Fever
Herpes gingivostomatitis	• Vesicles & ulcers on **anterior** oral mucosa & around mouth • Fever
Group A streptococcal pharyngitis	• **Tonsillar** exudates • Fever, anterior cervical lymphadenopathy
Infectious mononucleosis	• **Tonsillar** exudates • Fever, diffuse cervical lymphadenopathy • +/- Hepatosplenomegaly

DIFFERENCE BETWEEN HERPANGINA AND HERPETIC GINGIVOSTOMATITIS

Herpangina versus herpetic gingivostomatitis		
Diagnosis	**Herpangina**	**Herpetic gingivostomatitis**
Etiology	Coxsackie A virus	Herpes simplex virus type 1
Age	3-10 years	6 months-5 years
Seasonality	Summer/early fall	None
Clinical features	• Fever • Pharyngitis • Gray vesicles/ulcers on posterior oropharynx	• Fever • Pharyngitis • Erythematous gingiva • Clusters of small vesicles on anterior oropharynx
Treatment	Supportive management	Oral acyclovir

HERPANGINA

- Vesicles can progress to fibrin-coated ulcerations
- Supportive Rx: analgesia and oral hydration
- Usually self-resolve within a week

MENINGITIS

Cerebrospinal fluid analysis			
Diagnosis	**WBC count (cells/μL)**	**Glucose (mg/dL)**	**Protein (mg/dL)**
Normal	0–5	40–70	<40
Bacterial meningitis	>1000	<40	>250
Tuberculosis meningitis	5–1000	<10	>250
Viral meningitis	100–1000	40–70	<100
Guillain-Barré	0–5	40–70	45–1000

BACTERIAL MENINGITIS

Risk group	Most common organisms	Empiric antibiotic choice
Age 2- 50 years	*N. meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin
Age > 50 years	*S. pneumoniae, N. meningitidis, Listeria*	Vancomycin plus ampicillin plus a third-generation cephalosporin
Neurosurgery/Shunt	Gram-negative rods, *S. aureus*, and coagulase-negative *Staphylococcus*	Vancomycin plus cefepime
Immunocompromised state	*Pneumococcus, N. meningitidis, Listeria*, gram-negative rods	Vancomycin plus ampicillin plus cefepime
Penetrating trauma to skull	*S. aureus*, coagulase-negative *Staphylococcus*, and gram-negative rods	Vancomycin plus cefepime
• Third generation cephalosporins: ceftriaxone or cefotaxime • Alternatives to cefepime: ceftazidime or meropenum • Alternative to ampicillin: trimethoprim and sulfamethizole for *Listeria*		

- **Evaluation of bacterial meningitis**:
  - Head CT scan, blood cultures, and LP. **Indications for CT scan** include immunocompromised state, previous central nervous system disease, new-onset seizures, papilledema, altered mental status, or focal neurologic deficits.
  - If there is a delay in performing LP, empiric antibiotics must be administered after blood cultures are obtained.
  - Studies have shown that in most cases of bacterial meningitis (except meningococcus), a pathogen can still be identified in the cerebrospinal fluid up to 4 hours after starting antibiotics.
- **Treatment for bacterial meningitis**:
  - Depends on risk factors and specific pathogens (as shown in table). Adults who present with suspected bacterial meningitis should also be treated with dexamethasone, which must be given at the same time as the first dose of antibiotics. Dexamethasone is helpful in preventing complications of meningitis due to S. pneumoniae and is usually continued for 4 days. It must be discontinued if cultures show another pathogen.
  - Ceftriaxone alone is used for H. influenza and N. meningitis but it is not adequate for S. pneumonia because of resistance.

Clinical features of meningococcal meningitis	
Clinical presentation	• **Symptoms:** Headache, nausea/vomiting, severe **myalgias** • **Signs:** Neck stiffness, altered mental status, **petechial/purpuric rash**, meningeal (Kernig & Brudzinski) signs • **Complications:** Multiorgan failure, DIC, adrenal hemorrhage, shock
Treatment	• Third-generation cephalosporin + vancomycin • Glucocorticoids not helpful • Chemoprophylaxis (eg, rifampin, ciprofloxacin, ceftriaxone) of all respiratory contacts

- *N.meningitidis* is a gram-negative **diplococcus**.

- D.O.C = Ceftriaxone

- Dexamethasone is not beneficial in meningococcal meningitis but is often administered prior to organism isolation (once isolated, dexamethasone can be discontinued).

BACTERIAL MENINGITIS IN CHILDREN >1 MONTH

Bacterial meningitis in children age >1 month	
Clinical features	• Fever • Vomiting/poor feeding • Seizures • Altered mental status (eg, lethargy, irritability) • Nuchal rigidity, Kernig & Brudzinski signs • Bulging anterior fontanelle
Workup	• CBC & electrolytes • Blood cultures • LP & CSF studies
Indications for imaging prior to LP	• History of hydrocephalus or neurosurgical procedure • History of head trauma • Coma or focal neurologic findings
Treatment	• Intravenous vancomycin & ceftriaxone OR cefotaxime • Dexamethasone for *Haemophilus influenzae* type b meningitis

CBC= complete blood count; CSF= cerebrospinal fluid; LP = lumbar puncture.

3rd gen. cephalosporins effective against most strains. Vancomycin is added cox of ↑ing prevalence of resistant S. pneumoniae.

↓ risk of sensorineural hearing loss

- Most common causative organisms: **S. pneumoniae and N. meningitides**
- Children <2 are at greatest risk of contracting **N. meningitides** (petechial rash appears in 75% cases—more prominent in axilla, wrists, flanks and ankles—appears within 24 hours of infection—progresses over few hours and ↑ morbidity and mortality)
- Preferably perform LP before start of antibiotics. Give antibiotics before LP if:
  - Infant is critically ill (e.g. status epilepticus, hypotension) or
  - Who cannot receive LP immediately
- In neonates </=28 days, **give cefotaxime instead of ceftriaxone** as it displaces bilirubin from albumin and ↑ risk of kernicterus. This is not the case in children > 28 days as hyperbilirubinemia is unlikely

VIRAL MENINGITIS

- Usually self-limited inflammation of leptomeninges
- 90% are caused by non-polio enteroviruses like echo and coxsackie viruses
- Incidence ↓es with ↑ing age. Infants are most susceptible and mortality and morbidity is highest in this group
- Presentation:
  - Can present with viral prodrome of constitutional and upper respiratory symptoms with low grade fever
  - Over next 36-48 hours: high fever, headache, irritability and nuchal rigidity develop
  - Pt may also present with seizure
  - Other signs of enteroviral infection may be present like pharyngitis, herpangina or rash
- Neutrophils may predominate early in course but later lymphocytes predominate
- No organism on gram stain

- Rx: supportive; in most pts, symptoms resolve in 7-10 days

NEONATAL SEPSIS

- Systemic bacterial infection that occurs in infants <28 days old

Causes of neonatal bacterial sepsis & associations	
Group B *Streptococcus* and *Escherichia coli*	Most common causes of early- & late-onset sepsis
Staphylococcus aureus	Associated with skin, bone, or joint infections
Listeria monocytogenes	Causes early-onset sepsis during outbreak of listeriosis
Enterococcus	Causes sepsis in preterm infants
Coagulase-negative staphylococcus	Affects infants with indwelling intravascular catheters
Other Gram-negative bacteria (eg, *Klebsiella, Enterobacter, Pseudomonas aeruginosa*)	Causes late-onset sepsis especially in infants in intensive care units

</=3-7days

Pregnant woman e' listeria feels fatigue, body aches and fever prior to delivery

- Studies have shown that GBS is most common in term neonates and E. coli in preterm neonates

Clinical manifestations of neonatal sepsis (including meningitis)	
Present in >50% of cases	• Temperature instability (fever >38 C [100.4 F] or hypothermia <36 C [96.8 F]) • Poor feeding • Irritability or lethargy
Present in 25%-50% of cases	• Respiratory distress • Vomiting • Seizures • Jaundice
Present in <25% of cases	• Apnea • Cyanosis • Bulging fontanelle

- Clinical manifestations in neonatal sepsis are often subtle and non-specific

- It should be high on differential in neonates </=28 days presenting with difficulty feeding, ↓ed activity or not waking for feeds
- PE does not reliably distinguish between sepsis and meningitis—neonates do not present with headache and neck stiffness, Kernig and Brudzinski are not useful, instead are irritable, lethargic and hypotonic
- Neutrophilia with a significant left shift (bands of >700/µL or a band to total neutrophil count ratio >0.16) usually indicates neonatal sepsis from bacterial infection.
- **Management:**
    - Neonates with suspected infection require full evaluation, including: **CBC, blood cultures, lumbar puncture, urinalysis and urine culture.** CT before LP is not required in neonates as open fontanelles serve to relieve ICP and herniation does not occur
    - Give **empiric antibiotics** (e.g. ampicillin and gentamicin, or ampicillin and cefotaxime) after cultures are obtained—antibiotic before culture should be avoided if possible. However, infants who are critically ill or who cannot undergo lumbar puncture immediately should receive antibiotics first

JOINT FLUID CHARACTERISTICS

Joint fluid characteristics				
	Normal	**Noninflammatory (eg, OA)**	**Inflammatory (eg, crystals, RA)**	**Septic joint**
Appearance	Clear	Clear	Translucent or opaque	Opaque
WBC count (mm^3)	<200	200-2,000	2,000-100,000	50,000-150,000
PMNs	<25%	25%	Often >50%	>80%-90%

OA = osteoarthritis; **PMN** = polymorphonuclear leukocytes; **RA** = rheumatoid arthritis; **WBC** = white blood cells.

SEPTIC ARTHRITIS IN CHILDREN

Features of septic arthritis in children	
Clinical manifestations	• Acute onset of fever and joint pain • Fatigue or malaise • Refusal to bear weight due to pain
Physical examination	• Erythema of the overlying skin • Warmth and swelling of the joint • Pain with active and passive range of motion
Laboratory findings	• Elevated WBC • Elevated ESR & CRP • Synovial fluid WBC > 50,000 cells/μL
Treatment	**Birth to 3 months** Organisms - *Staphylococcus,* group B streptococcus & and Gram-negative bacilli • Antibiotics - Antistaphylococcal agent (nafcillin or vancomycin), PLUS gentamicin or cefotaxime **Older than 3 months** Organisms – *Staphylococcus,* group A streptococci & *Streptococcus pneumoniae* • Antibiotics – Nafcillin, clindamycin, cefazolin, or vancomycin

- Septic arthritis— bacterial joint infection, often preceded by skin or upper respiratory tract infections that leads to intermittent bacterial showers→ hematogenous spread to synovial fluid
- **Management:**
  1. **Arthrocentesis**: both diagnostic and therapeutic—perform as soon as possible due to risk of permanent joint destruction—obtain **blood and synovial fluid cultures** before administering empiric antibiotics—
  2. **IV empiric antibiotics**—antibiotics should be narrowed after culture results are obtained (gram stain and culture can be falsely negative in pt already treated with antibiotic)
  3. If synovial fluid aspiration shows septic characteristics→ prompt orthopedic consultation for emergency **surgical drainage. Debridement and irrigation of joint space is the most important intervention in preventing long-term disability**—even a delay of 4-6 hours can lead to femoral head necrosis
  4. If the patient remains febrile or fails to improve after arthrocentesis and 48 hours of appropriate antibiotic therapy, MRI should be performed to evaluate for concomitant osteomyelitis

PROSTHETIC JOINT INFECTION

Prosthetic joint infection		
	Early-onset infection	**Delayed-onset infection**
Timing	Within 3 months of primary arthroplasty	>3 months after primary arthroplasty
Presentation	Wound drainage, erythema, swelling often with fever	Persistent joint pain, implant loosening or sinus tract formation
Most common organisms	*Staphylococcus aureus*, Gram-negative rods, anaerobes Pseudomonas aeruginosa	Coagulase-negative staphylococci, *Propionibacterium* species, enterococci
Management	Implant removal/exchange, may consider debridement & implant retention	Implant removal/exchange generally recommended

S. epidermidis

CAT BITES

Cat bites	
Microbiology	• *Pasteurella multocida* • Anaerobic bacteria
Management	• Copious irrigation & cleaning • Prophylactic amoxicillin/clavulanate • Tetanus booster as indicated • Avoid closure

- Cat bites are more dangerous than dog and human bites as they have sharper teeth and can inoculate oral flora in the deeper tissues
- Amoxicillin has activity against P. mutocida and clavulanate acts against oral anaerobes
- Tetanus booster is given to children who are incompletely vaccinated or who were last vaccinated >/=5 years ago
- Observation and close follow-up without antibiotic prophylaxis are appropriate for immunocompetent individuals with minor human or dog bites that are not located on hands, feet, or genitalia

CAT SCRATCH DISEASE

Cat-scratch disease	
Etiology	• *Bartonella henselae*, fastidious gram-negative bacilli • Can be transmitted by cat scratch or bite
Clinical manifestations	• Papule at scratch/bite site • Regional adenopathy • +/− Fever of unknown origin (≥14 days)
Diagnosis	• Usually clinical • +/− Serology
Treatment	• Generally self-limiting • Azithromycin recommended in disseminated disease or for immunocompromised hosts

- Regional lymph nodes follow bite after 1-2 wks and resolve within 4-6wks.
- Observation alone is sufficient for immunocompetent host with mild to moderate disease.
- Confirmatory test: serology or lymph node biopsy (although history and clinical diagnosis is sufficient). LN biopsy reveals non-caseating granuloma and Warthin Starry stain demonstrating organism. Biopsy is reserved for those in whom diagnosis is uncertain, material is needed for culture or malignancy is a concern

NOCARDIOSIS

Nocardiosis	
Microbiology	• Gram-positive rod (beaded or branching) • Partially acid-fast • Aerobic
Epidemiology	• Endemic in soil • Disease follows inhalation of aerosolized saprophytes **OR** traumatic inoculation into skin • Most common in immunocompromised or elderly patients
Clinical features	• Systemic symptoms • Pneumonia – can appear similar to tuberculosis • Neural tropism (CNS involvement) – brain abscess • Cutaneous involvement
Treatment	• **Trimethoprim-sulfamethoxazole** • Second agent if severe or disseminated disease • Surgical drainage of abscesses if possible

Pulmonary nocardiosis develops within a period of days to weeks. Pulmonary nodules are the most common manifestation, and tissue necrosis or empyema is present in 1/3rd cases. High fever, chills and weight loss are common and can mimic TB.
50% have extrapulmonary manifestations (CNS and skin being most common).
Second line agents that can be used include meropenem, linezolid etc /

ACTINOMYCOSIS

Cervicofacial *Actinomyces*	
Risk factors	• Dental infections & **trauma** (extraction) • Immunosuppression, diabetes mellitus, malnutrition
Manifestations	• Upper/lower jaw **(mandible)** • **Slowly progressive**, **nonpainful**, indurated mass • Sinus tracts with **sulfur granules** • Fever/lymphadenopathy are uncommon
Diagnosis	• Fine needle aspiration • Culture >14 days
Treatment	• **Penicillin** 2-6 months • Surgery (severe disease)

The organism also forms draining yellow pus “sulfur granules”.
Dx is confirmed by tissue culture, but Actinomyces is a fastidious organism that may take up to 3 weeks to grow.
Rx: high dose pencillin, usually for a prolonged period of time (12 weeks). Clindamycin is an alternative for pts allergic to pencillin. Surgical resection is often required for more severe cases (e.g. persistent sinus tract, extensive abscesses)but rarely curative without concurrent antibiotic course

LEGIONELLA PNEUMOPHILA

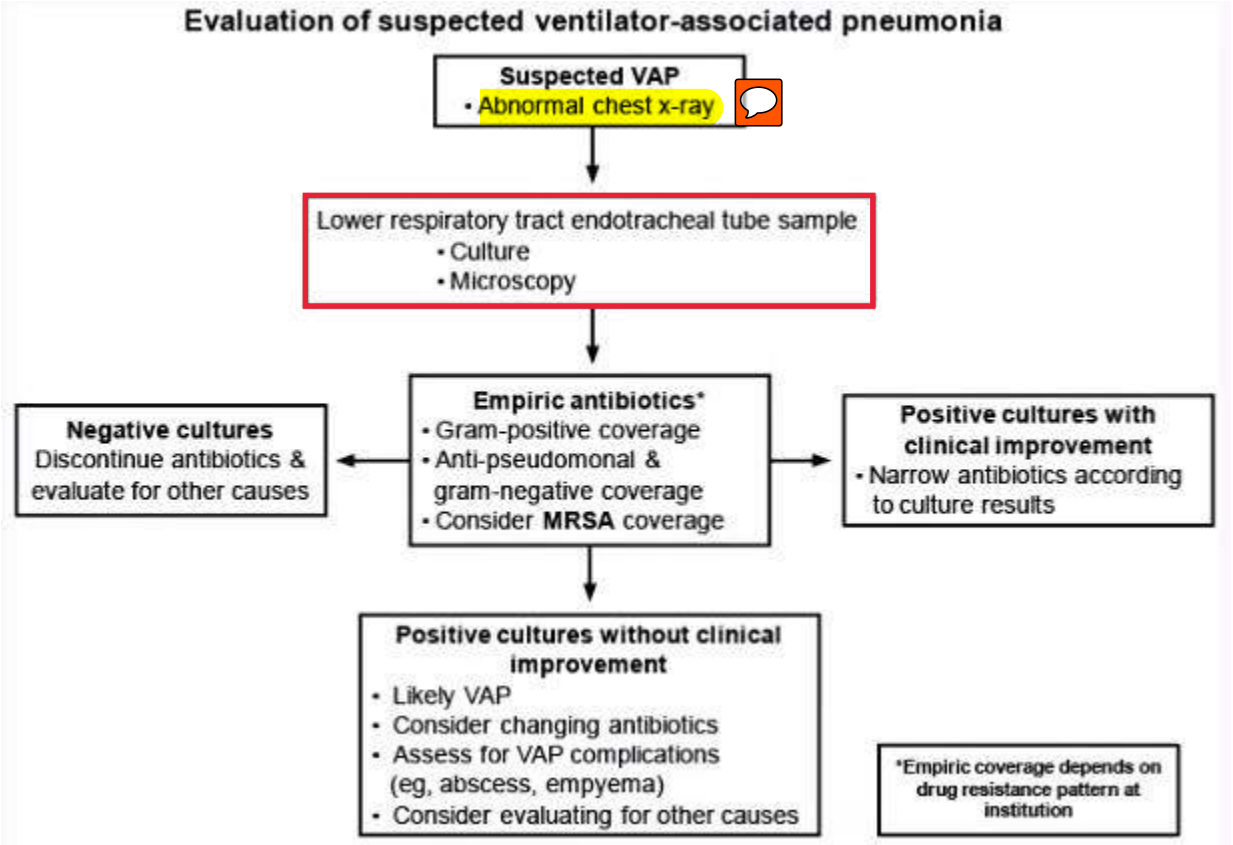
Clues for increasing index of suspicion for *Legionella* pneumonia	
Exposure to possibly contaminated water	• Recent travel (especially cruise or hotel stay) within the previous 2 weeks • Contaminated potable water in hospitals/nursing homes
Clinical clues	• Fever >39 C (102.2 F) • Bradycardia relative to high fever • Neurological symptoms (especially confusion) • Gastrointestinal symptoms (especially diarrhea) • Unresponsive to beta-lactam & aminoglycoside antibiotics
Laboratory clues	• Hyponatremia • Hepatic dysfunction • Hematuria & proteinuria • Sputum Gram stain showing many neutrophils, but few or no microorganisms

Overview of *Legionella* pneumonia	
Clinical features	• High fever with relative bradycardia • Headache & confusion • Watery diarrhea
Laboratory findings	• Hyponatremia • Sputum Gram stain showing many neutrophils, but few or no organisms
Diagnosis	• *Legionella* urine antigen test
Treatment	• Respiratory fluoroquinolones or newer macrolides

- Primary source is water where it lives inside a protozoan
- Pulmonary involvement often accompanied by other organ dysfunction, ranging from CNS and GI involvement to fulminant course with multi-organ failure.

- Chest examination reveals rales and CXR shows interstitial infiltrates
- **Diagnosis** can generally be made from culture from bronchoscopy, though organism is hard to culture even with special stains. **Urine Ag test** is highly specific and readily available. Definitive diagnosis is made by combination of these two tests.
- Fluoroquinolones are favored when condition is severe enough to warrant admission

VENTILATOR ASSOCIATED PNEUMONIA



- VAP is a type of nosocomial pneumonia that usually develop >/=48 hours after intubation.
- Commonly caused by gram –ve bacilli (e.g. Pseudomonas, E. coli and Klebsiella) and gram +ve cocci (e.g. MRSA and streptococci)
- C/F: fever, purulent discharge, difficulty with ventilation (increased RR, dec. tidal volume) and leukocytosis
- Perform **CXR** and follow the above table if abnormal. If normal, VAP is unlikely present.
- Respiratory tract sampling should be performed prior to antibiotics as antibiotics dec. reliability of culture but empiric antibiotics are started asap because of high mortality rate.
- CT scan may be needed to look for complications, if pt with VAP does not improve. It may also be needed for other causes if C/S is negative.

OSTEOMYELITIS

Osteomyelitis in children	
Age/condition	**Most common organisms**
≤2 months	• Group B *Streptococcus* • *Escherichia coli*
2 months-4 years	• *Kingella kingae*
>4 years	• *Staphylococcus aureus*
Sickle cell disease	• *Salmonella* spp • *Staphylococcus aureus*

- **Most frequently involved organism**: **S. aureus** (also in infants and children). Other organisms in infants: **GBS and E.coli** and in children : **S. pyogenes**
- Prosthetic devices: **S. epidermidis**
- UTI or urinary tract instrumentation: **P. aeruginosa and Klebsiella**

OSTEOMYELITIS DUE TO NAIL PUNCTURE WOUND

- In case of nail puncture wound (esp. through rubber sole shoe): **P. aeruginosa**
- **C/F in case of nail puncture wound associated osteomyelitis**: local pain and swelling, fever and raised leukocyte count
- Blood culture may reveal infecting microrganism otherwise, bone biopsy may be needed
- Plain xray require about 2 wks or more to show evidence of disease.
- **Rx:** oral or parenteral quinolones and aggressive surgical debridement.

OSTEOMYELITIS IN SICKLE CELL DISEASE

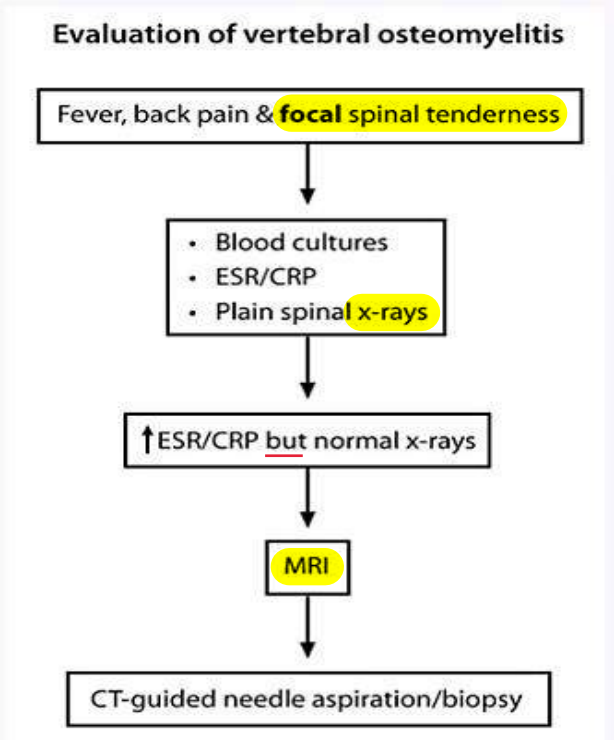
- 2/3rd cases→ Salmonella
- 1/3rd cases→ S. aureus
- Empiric antibiotic coverage against both is indicated while cultures are pending. Administer:
  - 3rd generation cephalosprin (e.g. ceftriaxone)

    AND
  - Anti-staphylococcal therpay e.g. oxacillin, vancomycin

Diabetic foot infections: (can progress to osteomyelitis)
- Deeper infections should be suspected in those with:
1. long-standing wounds (>1-2weeks).
2. systemic symptoms (fever, chills).
3. large ulcer size (≥2 cm).
4. elevated ESR.
5. the presence or palpation of bone in the ulcer base.

- Pts with these features almost always have **polymicrobial** infections. (g+, g-, anaerobes)
- Underlying osteomyelitis is common due to **contiguous** spread from the wound.
- Tx would be wound debridement + IV Ab (eg, piperacillin-tazobactam plus vancomycin).

VERTEBRAL OSTEOMYELITIS



- highest risk for osteomyelitis
1. **Injection drug users**.
2. sickle cell anemia.
3. immunosuppressed patients.
4. recent infx (e.g. UTI).

tenderness to gentle percussion over the spinous process of the involved vertebra can be an important clue.
"**most reliable sign for spinal osteomyelitis**"

- Most likely due to hematogenous spread of recent infection (e.g. UTI).
- ***Staphylococcus aureus***—about 50% of cases of pyogenic spinal osteomyelitis. Other pathogens, including Gram-negative bacilli can also cause osteomyelitis.
- Patients often present with back pain that maybe misdiagnosed as degenerative spine disease. **Fever may or may not be present.**
- PE usually **shows exquisite focal tenderness on percussion at the posterior spinous process of the affected vertebra, increased muscle spasm in the contiguous area, and decreased range of motion in the back.** Epidural abscess may result if the infection extends posteriorly into the epidural space and often causes severe back pain with motor and sensory abnormalities, which can progress to paralysis.
- **Initial workup** includes complete blood count, blood cultures (positive in 50%-70% of patients), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and plain spinal x-rays. Leukocyte count may be normal, but ESR and CRP are usually markedly elevated. Plain x-rays can be normal in the first 2-3 weeks of infection. **Magnetic resonance imaging (MRI) is the modality of choice** for patients with suspected vertebral osteomyelitis. It can also detect epidural abscess and cord compression. **Radionuclide bone scanning** using gallium is an alternate for patients who cannot undergo MRI. **Computed tomography (CT)-guided aspiration and culture** of infected intervertebral disc space or bone are needed to confirm the diagnosis.

➔ prostate biopsy is needed if there are nodules, induration or asymmetry on DRE

PARASITOLOGY

AMEBIC LIVER ABSCESS

- H/o dysentery, fever, leukocytosis RUQ pain and liver abscess on imaging in a young patient
- D/D:
  ➔ **Entameba histolytica**—h/o dysentery, fever, RUQ pain and liver abscess on imaging

➔ Pyogenic bacterial abscess—fever, RUQ pain but it is more common in elderly with other comorbid conditions like diabetes, hepatobilliary disease or following peritonitis, liver abscess on imaging. IV antibiotics and drainage is needed for treatment

➔ Echinococcus granulosus hydatid cyst—RUQ pain and liver abscess on imaging, contact with animals like sheep and dog is needed for its diagnosis, fever is usually absent, eosinophilia is present

- **E. histolytica** is coomon in areas of poor sanitation
- Most infections are asymptomatic but symptomatic ones present with dysentery
- Extraintestinal manifestation-rare and limited to liver where abscess is formed by organism
- **Labs:** Elevated alkaline phosphatase and elevated aminotransferases may be present
- **Imaging:** solitary lesion usually in right lobe of the liver
- **Serologic testing** for E. histolytica confirms the diagnosis. Stool microscopy is insensitive by the time liver abscess has formed (generally months later)
- **Rx:** Metronidazole is the DOC for amebic liver abscess (>90% cure with oral metronidazole). A luminal agent (i.e. paromomycin) is also used for eradication of intestinal infection.
- **Drainage** is **not** recommended as it responds well to oral therapy and also because of risk of rupture in to peritoneum. It is reserved for those with mass effect, imminent rupture, no response to therapy or when diagnosis is uncertain

TOXOPLASMA GONDII

MATERNAL INFECTION

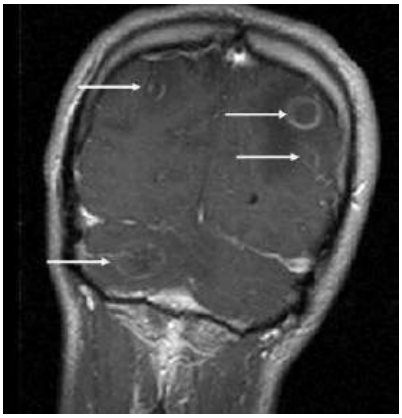
- Acquired by exposure to feces from infected cats, or ingestion of infected raw meat or unpasteurized goat milk

FETAL INFECTION

- Part of TORCHeS infection
- Risk of transmission ↑es with progression of pregnancy but severity of symptoms ↓es
- Approx. 75% infants are asymptomatic at birth, and 25-50% present with complications such as hydrocephalus, microcephaly, microphthalmia, chorioretinitis, seizures, intracranial calcifications, hepatosplenomegaly, jaundice, diffuse lymphadenopathy and diffuse petechiae may be seen
- Labs: may show hyperbilirubinemia and thrombocytopenia

TOXO ENCEPHALITIS

Toxoplasma encephalitis	
Clinical	• Headache • Confusion • Fever • Focal neurologic deficits/seizures
Diagnostic	• HIV with CD4 <100/mm^3 • Positive *Toxoplasma gondii* IgG • Multiple ring-enhancing brain lesions (MRI)
Therapeutic	• Sulfadiazine & pyrimethamine (plus leucovorin) • Antiretroviral initiation • Prophylaxis - TMP-SMX (CD4 <100/mm^3)

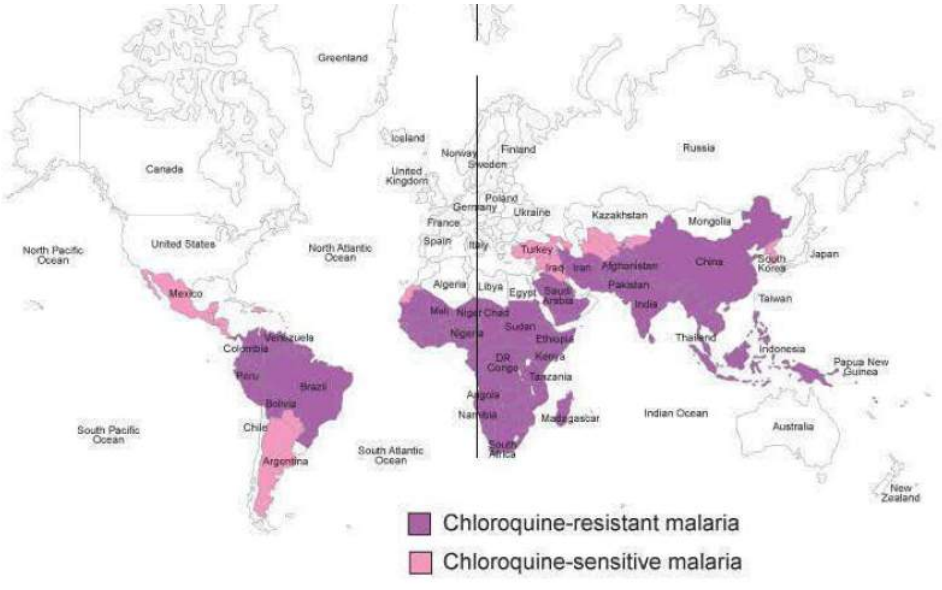


MALARIA

Malaria	
Pathogenesis	Transmission of *Plasmodium falciparum, P vivax, P ovale,* or *P malariae* parasites by the bite of an infected *Anopheles* mosquito
Clinical features	• Periodic febrile paroxysms • Nonspecific malaise, headache, nausea, vomiting, abdominal pain, diarrhea, myalgia, pallor, jaundice, petechiae, hepatosplenomegaly
Complications	• Children: Seizure, coma, hypoglycemia, metabolic acidosis • Adults: Jaundice, acute renal failure, acute pulmonary edema
Diagnosis	Thin & thick peripheral blood smears
Protection	• Hemoglobinopathies (Hgb S, Hgb C, thalassemia) • Partial immunity from previous malarial illness

Prevention	• Antimalarial drugs
	  • Atovaquone-proguanil
	  • Doxycycline
	  • Mefloquine
	  • Chloroquine
	  • Hydroxychloroquine
	• Insecticide-treated nets
	• Household insecticide residual spraying

- The typical cycle (uncommon) consists of: **cold phase** (chills and shivering), then a **hot phase** (high grade fever) and then **sweating phase (**sweating and fever resolution)
- **Anemia & thrombocytopenia** are classic.
- Travelers get malaria because of non-adherence to chemoprophylaxis

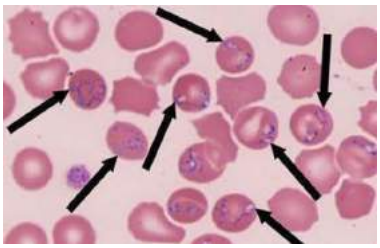


Recommended antimalaria chemoprophylaxis options for short-term travelers		
	Medication	**Adverse effects/comments**
Areas with **chloroquine-resistant *P falciparum*** (Sub-Saharan Africa, southern & Southeast Asia)	Atovaquone-proguanil	• Expensive • GI disturbance (eg, abdominal pain), ↑ liver function tests
	Doxycycline	• Inexpensive • GI disturbance, sun sensitivity, teratogenic
	Mefloquine	• Neuropsychiatric effects • **Agent of choice in pregnancy** • Weekly dosing
Areas with **chloroquine-susceptible *P falciparum*** (in addition to options above)	Chloroquine, hydroxychloroquine	• Need to be started 1-2 weeks in advance • Potential exacerbation of some skin conditions • Weekly dosing
Areas **without *P falciparum*** (parts of South America, Mexico, Korean peninsula)	Primaquine	• Potential teratogenicity • Hemolysis in patients with G6-PD deficiency • Weekly dosing

GI = gastrointestinal; G6-PD = glucose-6-phosphate dehydrogenase.

BABESIOSIS

Babesiosis	
Epidemiology	• *Babesia microti* • *Ixodes scapularis* **tick** bite (Lyme disease & HGA) • Northeastern United States
Manifestations	• Fever, fatigue, myalgias, headache (**flu-like** symptoms) • If severe: ARDS, CHF, DIC, splenic rupture • **Anemia, thrombocytopenia**, ↑ bilirubin/LDH/LFTs
Diagnosis	• Thin blood smear - **intraerythrocytic rings** ("Maltese cross")
Treatment	• Atovaquone + azithromycin • Quinine + clindamycin (if severe)



ARDS = acute respiratory distress syndrome; **CHF** = congestive heart failure; **DIC** = disseminated intravascular coagulation; **HGA** = human granulocytic anaplasmosis; **LDH** = lactate dehydrogenase; **LFTs** = liver function tests.

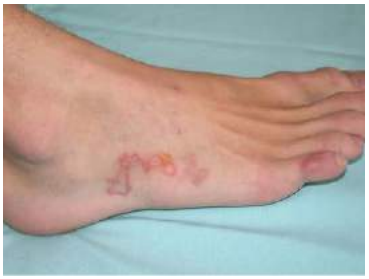
- Babesiosis is a tick-borne **protozoal** illness endemic to the northeastern United states.
- Infection is often asymptomatic or mild, but patients with immunocompromise, age >50, or a history of **splenectomy** are at higher risk for severe illness.

ENTEROBIUS VERMICULARIS

- Adult worm thrives in cecum and appendix
- Female worm lays eggs in perianal region at night
- **Sx**: nocturnal pruritis, abdominal pain, N/V, vulvovaginitis
- **Rx**: albendazole and pyrantal pamoate (later preferred for pregnant women). Treat all patients and household contacts as it is **highly contagious**

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans	
Epidemiology	• **Hookworm larvae** ○ Dog (*Ancylostoma caninum*) or cat (*A braziliense*) • Humans are incidental hosts • **Barefoot** contact with contaminated **sand** or soil
Clinical	• Primarily lower extremity • Cutaneous (deeper infection rare) • Erythematous, pruritic papule at site of entry • **Intensely pruritic**, migrating, serpiginous, **reddish-brown tracks**
Diagnosis	• History and clinical findings • Eosinophils usually normal
Treatment	• Antihelmintic (eg, **ivermectin**)



TRICHINELLOSIS

Clinical features of trichinellosis	
Epidemiology & life cycle	• Ingestion of undercooked meat (usually pork) • More endemic in Mexico, China, Thailand, parts of central Europe & Argentina • Gastric acid releases larvae (within 1st week of ingestion) that invade small intestine & develop into worms • Female worms release larvae (up to 4 weeks later) that migrate & encyst in striated muscle
Clinical presentation	**Intestinal stage (within 1 week of ingestion)** • Can be asymptomatic or include abdominal pain, nausea, vomiting & diarrhea **Muscle stage (up to 4 weeks after ingestion)** • Myositis • Fever, subungual splinter hemorrhages • Periorbital edema • **Eosinophilia** (usually >20%) with possible elevated creatinine kinase & leukocytosis

- Infection usually occurs after eating undercooked meat (esp. pork) containing encysted Trichinella larvae
- During muscle stage, conjunctival and retinal hemorrhages can also occur
- Larvae entering muscle can cause pain, tenderness, swelling and weakness (e.g. neck, shoulders and arms)
- Classic triad: myalgias+periorbital edema+eosinophilia
- Severe disease can involve hearts, lungs or CNS.

NEUROCYSTICERCOSIS

Cysticersosis: parasitic infection caused by larval stage of pork tapeworm Taenia solium. Contracted by consumption of eggs excreted by other person.

Host:

Definitive host: only humans. Meaning only humans become infected with adult tapeworm. Adult tapeworm resides in upper jejunum and excretes eggs in feces.

Intermediate host: animals esp. pig. When an animal consumes eggs, the larva becomes encysted in tissues. When human consumes these larvae by eating undercooked animal, they get intestinal infection.

Ingestion of eggs excreted by other humans result in cysticercosis. After ingestion, embryos are released in intestine and larvae invade intestinal wall→disseminate hemtogenously to encyst in human brain, skeletal muscle, subQ tissue and eye.

Most common presentation: neurologic→neurocysticercosis → multiple, small (<1cm), fluid-filled cysts in brain parenchyma→cysticerci have a membranous wall and often demonstrate invaginated scolex on neuroimaging.

Common areas: rural areas of Latin America, sub-Saharan Africa, China, southern ans South-East Asia and Eastern Europe, esp. places where pigs are raised and sanitary conditions are poor. 80% cases of NCC are asymptomatic and accidentally diagnosed on brain autopsy.

ECHINOCOCCUS GRANULOSUS

Four species of Echinococcus can produce infection in humans, the two most common being E. granulosus, causing cystic echinococcosis, and E. multilocularis, causing alveolar echinococcosis.

Majority are due to sheep strain of **E. granulosus**:

Definitive hosts: dogs and other canids

Intermediate hosts: sheep. Humans are dead end accidental hosts

Transmission: common in areas where sheep are raised and transmission occurs when dogs living in close proximity to humans are fed with home- slaughtered animal viscera. Humans contract it by intimate and close contact with dogs

Infectious eggs excreted by dogs in feces are consumed by humans and other animals. After ingestion of eggs by humans, onchospheres are hatched and penetrate the bowel wall disseminating hemtogenously to various visceral organs, leading to formation of hydatid cysts. Liver, followed by lungs are the most frequently involved viscera, although any viscera can be involved. Hydtaid cyst is fluid filled cyst with inner germinal and outer acellular laminated membrane. Germinal layer gives rise to various secondary daughter cysts.

Can cause unilocular lesion in any organ (e.g liver, lungs, muscle, bone); small daughter cysts may be present. Multiple lesions can be caused by E. multilocularis.

Diagnosis: Usually diagnosed incidentally. Can cause compression of surrounding tissue. Imaging technique and serological testing can be used for diagnosis. Eggshell calcification of liver cyst on CT is highly suggestive of hydatid cyst.

Treatment: surgical resection under the cover of albendazole. In some cases, aspiration of cyst may be performed but there is risk of anaphylactic shock due to spillage of cyst content.

→Amebic liver abscess may occur within weeks of intestinal amebiasis and present with fever and RUQ pain. Eggshell calcifications are unusual.

Diagnosis	• Imaging – large, smooth **hydatid cyst** often with **internal septations** • IgG *E granulosus* **serology**
Treatment	• **Albendazole** • Percutaneous therapy (>5 cm or septations) • Surgery (if rupture)

3789

→Pyogenic liver abscess usually occur after surgery, GI infection or acute appendicitis. CF: high grade fever, extreme pain and leukocytosis
→Simple hepatic cysts are believed to be congenital. Pathophysiology: fluid secretion by epithelial lining. Sx: dull RUQ pain, early satiety or abdominal bloating. No calcification on CT

➔ Benznidazole is 1st line rx for Chagas disease

MYCOLOGY

HISTOPLASMOSIS

Histoplasmosis	
Epidemiology	• Widespread distribution, but most common in central & southern United States • Present in soil, bird & bat droppings • No spread from person to person

Clinical features	• Immunocompetent: Asymptomatic or mild pulmonary disease
	• Immunocompromised:
	  • Involves reticuloendothelial system: Pancytopenia, hepatosplenomegaly & adenopathy
	  • Pneumonia: Diffuse reticulonodular or cavitary
	  • Mucocutaneous lesions

Diagnosis	• Cytopenias (anemia, leukopenia & thrombocytopenia) • Markedly elevated serum lactate dehydrogenase & ferritin • Elevated liver enzymes • **Urine or serum antigen (rapid, very sensitive & specific)** • Culture (blood, sputum, tissue specimens) • Microscopy (sputum, tissue)
Treatment	• Mild to moderate pulmonary infection, immunocompetent patients: no treatment or oral itraconazole • Severe pulmonary infection, disseminated disease or immunocompromised patients: Amphotericin B (switch to oral itraconazole once initial response is documented)

- infections are asymptomatic in immunocompetent

- HIV (CD4 <100 mm^3), are far more likely to develop progressive disseminated histoplasmosis

- Antiretroviral therapy should be initiated in all patients with HIV who develop PDH (usually 2 weeks after antifungal treatment).

- patients often have a history of interacting with chicken coops, farm buildings, bird roosts, or **caves.**

- Biopsy reveals **granulomas** with **budding yeasts**

- Xray: **Hilar LAD**, reticulonodular pattern.

- Disseminated disease in IC present with pancytopenia, LAD and HSM because the organism attacks histiocytes and reticuloendothelial system
- Mortality is >90% in untreated disseminated disease due to septic shock and multiorgan failure.
- Histoplasma urine/serum antigen immunoassay is the most rapid and sensitive test to detect disseminated dis. In immunocompromised pt
- Fungal blood cultures are used for confirmation but have less sensitivity.
- Cultures may also be sent from involved organs.
- Mild to moderate dis in immunocompromised pt can be treated with oral itraconazole alone. Further monitoring for relapse should continue after intraconazole course is complete

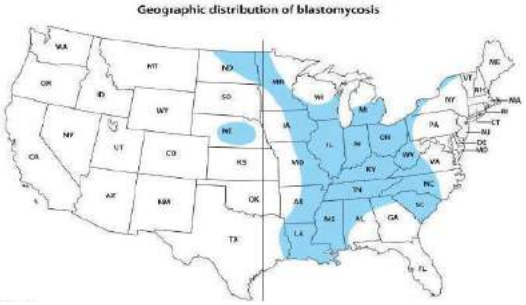
- Severe disease needs to be treated with IV liposomal amphotericin B and switched to oral itraconazole for 1 year
- Histoplasmosis closely mimics sarcoidosis (caseating granulomas are most common but non-caseating granuloma may be the only finding in histoplasmosis), and thus, histoplasmosis should be considered when a pt with suspected sarcoidosis deteriorates following immunosuppressive therapy. In endemic regions, dimorphic fungi (e.g. Histoplasmosis, Blastomycosis & Coccidioidomycosis) must be ruled out before starting immunosuppressive therapy.
- Hilar LAD is more suggestive of histoplasmosis than blastomycosis.

BLASTOMYCOSIS

Epidemiology	• South/south-central states, Mississippi & Ohio River valleys, Upper Midwest states, Great Lakes states & Canadian provinces • Disseminated disease may occur even in immunocompetent patients • Generally more severe in immunocompromised patients
Clinical features	• **Lung**: Acute & chronic pneumonia (usually mild to moderate but may be severe) • **Skin**: Wartlike lesions, violaceous nodules, skin ulcers • **Bone**: Osteomyelitis • **Genitourinary**: Prostatitis, epididymo-orchitis • Central nervous system: Meningitis, epidural or brain abscesses
Diagnosis	• Culture (blood, sputum, tissue specimens) • Microscopy (body fluids, sputum, tissue specimens) • Antigen testing (urine, blood)
Treatment	• Mild pulmonary disease in immunocompetent patients: May consider not treating • Mild-to-moderate pulmonary disease, mild disseminated disease: Oral itraconazole • Severe pulmonary disease, moderately severe to severe disseminated disease, immunocompromised patients: Intravenous amphotericin B

Wisconsin has highest infection rate

- Broad based budding yeast
- Skin lesions have a characteristic presentation of heaped up verrucous or nodular lesions with a violaceous hue that may evolve in to microabscesses.
- Histoplasmosis can also lead to formation of papular, crusted lesions, but disseminated dis. Is rare in immunocompetent.



Cryptococcus neoformans **CRYPTOCOCCAL MENINGOENCEPHALITIS**

Cryptococcal meningoencephalitis	
Presentation	• Headache, fever & malaise • Develops over 2 weeks (subacute) • Can be more acute & severe in HIV
Diagnosis	**Cerebrospinal fluid** • High opening pressure • Low glucose, high protein • White blood cells <50/μL with mononuclear predominance • Transparent capsule seen with India ink stain • Cryptococcal antigen positive • Culture on Sabouraud agar
Treatment	**Initial** • Amphotericin B with flucytosine **Maintenance** • Fluconazole

Altered mental status and coma may develop if left untreated

- Serial lumbar punctures may be required to reduce increased intracranial pressure.

- Antiretroviral therapy should be deferred for at least **2 weeks** after antifungal therapy is started. (due to risk of immune reconstitution syndrome

- Raised ICP is because the organism occludes the flow of CSF. Neuroimaging is performed to exclude mass lesion and lumbar puncture is not CI in the absence of mass lesion, in fact it has therapeutic effect in relieving pressure
- Antiretroviral therapy should be deferred for at least 2 wks after antifungal therapy is started.

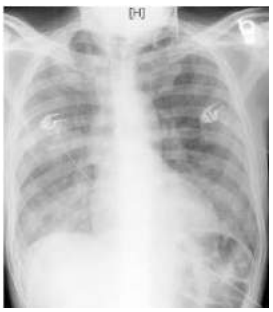
PNEUMOCYSTIS PNEUMONIA (PCP)

- Most notable opportunistic infections in immunosuppressed pts (e.g. organ transplant pts): PCP and CMV
- **S/S of PCP:** typically **acute respiratory failure** (tachypnea, hypoxia), **dry cough**, and **fever** (course is more indolent in HIV pts)
- **Labs:** lactate dehydrogenase (LDH) often ↑ed
- **X-ray:** b/l diffuse interstitial infiltrates, ground glass opacities
- **Dx:** cannot be cultured, dx made by examination of resp. samples using **microscopy with specialized stains**. Induced sputum—least invasive for obtaining adequate resp. sample, if does not yield diagnosis→ **bronchoscopy with bronchoalveolar lavage** is needed

Pneumocystis jirovecii pneumonia	
Clinical	• Indolent (HIV) or acute respiratory failure (immunocompromised) • Fever, dry cough, ↓ O_2
Workup	• ↑ LDH level • Diffuse reticular infiltrates on imaging • Induced sputum or BAL (stain)
Treatment	• TMP-SMX • Prednisone if ↓ O_2
Prevention	• TMP-SMX • Antiretrovirals (in HIV)

Patients with HIV require prophylaxis to prevent *Pneumocystis jirovecii* pneumonia with CD4 <200/mm^3.

BAL = bronchoalveolar lavage; **LDH** = lactate dehydrogenase; **TMP-SMX** = trimethoprim-sulfamethoxazole.



Adverse effects of drug regimens for *Pneumocystis* pneumonia	
Preferred regimen	**Trimethoprim-sulfamethoxazole** (IV for acutely ill, oral for non-acutely ill patients) • Rash, neutropenia, hyperkalemia, elevated transaminases
Alternate regimens	**Pentamidine (IV)** • Nephrotoxicity, hypotension, hypoglycemia, cardiac arrhythmias, pancreatitis, elevated transaminases **Atovaquone (oral)** • Gastrointestinal distress, rash **Trimethoprim + dapsone (both oral)** • Dapsone: Hemolytic anemia (check for G6PD deficiency) **Clindamycin (IV or oral) + primaquine (oral)** • Primaquine: Methemoglobinemia, hemolytic anemia (check for G6PD deficiency)

Add corticosteroids if PaO_2 ≤70 mm Hg or A-a gradient ≥35 mm Hg on room air.

A-a = alveolar-arterial; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; PaO_2 = arterial partial pressure of oxygen.

- **Patients with mild disease and good respiratory reserve**— considered for outpatient oral therapy provided arrangements can be made for adequate follow-up. However, many patients will experience an initial worsening in pulmonary function with possible respiratory failure when antibiotic therapy is started, likely due to the inflammatory effects of dead organisms in lung tissue.
- **Patients with moderate to severe disease, significant pulmonary comorbidity, or uncertain access to follow-up care** should be managed initially in a hospital setting (even if receiving oral antibiotics).
- **Corticosteroid therapy**— minimize the initial antibiotic-induced worsening of respiratory function.
- **Alternate oral regimes for PCP:**
  - **Mild to moderate:** Dapsone + TMP, primaquine+clindamycin or atovaquone suspension
  - **Moderate to severe:** IV pentamidine or primaquine with IV clindamycin. Pentamidine has high rate of adverse effects so it is reserved for pts intolerant to TMP-SMX

Anti-retroviral treatment is started after PCP treatment to reduce drug interaction, pill burden and risk of immune reconstitution syndrome

VIROLOGY

HERPES SIMPLEX VIRUS

HSV ENCEPHALITIS

Viral (herpes simplex virus) encephalitis

Symptoms
- Fever
- Altered mental status with confusion & agitation
- Risk of seizures & coma

Examination
- Hemiparesis, cranial nerve palsies (signs of focal neurologic deficits)
- Hyperreflexia

Laboratory/imaging
- Cerebrospinal fluid analysis: ↑white blood cells (lymphocyte predominant), normal glucose, ↑protein
- Brain magnetic resonance imaging: Temporal lobe abnormalities
- Diagnosis: CSF analysis shows presence of viral DNA on PCR

Treatment
- Intravenous acyclovir: Start immediately after obtaining CSF fluid

- Majority of cases of viral encephalitis are due to unknown causes
- Herpes viruses cause encephalitis in immunocompetent hosts usually
- Signs of meningeal irritation are usually absent in pure encephalitis
- Empiric IV acyclovir should be started immediately after lumbar puncture is obtained and PCR results are still awaited

RISK FACTORS FOR NEONATAL HSV INFECTION

Risk factors for neonatal herpes simplex virus infection

- Primary maternal infection
- Longer duration of rupture of membranes
- Vaginal delivery with active lesions
- Impaired skin barrier (eg, fetal scalp electrode)
- Preterm birth

- Acquired during delivery and not in-utero.
- Newborn can deteriorate quickly due to meningoencephalitis which can also cause permanent hearing loss and/or blindness. But heart defects, blindness and hearing loss are not present at birth
- Indications for C-sec:
  - All women who are in labor with active genital HSV lesions or prodromal symptoms (eg, burning, pain)
  - Pregnant women with a history of genital HSV infection— should receive prophylactic acyclovir or valacyclovir beginning at 36 weeks of pregnancy→ ↓ the risk of outbreak around the time of

delivery→↓ need for C. sec. However, not effective if active lesion is present at the time of delivery

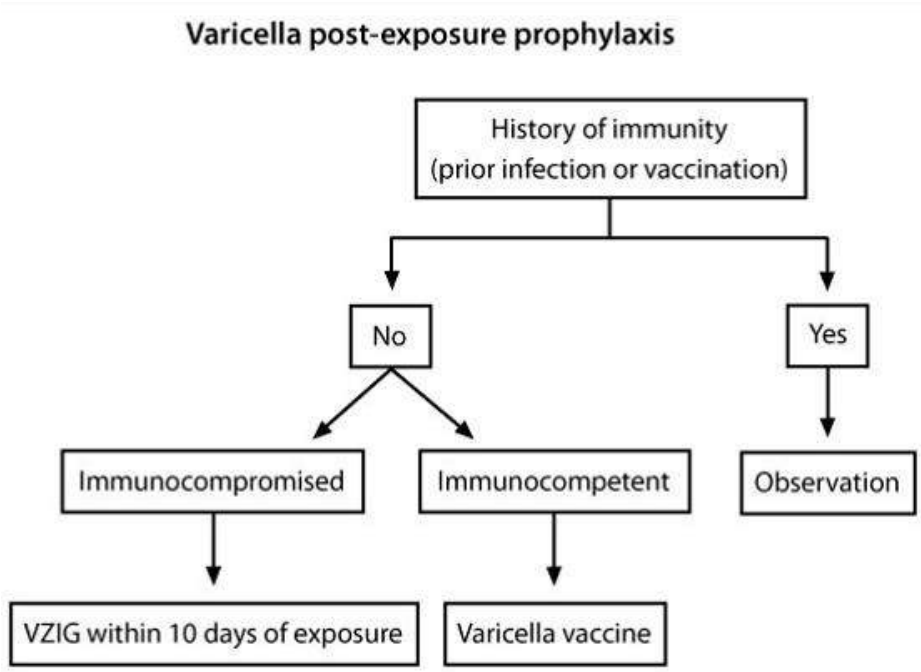
ECZEMA HERPETICUM

- Eczema herpeticum is a superinfection of herpes simplex virus (HSV) in areas of severe eczema. The rash can progress rapidly and is accompanied by fever.

VARICELLA ZOSTER

- 90% infections occur in children <14 yrs
- Incubation period 3 wks—most infections occur within 2 wks of exposure
- Pruritic vesicular rash in different stages—usually become fully crusted within a week
- **Potential complications:** bacterial superinfection in children and pneumonia in adults. Immunocompromised pts are at risk for potentially fatal disseminated disease
- Contagious 2 days prior to rash onset until all vesicles are crusted and should be isolated during this period

Post-exposure prophylaxis



- Acyclovir is treatment of choice for active varicella infection
- Patients age >/=1 year who are non-immune, asymptomatic, and immunocompetent should receive the varicella vaccine for post-exposure prophylaxis. The vaccine is 70%-100% effective in preventing infection if given within 3-5 days of exposure
- Vaccine is live attenuated and in CI in pregnancy and immunocompromised
- Immunocompromised and neonates should receive VZIG within 10 days of exposure—they are at ↑ risk of complications
- VZIG may not prevent infection but ↓ severity—observe these pts closely as VZIG can prolong incubation period to >1mo
- Immunity is conferred by prior infection or vaccination→ these pts may be closely observed after exposure

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis	
Etiology	Epstein-Barr virus most common
Clinical features	• Fever • Tonsillitis/pharyngitis +/- exudates • Posterior or diffuse cervical lymphadenopathy • Significant fatigue • +/- Hepatosplenomegaly
Diagnostic findings	• Positive heterophile antibody (Monospot) test (25% false negative rate during first week of illness) • Atypical lymphocytosis • Transient hepatitis
Management	Avoid contact sports for ≥3 weeks due to the risk of splenic rupture

- Also known as kissing disease and glandular fever

CF:

1. Jaundice
2. Hepatitis
3. Toxic symptoms
4. Posterior cervical LAD more than anterior, inguinal and axillary LAD can also occur—usually tender and mobile
5. Tonsillar enlargement can cause airway compression
6. Mild palatal petechiae may also be present but this is a non-specific sign and can be present in strep throat and generalized maculopapular rash

DIAGNOSIS:

1. Anti-heterophile antibodies (Monospot test)—sensitive and specific for IM but may be negative initially in 1st week— -ve does not rule out IM— repeat test later— EBV- specific Ab may be ordered in pts with more prolonged illness and –ve heterophile testing—may persist at low level for up to 1 year after initial infection
2. Atypical lymphocytosis—non-specific—can be seen in toxoplasmosis, rubella, roseola, viral hepatitis, mumps, CMV, acute HIV infection, and some drug reactions.

COMPLICATIONS:

1. Autoimmune hemolytic anemia and thrombocytopenia due to cross-reactivity of EBV induced antibodies against RBCs and platelets. These are IgM cold-agglutinin antibodies known as anti-I antibodies, which lead to complement mediated destruction of RBCs (usually Coomb's test +). This complication can occur 2-3wks after the onset of symptoms, even though initial labs may not show anemia or thrombocytopenia
2. Splenic rupture (and not infarction) can occur as a result of trauma— highest risk of rupture within 3 wks of symptom onset. Avoid contact sports for >/=3-4 wks until all symptoms resolve. Spleen is not palpable until it is 2-3 times the normal size, so it is not a reliable method to check whether a person can return to sports. USG may be used to consider return to strenuous sports which cause increase in intra-abdominal pressure

Primary HIV infection causes a febrile illness that can closely resemble infectious mononucleosis The key distinctions between the two are that **rash** (unless antibiotics have been administered) and **diarrhea** are LESS common in infectious mononucleosis and the finding of a **tonsillar exudate** is uncommon in primary HIV.

CMV

CONGENITAL INFECTION

- Congenital CMV and rubella share similar presentation e.g. deafness, purpura, HSM, jaundice but differences are:
  - Deafness is u/l in CMV
  - Blindness due to chorioretinitis
  - Heart is unaffected

PARVOVIRUS B19

Clinical features of parvovirus B19 infection	
Signs & symptoms	• Up to 75% of patients are asymptomatic or have flulike symptoms • Erythema infectiosum (fifth disease); more common in children with fever, nausea & a malar rash on the cheeks • Acute, symmetrical arthralgia/arthritis usually in the hands, wrists, knees & feet (resembles RA) • Transient aplastic anemia in patients with a history of hematologic disease (eg, sickle cell)

Diagnosis	• Acute infection
	  ○ B19 IgM antibodies in immunocompetent
	  ○ NAAT in immunocompromised
	• Previous infection by B19 IgG antibodies (documents immunity)
	• Reactivation of previous infection by NAAT to detect B19 DNA

NAAT = nucleic acid amplification testing; **RA** = rheumatoid arthritis

- Nearly 75% adults develop a non-specific rash, but <20% develop characteristic erythema infectiosum rash.
- Parvovirus does not cause joint destruction or chronic arthritis.
- IgM Ab develop in 10-15 days after infection and usually remain positive for 1-6 months
- Sx resolve spontaneously in 2-3 wks without need of specific treatment.
- Morning stiffness lasts less than an hour unlike RA. No joint swelling or redness is present in parvo. For RA, symptoms should be present for >6wks

CHIKUNGUNYA FEVER

Chikungunya fever	
Epidemiology	• Central & South America, tropical regions of Africa, South Asia • Vector: *Aedes* **mosquito** (same as Dengue fever)
Clinical manifestations	• Incubation period: 3-7 days • High fevers, severe **polyarthralgias** (virtually always present) • Headache, myalgias, conjunctivitis, maculopapular rash, LAD • Lymphopenia, thrombocytopenia, elevated liver enzymes
Management	• Supportive care (resolves within 7-10 days)

- Mosquito borne viral illness with recent outbreaks in Americas and Caribbean islands.
- **Dx:** Serologic testing confirms the diagnosis and rarely, patients develop persistent arthritis.
- Disseminated gonococcemia presents with tenosynovitis, polyarthralgia, dermatitis (pustular or vesicopustular lesions) but usually not associated with macular lesions or LAD.

RUBELLA

Rubella (German measles)	

Clinical presentation	• **Congenital disease:**
	  ◦ Sensorineural hearing loss
	  ◦ Intellectual disability
	  ◦ Cardiac anomalies
	  ◦ Cataracts, glaucoma
	• **Children:**
	  ◦ Low-grade fever
	  ◦ Conjunctivitis, coryza, cervical lymphadenopathy, Forschheimer spots
	  ◦ Cephalocaudal spread of blanching, erythematous maculopapular rash
	• **Adolescents/Adults:**
	  ◦ Same as children + arthralgias/arthritis

Diagnosis	• Polymerase chain reaction • Acute & convalescent serology for anti-rubella IgM & IgG
Prevention	• Live attenuated rubella vaccine
Treatment	• Supportive care

Non-exudative coniunctivitis

- Can be asymptomatic in 25-50% adults
- Contagious up to 3 weeks during incubation period prior to onset of Sx. Children may remain asymptomatic or develop mild disease 2-3 wks after inhalation of infected respiratory droplets
- **Prodrome:** fever, tender LAD and malaise (may occur with rash)
- **Maculopapular erythematous rash** that spreads in cranial-caudal and centrifugal direction within 24 hours and spares palms and soles—lasts **<3 days**
- **Resolution:** most Sx resolve within a few days but joint problems can last up to several months.
- **Complications:** post-infectious encephalitis is a rare complication that can occur within a week of exanthema
- **Pregnant women** who develop infection in 1st trimester are at ↑ risk of miscarriage or severe birth defects—most devastating during this period
  - Can be prevented by selective immunization of females of reproductive age, but widespread immunization is preferable for eradication

MEASLES

- Rash similar to rubella but more gradual spread and appears darker (reddish brown)
- Fever is also high grade up to 40 C (104 F) as compared to rubella

Measles (rubeola)	
Clinical presentation	**Prodrome:** • Fever, malaise & anorexia • **Conjunctivitis, coryza, cough, Koplik spots** **Exanthem:** • Blanching, reddish-brown maculopapular rash • Cephalocaudal & centrifugal spread • Usually spares palms/soles
Diagnosis	• Polymerase chain reaction • Acute & convalescent serology for anti-measles IgM & IgG
Prevention	• Live attenuated measles vaccine
Treatment	• Supportive care • **Vitamin A** for hospitalized children

Complications	• Otitis media
	• Pneumonia
	• Neurologic
	  • Encephalitis (within days)
	  • Acute disseminated encephalomyelitis (within weeks)
	  • Subacute sclerosing panencephalitis (within years)
	• Gastroenteritis

- **Incubation period:** 1-3 wks after inhalation of respiratory droplets which remain airborne for several hours
- **Disease spread:** most contagious during cough and coryza but can spread dis. 5 days before rash and 4 days after rash resolves
- **Preventive measures:** Patients with known or suspected disease should enter health care facilities through a **dedicated isolation entrance**. They should be placed immediately in a **private room with negative air pressure** and a minimum **of 6-12 air changes per hour** with the doors closed. All persons in the room should **wear an N95 facemask** with a tight seal over the nose and mouth.

KEY RESPIRATORY TRACT INFECTIONS IN CHILDREN

Key respiratory tract infections in children		
Diagnosis	**Classic pathogen**	**Presentation**
Laryngotracheitis (croup)	• Parainfluenza virus	• Age 6 months to 3 years • "Barky" coughing, stridor, hoarse voice
Epiglottitis	• *Haemophilus influenzae*	• Unvaccinated children • Sore throat, dysphagia, drooling, "tripod" positioning
Bronchiolitis	• Respiratory syncytial virus	• Age <2 years • Wheezing, coughing

CROUP (LARYNGOTRACHEOBRONCHITIS)

Croup (laryngotracheitis)	
Pathogenesis	• Parainfluenza viral infection → inflammation of larynx & trachea
Epidemiology	• Age 6 months to 3 years • Fall, early winter
Clinical features	• Inspiratory stridor • "Barky," seal-like cough • Hoarse voice
Treatment	• Mild (no stridor at rest): corticosteroids • Moderate/severe (stridor at rest): corticosteroids + nebulized epinephrine

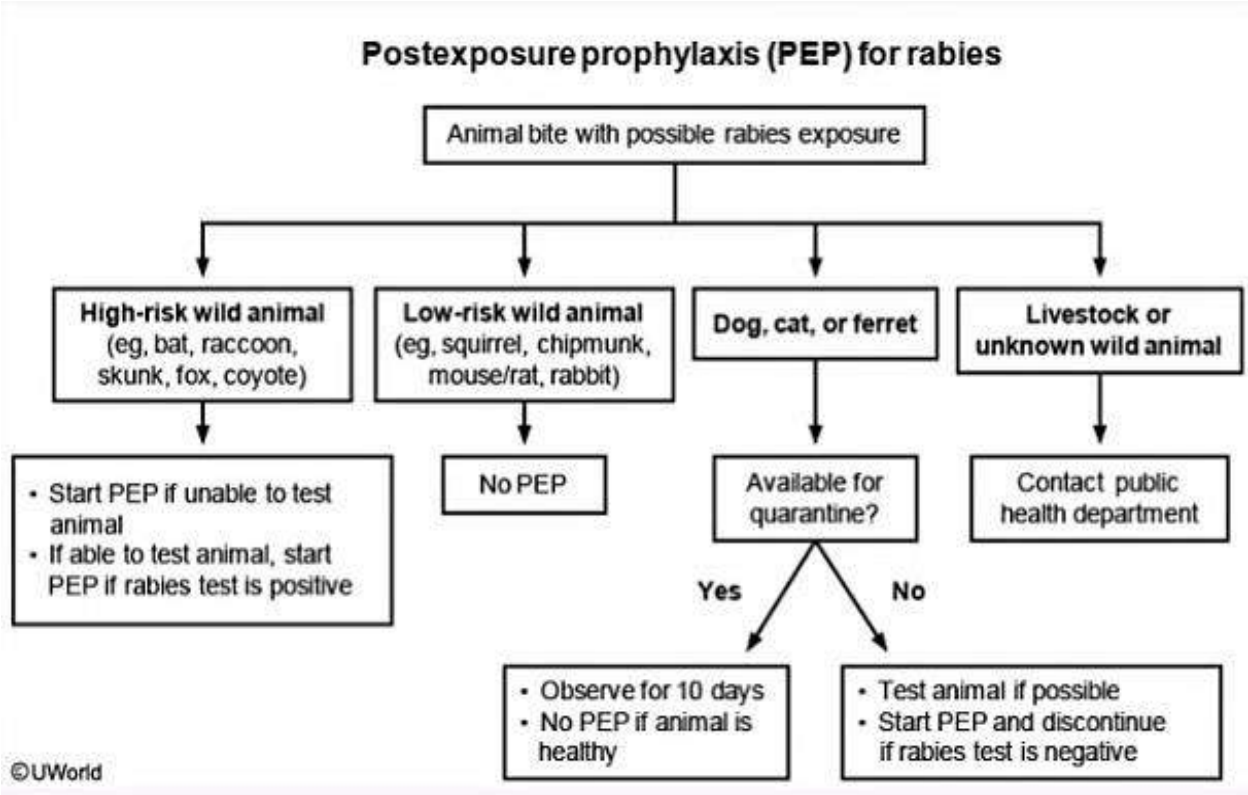
- The stridor worsens with agitation or excitement and may be inspiratory or biphasic (inspiratory and expiratory) in very severe cases
- **Dx:**
  - Typically clinical → if unclear→ AP neck x-ray: subglottic edema known as **"steeple sign"**
- **Treatment:**
  - **Corticosteroids:** ↓ airway edema
  - **Nebulized epinephrine:** constricts mucosal arterioles in upper airway and alters capillary hydrostatic pressure→↓ airway edema and ↓ secretions

- **Endotracheal intubation** reserved for those who have failed above two and/or have signs of impending respiratory failure (e.g. altered mental status, poor respiratory effort)

RABIES

Human rabies		
Pathogenesis	Transmission of rabies virus by bite from infected mammal	
Reservoir	• United States: Bats (most common), raccoons, skunks, foxes • Developing world: Dogs	
Clinical features	**Encephalitic**	• Hydrophobia • Aerophobia • Pharyngeal spasm, spastic paralysis • Agitation
	Paralytic	• Ascending flaccid paralysis
Postexposure prophylaxis	Rabies immune globulin & rabies vaccine immediately after exposure to high-risk wild animal	
Prognosis	Coma, respiratory failure & death within weeks	

- Incubation period is 1-3 months
- Bat bites are small and relatively painless, thus, often go unnoticed and mostly occur during night.
- Therefore, all patients with direct exposure to bats require rabies prophylaxis unless they were aware of the bat at all times and are certain they were not bitten or scratched

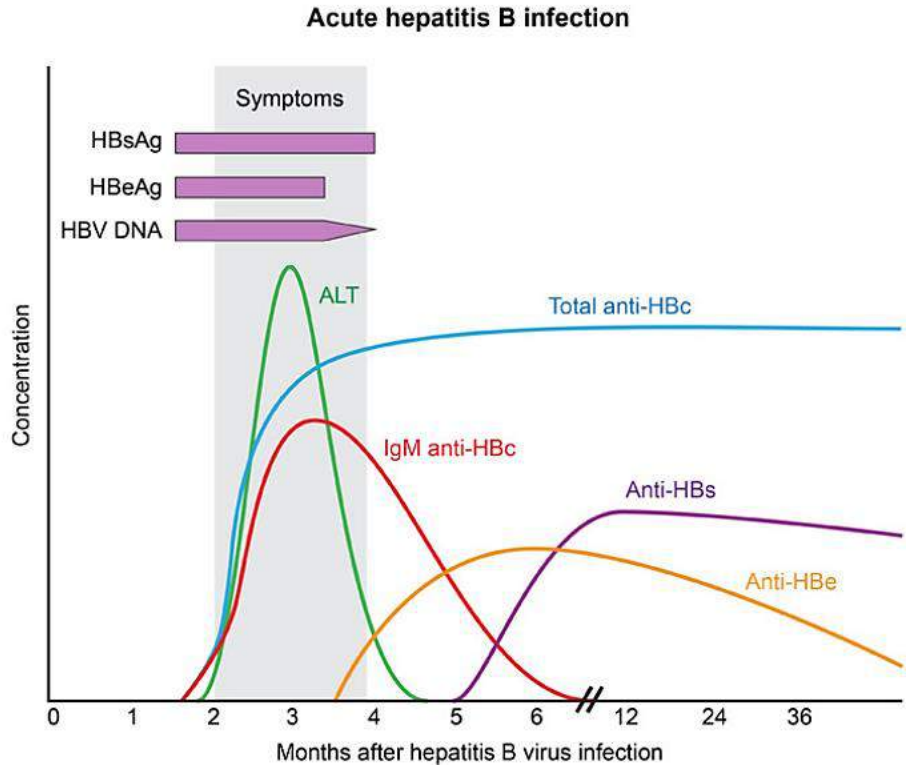


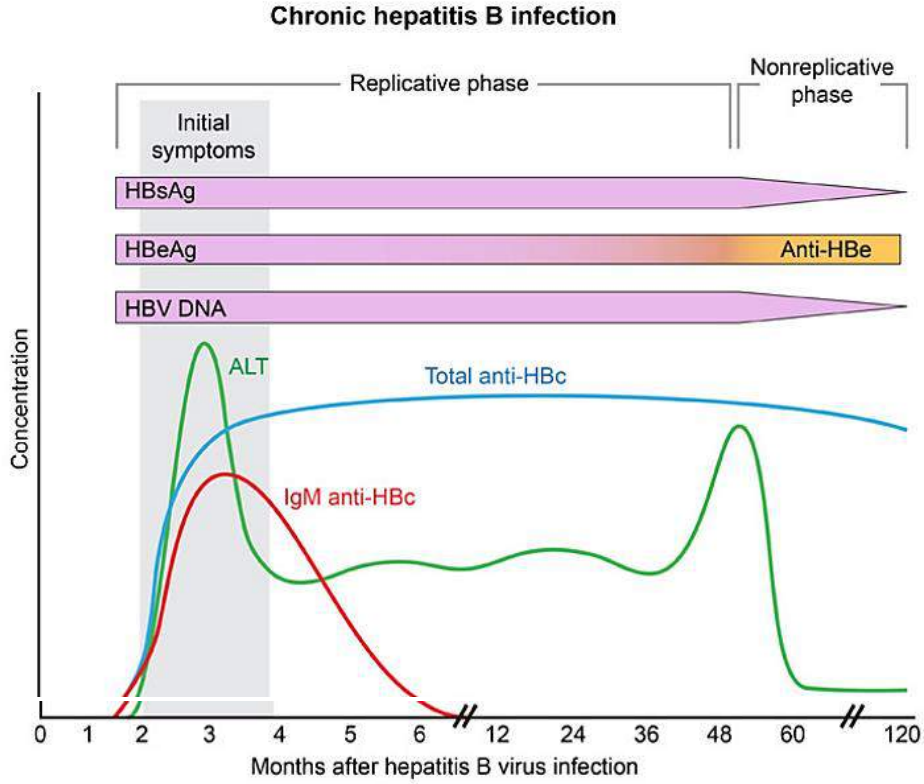
1. **Pt. bitten by high risk wild animal:** even if the animal is available for testing, start PEP and test the animal. If negative→ stop PEP
2. **Cats and dogs:** that can cause rabies in US are mostly the ones which arrive from other countries.
3. 1st step in the process of rabies prevention is cleansing the wound which reduce the risk by 90%. If the pt. is not vaccinated, then both passive (immunoglobulin) and active (rabies vaccines) immunization is needed. If the pt is previously vaccinated (with documented neutralizing antibodies response in the past) only need revaccination.
4. If the patient and animal are both not vaccinated but the animal appears healthy, then pt can wait for 10 days for the animal to be observed and if animal becomes sick, start PEP promptly.
5. If animal becomes sick during this time, then euthanize the animal and brain is tested for fluorescent antibodies to rabies.

HEPATITIS A

- Incubation period 30 days
- Mortality rate is <0.2% but a significantly prolonged PT correlates with ↑ mortality
- Rx: mainly supportive—complete recovery usually in 3-6 wks
- Close contacts should promptly be given immune globulin
- High risk pts like ppl living or travelling to endemic areas, those with CLD or clotting factor disorders or men who have sex with men should be given vaccination prophylactically

HEPATITIS B


Acute hepatitis B infection
Symptoms
HBsAg
HBeAg
HBV DNA
ALT
Total anti-HBc
IgM anti-HBc
Anti-HBs
Anti-HBe
Concentration
0 1 2 3 4 5 6 12 24 36
Months after hepatitis B virus infection


Chronic hepatitis B infection
Replicative phase
Nonreplicative phase
Initial symptoms
HBsAg
HBeAg
Anti-HBe
HBV DNA
ALT
Total anti-HBc
IgM anti-HBc
Concentration
0 1 2 3 4 5 6 12 24 36 48 60 120
Months after hepatitis B virus infection

	HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute HBV							
Early phase	+	+	+				+++
Window phase			+				+
Recovery phase				+	+	+	Likely +
Chronic HBV carrier	+			+			
Acute flare of chronic HBV	+	Likely +	+	+			+
Vaccinated for HBV					+		
Immune due to natural HBV infection				+	+		

- Health care workers (HCW) with previous hep B vaccination and known antibody response do not need PEP. However, some physicians recommend that they should receive 1 HB booster if they are exposed to an infected person
- Pts with no previous vaccination or inadequate antibody response should receive series HB vaccines as soon as possible, if they are exposed to blood of infected pts.
- 1st dose of vaccine is recommended within first 12 hours, with the next two doses according the standard schedule
- Unvaccinated HCW pts exposed to hepB +ve source should also receive HB immunoglobulin as soon as possible, preferably within 24hours
- Window period: time lag between disappearance of HBs antigen and appearance of anti-HBs
- HBs appears 4-8 wks after infection. IgM anti-HBc develops around same time when symptoms develop and aminotransferase rise (>25 times)—these two markers are most useful for diagnosis of acute infection

Reassurance is the most appropriate course of action for a patient with known immunity to hepatitis B who is exposed to the disease. The HBIG and the hepatitis B vaccination series should be given to patients with unknown immunity after exposure.

Overview of hepatitis B virus treatment	
Patients to treat	• Acute liver failure • Clinical complications of cirrhosis • Advanced cirrhosis with high serum HBV DNA • Patients without cirrhosis but with positive HBeAg, HBV DNA >20,000 IU/mL & serum ALT >2x upper limit of normal • Prevent HBV reactivation during chemotherapy or immunosuppression
Available treatments	• **Interferon**: Usually for younger patients with compensated liver disease; short-term treatment • **Lamivudine**: Diminished role due to higher drug resistance; may have role in HIV patients • **Entecavir**: Can be used in decompensated cirrhosis; lower rate of drug resistance than lamivudine • **Tenofovir**: Most potent with limited drug resistance; preferred drug (in countries that have approved it)

Entecavir and **tenofovir** have become preferred therapies due to lower drug resistance and ability to be used in decompensated cirrhosis.

- Interferon is a short-term treatment and cannot be given to patients with decompensated cirrhosis.

- Pegylated interferon + Ribavirin is used for the treatment of Hepatitis C. Telepravir is added to this combination for pts with Genotype 1 hep C infection.

HEPATITIS B AND FULMINANT HEPATIC FAILURE

- >90% adults with hep B recover completely, minority develop chronic hep B and 0.1-0.5% progress to fulminant hepatic failure (FHF).
- **Fulminant hepatic failure-** hepatic encephalopathy that develops within 8wks of onset of acute liver failure.
- **Risk factors for FHF:** heavy users of acetaminophen, alcohol, methamphetamine, and in those who are coinfected with hepatitis B and D viruses.
- **FHF** has a high mortality >80%, patients with this condition are considered high-priority candidates for liver transplantation if suitable donor is available. Orthotopic liver transplantation (i.e original liver is removed and new liver is transplanted in the same place) is the only effective mode of treatment of FHF and must be considered in all patients presenting with this condition.
- Regardless of etiology, these pts have high risk of dying within a few days of symptom onset.
- **General contraindications for liver transplantation:** irreversible cardiopulmonary disease causing prohibitive risk, incurable or recent (<5years) malignancy external to liver and active alcohol or drug abuse.

HEPATITIS C

- Most common mode of transmission: exposure to contaminated blood

CLINICAL FEATURES OF CHRONIC HEPATITIS C

Clinical features of chronic hepatitis C	
Clinical presentation	• Can be asymptomatic or develop fatigue (most common) • Other nonspecific symptoms (eg, nausea, anorexia, myalgia, arthralgia, weakness, weight loss) • Serum **transaminases** can be elevated or **normal** (up to 1/3 of patients) Intermittent elevation of transaminases • Can progress to cirrhosis in up to 20% of patients • Increased risk of hepatocellular carcinoma
Extrahepatic manifestations	• Heme: Essential mixed cryoglobulinemia • Renal: Membranoproliferative glomerulonephritis • Skin: Porphyria cutanea tarda, lichen planus Palpable purpura, leukocytoclastic vasculitis • Endocrine: Increased risk of diabetes

- Porphyria cutanea tarda: fragile skin, photosensitivity, vesicles and erosions on dorsum of hands—all pts with PCT should be screened for HCV (strong correlation)
- Essential mixed cryoglobulinemia: 90% pts of EMC have HCV and 50% pts with HCV have EMC—due to circulating immune complexes that deposit in small and medium blood vessels→ low complement level

SCREENING

- Patients, who have received clotting factors before 1987 or blood transfusion before 1992, have needle-stick exposure at workplace or injection drug use, elevated ALT, HIV positive status, chronic hemodialysis, or born in US between 1945 and 1965, are at increased risk of HCV and should be screened for HCV. Sexual contacts of pts with HCV should also be screened. Screening is also recommended for needle stick exposure to HCV positive blood or for children born to pts with HCV

HEPATITIS C IN PREGNANCY

Hepatitis C in pregnancy	
Potential complications	• Gestational diabetes • Cholestasis of pregnancy • Preterm delivery
Maternal management	• Ribavirin is **teratogenic** & should be avoided • No indication for barrier protection in serodiscordant, monogamous couples • Hepatitis A & B vaccination
Prevention of vertical transmission	• Vertical transmission strongly associated with maternal viral load • Cesarean delivery not protective • Scalp electrodes should be avoided • Breastfeeding should be encouraged unless maternal blood present (eg, nipple injury)

Acute viral infection can be life-threatening in pt with pre-existing chronic hep. Hence, vaccinate. These two killed vaccines are safe in pregnancy

- HIV co-infection is also a strong risk factor for vertical transmission
- C-sec. does not ↓ risk as vertical transmission mostly occurs in late 3rd trimester before delivery

HIV

ACUTE HIV INFECTION

- Acute HIV infection means symptoms within 1st 6 months of infection
- Painful mucocutaneous ulcers (a characteristic manifestation), persistent diarrhea (~50%) and rash (~30%) help differentiate mononucleosis from HIV. Headache and dry cough are also common in HIV
- A low threshold for HIV testing should be adopted
- Blood tests are generally readily available, relatively inexpensive and minimally invasive.
- In addition, early diagnosis has important implication from both an individual perspective (early diagnosis→better recovery) and public health standpoint

Acute HIV infection	
Epidemiology	• Typically presents 2-4 weeks after exposure
Clinical features	• **Mononucleosis-like syndrome** (eg, fever, lymphadenopathy, sore throat, arthralgias) • Generalized macular rash • Gastrointestinal symptoms
Diagnosis	• Viral load is markedly **elevated** (>100,000 copies/mL) • HIV antibody testing may be **negative** (not yet seroconverted) • CD4 count may be normal
Management	• Combination antiretroviral therapy • Partner notification, consider secondary prophylaxis

RECOMMENDED SCREENING FOR HIV

HIV screening indications	
Initial screening	• **Age 15-65** (+ younger or older if at risk) • Treatment for tuberculosis • Treatment for another STD
Annual (or more frequent) screening	• **IVDU** + sex partners • **MSM** • Sex for money or drugs • Partner of HIV-positive • Patient or partner has had >1 partner since last HIV test • Homeless shelter living • Correctional facility incarceration
Additional screening	• Pregnancy • Occupational exposure to blood/body fluids • Any new STD symptoms • Suggested: Prior to any new sexual relationship

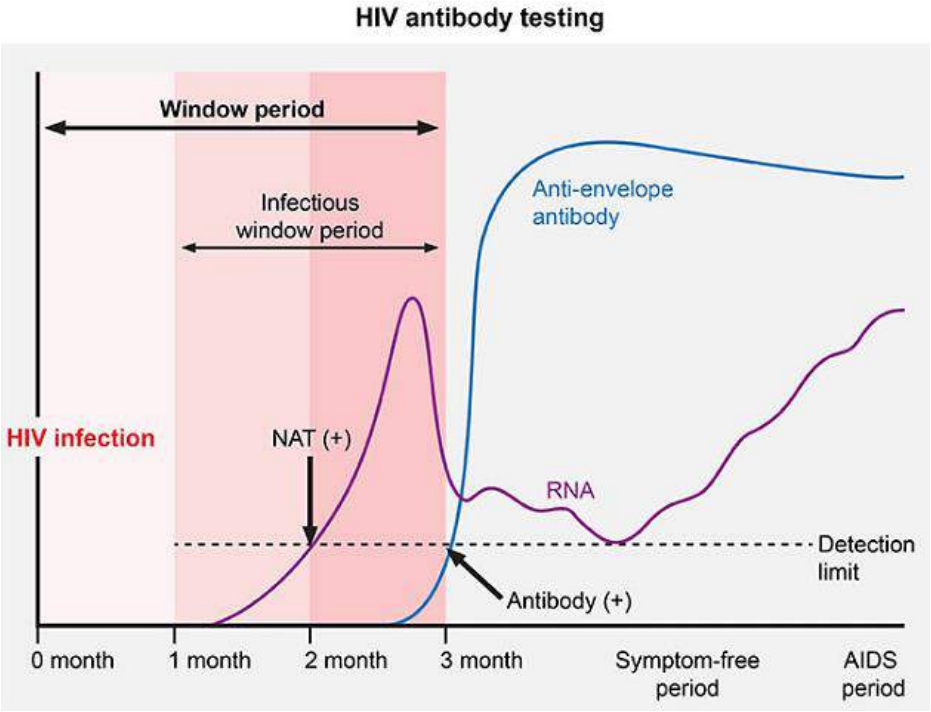
IVDU = intravenous drug use; **MSM** = men who have sex with men; **STD** = sexually transmitted disease.

- Pts who have high risk sexual intercourse should be tested for HIV and HBV.

- Preferred HIV screening is a 4th generation assay that detects the both HIV p24 antigen and HIV antibodies. The combination can more effectively diagnose both acute or early infection compared to antibody testing alone.
- Pts with positive test should then undergo confirmatory testing with HIV1/HIV2 antibody differentiation immunoassay
- Plasma HIV RNA testing is recommended for those with –ve serologic testing and high clinical suspicion of acute HIV

HIV SCREENING IN PREGNANCY

- All pregnant women should undergo **universal HIV antibody screening** in 1st trimester
- High risk pts should be retested during 3rd trimester or at delivery as it can take up to 3 months for antibodies to become detectable—**"window period"**→ high level of HIV present but Ab screen is falsely negative



HIV SCREENING IN INFANCY

- HIV Ab screening is unreliable in infancy
- **PCR**→ gold standard from birth to 18 months
- **Infected newborns** are generally asymptomatic and gradually develop symptoms→ immediately start HAART as soon as diagnosis is confirmed as half of untreated pts will progress to AIDS in first year

HIV in infancy	
Risk factors	• High maternal viral load • Breastfeeding by infected mother
Clinical features	• Failure to thrive • Chronic diarrhea • Lymphadenopathy • *Pneumocystis* pneumonia
Diagnosis	• DNA polymerase chain reaction testing • Persistence of HIV antibody after age 18 months
Treatment	• Immediate combination antiretroviral therapy

PRENATAL, INTRAPARTUM AND POSTNATAL MANAGEMENT OF HIV PATIENT

HIV management during pregnancy	
Antepartum	• HIV RNA viral load at initial visit, every 2-4 weeks after initiation or change of therapy, monthly until undetectable, then every 3 months • CD4 cell count every 3-6 months • Resistance testing if not previously performed • ART initiation as early as possible • Avoid amniocentesis unless viral load ≤1,000 copies/mL
Intrapartum	• Avoid artificial ROM, fetal scalp electrode, operative vaginal delivery • Viral load ≤1,000 copies/mL: ART + vaginal delivery • Viral load >1,000 copies/mL: ART + zidovudine + cesarean delivery
Postpartum	• Mother: Continue ART • Infant (maternal viral load ≤1,000 copies/mL): Zidovudine • Infant (maternal viral load >1,000 copies/mL): Multi-drug ART

- Antiretroviral therapy should be administered as soon as possible (even in 1st trimester)—regardless of maternal CD4 count and viral load
- Mothers with undetectable viral load at delivery have <1% risk of transmitting infection to infants
- Mothers who did not receive antenatal antiretroviral therapy, the addition of nevirapine therapy to the infant's regimen can reduce the risk of maternal-to-child HIV transmission.

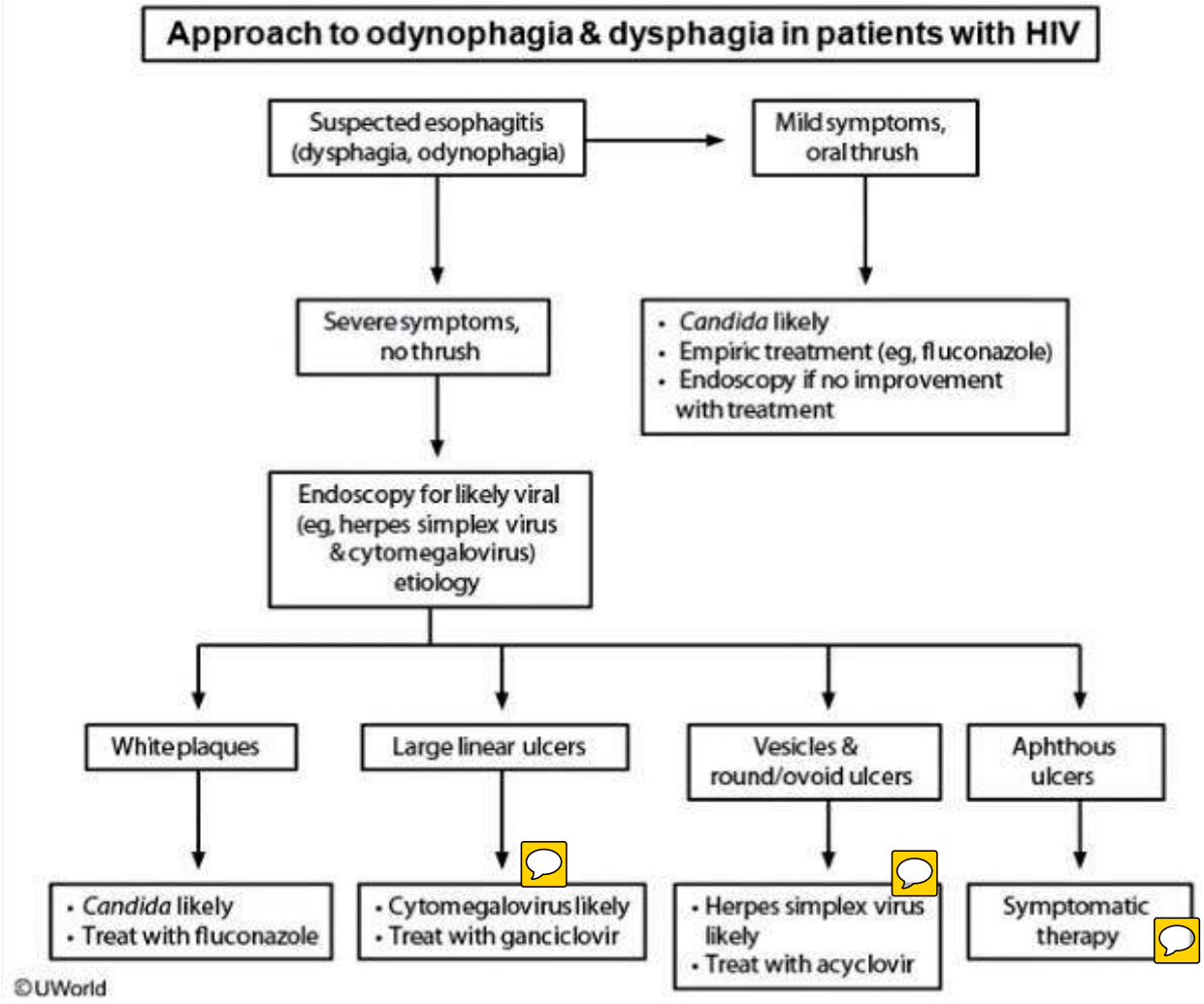
Adverse effects of some HIV antiretroviral medications		
Class	**Example(s)**	**Adverse effects**
NRTI	Abacavir, tenofovir, emtricitabine, didanosine, stavudine, lamivudine, zidovudine	• Lactic acidosis • Lipodystrophy • Hypersensitivity reaction (abacavir) • Pancreatitis (didanosine) • Bone marrow suppression (zidovudine)
NNRTI	Efa**vir**enz, nev**ir**apine	• Rash, including SJS • Hepatotoxicity • Neuropsychiatric effects & teratogenicity (efavirenz)
PI	Ataza**nav**ir, daru**nav**ir, indi**nav**ir, rito**nav**ir	• Metabolic complications (lipodystrophy, dyslipidemia, insulin resistance)
Integrase inhibitor	Dolute**gravir**, ralte**gravir**	• Myopathy

OPPORTUNISTIC INFECTIONS IN HIV

Opportunistic infections in HIV		
Infection	**Risk factors**	**Prophylaxis**
Pneumocystis jirovecii	• CD4+ count < 200 cells/μL • Oropharyngeal candidiasis	• Trimethoprim-sulfamethoxazole
Toxoplasma gondii	• CD4+ count < 100 cells/μL • Positive *Toxoplasma* IgG antibody	• Trimethoprim-sulfamethoxazole
Mycobacterium avium complex (*M avium* & *M intracellulare*)	• CD4+ count < 50 cells/μL	• Azithromycin
Histoplasma capsulatum	• CD4+ count < 150 cells/μL • Endemic area (Ohio and Mississippi river valleys)	• Itraconazole

- Optimal approach to preventing opportunistic infections in HIV/AIDS patients include antiretroviral therapy which maintain high CD4 count and prevent OIs.
- Adjunctive therapies include: vaccination (i.e. pneumococcal vaccine) and antibiotic prophylaxis.
- Antibiotic prophylaxis include primary prophylaxis (before infection) and secondary prophylaxis (once infection has occurred and medicine given to prevent recurrence). Primary prophylaxis is given as above table
- Acyclovir or valacyclovir can be given to prevent HSV recurrences. It is used for pts with frequent or severe recurrences regardless of CD4 count.

ODYNOPHAGIA AND DYSPHAGIA IN PATIENTS WITH HIV



ESOPHAGITIS IN HIV

Common causes of esophagitis in HIV	
Diagnosis	**Typical features**
Candida albicans	• White plaques • Oral thrush
Herpes simplex virus	• Herpetic vesicles & **round/ovoid ulcers** • Concurrent perioral/oral HSV
Cytomegalovirus	• **Deep, linear ulcers** • Distal esophagus
Idiopathic/aphthous	• Concurrent oral aphthous ulcers

- Most common cause of esophagitis in HIV is Candida (>60% cases). Pts with oral thrush are treated with oral fluconazole for 3-5 days. If they don't respond or do not have thrush, then next step is esophagoscopy with culture, biopsy and cytology
- However, in pts with severe odynophagia (pain on swallowing) without dysphagia (difficulty swallowing) or thrush, viral esophagitis is more likely than Candida (mild to moderate odynophagia is present in Candida)
- **Dx:** upper GI endoscopy with biopsy. Diagnosis is confirmed on the basis of histopathology and culture

DIARRHEA IN AIDS

Common causes of diarrhea in patients with AIDS

Organism	CD4 count	Symptoms
Cryptosporidium	<180/mm^3	• **Severe watery diarrhea** • Low-grade fever • Weight loss
Microsporidium/ Isosporidium	<100/mm^3	• Watery diarrhea • Crampy abdominal pain • Weight loss • **Fever is rare**
Mycobacterium avium complex	<50/mm^3	• Watery diarrhea • **High fever (>39 C [102.2 F])** • Weight loss
Cytomegalovirus	<50/mm^3	• **Frequent, small volume diarrhea** • **Hematochezia** • **Abdominal pain** • Low-grade fever • Weight loss

- HIV-associated diarrhea has many potential causes, Work-up typically involves sending the stool for several tests including **culture, ova and parasites (first step),** acid-fast stain, and *Clostridium difficile* antigen.

- Any patient with HIV who has bloody diarrhea and a CD4 count <50/mm' should have a colonoscopy with biopsy to look for CMV colitis.

- Any patient with HIV who has active CMV disease requires ocular examination to rule out concurrent retinitis.

COMMON ANTIRETROVIRAL SIDE EFFECTS

Protease inhibitors:

1. Crystal induced nephropathy-because of precipitation of drug in urine and obstruction of urine flow. According to one study, 8% pts had urinary symptoms and 20% had urinary crystals composed of indinavir. Although adequate hydration may reduce the risk of nephrotoxicity but has been seen in well-hydrated pts as well. This complication may develop early or late in course of disease. For these reasons, some clinicians recommend periodic monitoring of urinalysis and serum creatinine levels every 3-4 months.
2. Didanosine-induced pancreatitis
3. Abacavir-related hypersensitivity syndrome
4. Lactic acidosis 2* to the use of any of the NRTIs
5. Steven Johnson syndrome 2* to the use of any NNRTIs
6. Nevirapine associated liver failure

VACCINATIONS

Vaccine types		
Live-attenuated vaccines	**Non-live (toxoid, subunit, conjugate, inactivated) vaccines**	
• Polio (oral)*	• Influenza (intramuscular)	• Human papillomavirus
• Measles/mumps/rubella	• Pneumococcus	• Meningococcus
• Rotavirus	• Diphtheria/tetanus/pertussis	• Polio (inactivated)
• Influenza (intranasal)	• Typhoid	
• Yellow fever	• Hepatitis A	
• Varicella, zoster	• Hepatitis B	
	• *Haemophilus influenzae* type b	

*Not available in the United States; advised only for developing countries.

- The administration of multiple vaccinations in a single office visit is safe and increases vaccine compliance and optimal protection at a young age. The exception is live-virus vaccines, which should be administered 4 weeks apart due to possible interference of immune response.
- Live virus vaccinations can be safely administered to household contacts of pregnant women because the virus is weak and not contagious
- Vaccination can be safely administered in mild infection. However, should be postponed in moderate to severe until recovery

RECOMMENDED VACCINES FOR PEDIATRIC PATIENTS

Standard pediatric immunizations	
Inactivated (killed)	• Polio • Hepatitis A
Toxoid (inactivated toxin)	• Diphtheria • Tetanus
Subunit/ conjugate	• Hepatitis B • Pertussis • *Haemophilus influenzae* type B • Pneumococcal • Meningococcal • Human papillomavirus • Influenza (injection)
Live attenuated	• Rotavirus • Measles • Mumps • Rubella • Varicella • Influenza (intranasal)

- Premature infants— especially high risk of dangerous complications from vaccine-preventable diseases
- Vaccinations for medically stable preterm infants should be **administered by chronologic age** and not gestational age → vaccination is safe and Ab response is adequate to confer immunity
- Therefore, all stable preterm infants should receive the **first dose of the hepatitis B vaccine at birth (unless the infant weighs <2 kg [4 lb 6 oz)**; and the **hepatitis B (second dose), rotavirus, tetanus, diphtheria, acellular pertussis, Haemophilus influenzae type B, pneumococcal, and inactivated polio vaccines at 2 months chronologic age**
- The only exception to scheduling vaccines by age is the hepatitis B vaccine, which should be administered when the patient weighs ~2 kg (4 lb 6 oz)
- Live attenuated vaccines safe for immunocompetent infants regardless of gestational age. The **first dose of measles, mumps, rubella, and varicella vaccines is typically administered around age 1 year**.
- Currently, all states allow medical exemption from vaccination (eg, allergy to vaccine components). Some states also allow for exemption based on a parent's religious and/or personal beliefs. If a child is unvaccinated and is not exempt, he/she may not be able to enroll in day care or school, depending on the state. The physician must respect the mother's decision but is obligated to inform her about the health-associated risks and benefits as well as the potential consequences (school enrollment). The discussion should be fully documented in the medical record.

RECOMMENDED VACCINES FOR ADULTS

Recommended vaccines for adults		
	Age 19-64	Age ≥65
Td/Tdap	Tdap once as substitute for Td booster, then Td every 10 years	
Influenza	Annually	
Pneumococcus	**PPSV23 alone** • Chronic heart, lung, or liver disease • Diabetes, current smokers, alcoholics **Sequential PCV13 + PPSV23 (very high risk patients)** • CSF leaks, cochlear implants • Sickle cell disease, asplenia • Immunocompromised (eg, HIV, malignancy) • Chronic kidney disease	**Sequential PCV13 + PPSV23** • 1 dose of PCV13 followed by PPSV23 in 6-12 months

CSF = cerebrospinal fluid; **PCV13** = 13-valent pneumococcal conjugate vaccine;
PPSV23 = 23-valent pneumococcal polysaccharide vaccine;
Td = tetanus-diphtheria toxoid booster; **Tdap** = tetanus-diphtheria-pertussis.

- Adults should be given Tdap as a one-time dose. It is also esp. true for pregnant women and all adults who are in close contact with small children.
- Intramuscular inactivated influenza vaccine is given annually to all adults. Healthy, non-pregnant adults <50 years may receive live attenuated intranasal influenza vaccine. However, its safety has not been established for patients with comorbidities like diabetes and should not be given to pts who are taking care of severely immunocompromised pts.
- In pts who are given PPSV23 alone before 65 are given sequential pneumococcal vaccine after 65 but pts with a prior history of PPSV23 should wait for at least 1 year before receiving PCV13
- People travelling to North Africa should be vaccinated against HAV, HBV and typhoid plus polio booster should also be given
- Of the most vaccine preventable infectious disease is hep A. People going to developing countries have higher risk of contracting it and chances increase with the duration of stay. Mortality increases with age and approaches 3% in adults over 55 years.
- European and North American countries are considered low risk zones for hep A; most Asian and African countries are high-risk zones
- A single dose of Hep A vaccine is considered sufficient for young immunocompetent adult; 2nd dose should be administered for long term immunity
- Yellow fever vaccination is recommended for people travelling to sub-Saharan African and South American countries

- Live-attenuated vaccines should b avoided in patients receiving tumor necrosis factor antagonists (e.g. IBD) like the live flu vaccine.

TETANUS PROPHYLAXIS

Tetanus prophylaxis		
	Clean or minor wound	**Dirty or severe wound**
≥3 tetanus toxoid doses	• Tetanus toxoid-containing vaccine* only if last dose was ≥10 years ago • **No** TIG	• Tetanus toxoid-containing vaccine* only if last booster given ≥5 years ago • **No** TIG
Unimmunized, uncertain, or <3 tetanus toxoid doses	• Tetanus toxoid-containing vaccine* only • **No** TIG	• Tetanus toxoid-containing vaccine* **PLUS** • TIG
* Booster given as tetanus/diphtheria toxoids adsorbed (Td) or tetanus toxoid/reduced diphtheria toxoid/acellular pertussis (Tdap)		

TIG = tetanus immune globulin.

- *Clostridium tetani*

- Typical symptoms include tonic contraction and spasm of skeletal muscle (eg, neck stiffness, masseter spasm), which can last up to 4-6 weeks

- Tetanus toxoid containing vaccines are recommended once every 10 years
- Tetanus toxoid can be given as: tetanus toxoid (TT), or diphtheria-tetanus toxoids adsorbed (DT) or the above two in table
- Dirty wounds: contaminated with dirt, feces or saliva
- Severe wound: puncture wound, avulsion, wounds due to crushing, burns or frostbite

ROTAVIRUS

- Live attenuated vaccine
- Vaccine series normally administered at **2-6mo**
- **Contraindications:**

Contraindications to rotavirus vaccine
• Anaphylaxis to vaccine ingredients • History of intussusception • History of uncorrected congenital malformation of the gastrointestinal tract (eg, Meckel's diverticulum) • Severe combined immunodeficiency disease

- Safe to administer with other inactivated vaccines

MENINGOCOCCAL VACCINE

Meningococcal vaccination	
Regular schedule (vaccinate at age 11-18)	• Primary vaccination preferably at age 11-12 • **Booster** at age 16-21 (if primary vaccination at age <16)
High-risk patients (vaccinate even if age >18)	• Complement deficiency, asplenia • College students in residential housing (age ≤21), military recruits • Travel to endemic area, exposure to community outbreaks

Meningococcal vaccine is also recommended for those travelling to highly endemic environments, e.g. sub-Saharan Africa and Muslim pilgrimage to Mecca, Saudi Arabia

VACCINATION IN ASPLENIC PATIENTS

S. pneumonia is the most common cause of infection in post-splenectomy pts. Pts are given PCV 13 followed by PPSV 23 at 8 wks (rest in table)

All pts should receive vaccine either **>/=14 days before** planned splenectomy or **> 14 days after** splenectomy. Although antibody titers are comparable if given within 14 days and after 14 days, but functional activity is lower in pts who are given in less than 14 days post-splenectomy.

Recommended vaccines for asplenic adult patients	
Pneumococcus	• Sequential PCV13 **and** PPSV23 • Revaccination with PPSV23 5 years later and at age 65
H influenzae	• 1 dose Hib vaccine
Meningococcus	• Meningococcal quadrivalent vaccine • Revaccinate every 5 years
Influenza	• **Inactivated** influenza vaccine annually
Other vaccines	• HAV • HBV • Tdap once as substitute for Td, then Td every 10 years

HAV = hepatitis A vaccine; **HBV** = hepatitis B vaccine; **Hib** = *Haemophilus influenzae* type B; **PCV13** = 13-valent pneumococcal conjugate vaccine; **PPSV23** = 23-valent pneumococcal polysaccharide vaccine; **Td** = tetanus-diphtheria toxoid booster; **Tdap** = tetanus-diphtheria-acellular pertussis.

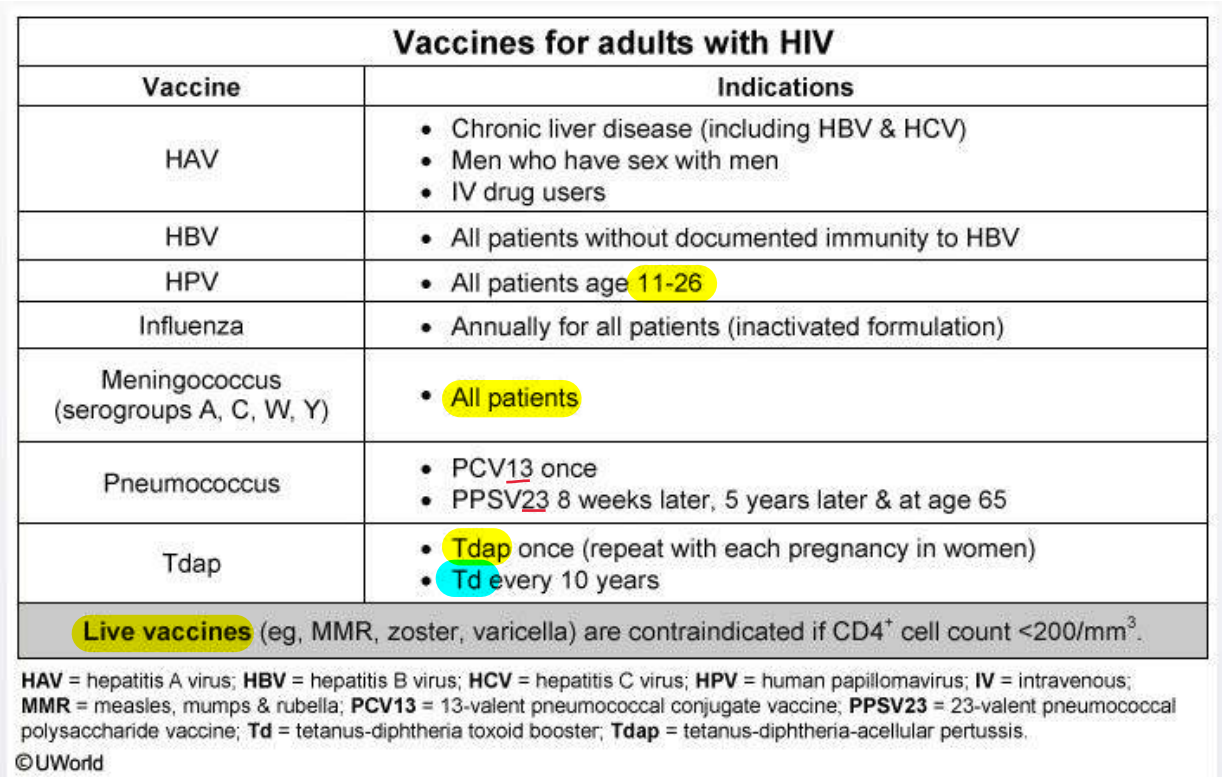
The spleen plays an important role in immune surveillance. Splenic dendritic cells identify antigens in the blood and present them to helper T cells, which activate B-cells and allow them to differentiate into antibody-secreting plasma cells. The antibodies allow phagocytes to recognize and engulf encapsulated organisms

VACCINES IN CLD PATIENTS

Recommended vaccines for chronic liver disease	
Tdap/Td	Tdap once as substitute for Td booster, then Td every 10 years
Influenza	Annually
Pneumococcal vaccines	PPSV23 once, then revaccination with sequential PCV13 & PPSV23 at age 65
Hepatitis A	2 doses 6 months apart with initial negative serologies
Hepatitis B	3 doses at 0 months, 1 month & at least 4 months with initial negative serologies

PCV13 = 13-valent pneumococcal conjugate vaccine; **PPSV23** = 23-valent pneumococcal polysaccharide vaccine; **Td** = tetanus-diphtheria toxoid booster; **Tdap** = tetanus-diphtheria-acellular pertussis.

VACCINES RECOMMENDED FOR ADULTS WITH HIV



Vaccines for adults with HIV	
Vaccine	**Indications**
HAV	• Chronic liver disease (including HBV & HCV) • Men who have sex with men • IV drug users
HBV	• All patients without documented immunity to HBV
HPV	• All patients age 11-26
Influenza	• Annually for all patients (inactivated formulation)
Meningococcus (serogroups A, C, W, Y)	• All patients
Pneumococcus	• PCV13 once • PPSV23 8 weeks later, 5 years later & at age 65
Tdap	• Tdap once (repeat with each pregnancy in women) • Td every 10 years
Live vaccines (eg, MMR, zoster, varicella) are contraindicated if $CD4^+$ cell count <200/mm^3.	

HAV = hepatitis A virus; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HPV** = human papillomavirus; **IV** = intravenous; **MMR** = measles, mumps & rubella; **PCV13** = 13-valent pneumococcal conjugate vaccine; **PPSV23** = 23-valent pneumococcal polysaccharide vaccine; **Td** = tetanus-diphtheria toxoid booster; **Tdap** = tetanus-diphtheria-acellular pertussis.

Most live vaccines like BCG, anthrax, oral polio, oral typhoid, yellow fever are contraindicated in HIV. The only exceptions of live vaccines that can be given, are MMR, varicella zoster and live attenuated influenza in the absence of evidence of immunity (birth before 1957documented evidence of prior vaccination or positive laboratory titers), and if CD4 count is >200 and there is no history of AIDS defining illness like PCP, MAC, CMV esophagitis and KS.

Pts who acquire HIV perinatally and receive MMR before initiation of antiretroviral therapy, should receive repeat MMR vaccination after the initiation of ART. However, if a person is not taking ART and has CD4>200, then MMR is not CI.

OCCUPATIONAL POST-EXPOSURE PROPHYLAXIS IN HIV PATIENTS

Occupational HIV post-exposure prophylaxis	
High-risk contact (prophylaxis recommended)	**Exposure of** • Mucous membrane, non-intact skin, or percutaneous exposure **Exposure to** • **Blood**, semen, vaginal secretions, or any body fluid with visible blood (uncertain risk: cerebrospinal fluid, pleural/pericardial fluid, synovial fluid, peritoneal fluid, amniotic fluid)
Low-risk contact (prophylaxis not recommended)	**Exposure to** • Urine, feces, nasal secretions, saliva, sweat, tears (with no visible blood)
Timing	• Initiate **urgently**, preferably in the first few hours • Continue for **28 days**
Regimen	**3 (or more)-drug regimen** recommended: • **Two** nucleotide/nucleoside reverse transcriptase inhibitors (eg, **tenofovir**, **emtricitabine**) **Plus** • Integrase strand transfer inhibitor (eg, **raltegravir**), protease inhibitor, **or** non-nucleoside reverse transcriptase inhibitor

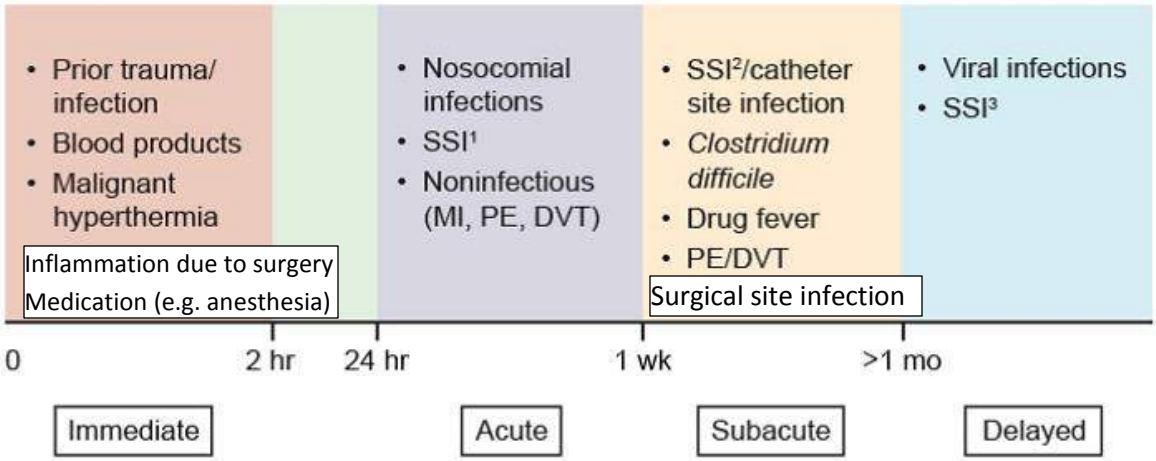
- Risk of seroconversion is low following needlestick exposure (<5%) and is seen primarily with hollow-bore (e.g. phlebotomy) as opposed to solid (e.g. suture) needle exposure.
- If HIV status of source pt is unknown but has risk factors for HIV, then prophylactic therapy should be started while awaiting results of HIV testing.
- Exposed health care worker should be immediately tested for HIV to establish baseline serologic status; testing should be repeated at 6 wks, 3mo and 6mo. In addition to baseline serologic testing, PEP should be started immediately, preferably with few hours of exposure. If possible, worker should be relieved of duties immediately to initiate PEP.
- Tenofovir-emtricitabine and raltegravir is the preferred therapy because of less SE and low drug-drug interaction.

ACUTE BACTERIAL PAROTITIS POST-OPERATIVELY

- Dehydrated post-operative patients and the elderly are most prone to develop this infection.
- **C/F:** Fever, leukocytosis, and parotid inflammation, painful swelling of the involved parotid gland that is aggravated by chewing.
- **PE:** tender, swollen and erythematous gland; with purulent saliva expressed from the parotid duct.
- **Most common cause:** Staphylococcus aureus.
- **Prevention:** Adequate fluid hydration and oral hygiene, both pre and post-operatively

POST-OPERATIVE FEVER

Timeline of cause of postoperative fever



SSI¹ = Due to group A *Streptococcus* (GAS) or *Clostridium perfringens*
SSI² = Due to other organisms (not GAS or *C perfringens*)
SSI³ = Due to indolent organisms

DVT = deep venous thrombosis; **MI** = myocardial infarction; **PE** = pulmonary embolism; **SSI** = surgical site infection.

Causes of postoperative fever (the 5 Ws)	
Wind (lungs)	• Pulmonary embolus • Pneumonia • Aspiration
Wound	Surgical site infection
Water	Urinary tract infection
Walk	Deep venous thrombosis
Wonder drugs/ products	• Drug fever • Blood products • Intravenous lines

- Drug fever is a diagnosis of exclusion that typically occurs 1-2 weeks after medication administration. It is often accompanied by rash and peripheral eosinophilia. Often associated with use of anticonvulsants, antibiotics (beta-lactams, sulfonamides), or allopurinol.
- Coagulase-negative Staphylococci (e.g. S. epidermidis)—part of normal flora but common cause of bloodstream infection in pts **with intravascular catheters**. Factors that favor infection over contamination include:
    - Systemic signs, such as fever, hypotension, or leukocytosis

    - Erythema and tenderness at the catheter entry site (the absence local signs does not rule out an infection)
    - Culture growth within 48 hours and in both aerobic and anaerobic bottles
    - Two or more blood culture samples with the same organism and drug susceptibility
- **Indwelling urinary catheters** increase the risk for urinary tract infection with enteric organisms such as Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis

POINTERS

- Azithromycin is safe for use in pregnancy—erythromycin estolate is CI as it can cause acute cholestatic hepatitis
- Severe coughing paroxysms→ ↑ intra-alveolar pressure→ air leaks from chest wall into subQ tissue→ subcutaneous emphysema. By similar procedure pneumothorax can occur, hence pts with subQ emphysema due to coughing paroxysms, should have chest xray emergently to rule out pneumothorax

Things commonly addressed in the peri-transplant period:

Vaccinations for **pneumococci** and **hepatitis B** are typically given prior to transplant to ensure an adequate immune response), and an inactivated, intramuscular) **Influenza** vaccine is usually given yearly

. PCP prophylaxis with TMZ-SMX

Many patients also require CMV prophylaxis with ganciclovir or valganciclovir if the donor or recipient are seropositive

- Patients with Neisseria gonorrhoeae are at high risk of simultaneous coinfection with several other sexually transmitted pathogens, including **Chlamydia trachomatis**, **HIV** . **syphilis,** and **hepatitis B virus**
Patients should be screened for these infections in addition to receiving appropriate antibiotics .(usually ceftriaxone plus azithromycin) and counseling on safe sexual practices

Contents

ALLERGY AND IMMUNOLOGY-IM

MECHANISM OF INFECTION IN POST-SPLENECTOMY PATIENTS

NORMAL RESPONSE TO BLOOD BORNE ANTIGENS

Blood borne antigen→ splenic artery→ enters spleen→ white pulp→ phagocytosed by dendritic cells→ dendritic cell present antigen via MHC-II to Th cells→ Th cells activated→ migrate to marginal zone→ come in contact with B-cells in primary follicles→ B-cell activation→ secondary follicles and plasma cell rich germinal centers forms→ produce antibodies→Abs enter systemic circulation→bind antigen→phagocytosis of pathogenic organism by opsonization

ASPLENIC PATIENTS

- Unable to mount this response as mentioned above
- High risk of overwhelming infection by encapsulated organisms like H. influenzae, S. pneumonia and N meningitidis

ANGIODEMA

HEREDITARY ANGIODEMA

- Characterized by the following:

1. Rapid onset of
   - Non-inflammatory edema of the face, limbs, and genitalia
   - Laryngeal edema - can be life-threatening
   - Edema of the intestines resulting in colicky abdominal pain
2. No evidence of urticarial

- Angioedema can be hereditary or acquired.
- **Pathology** in both forms can involve **C1 inhibitor deficiency, dysfunction, or destruction**.
- A defect or deficiency of C1 inhibitor→ ↑ levels of the edema-producing factors **C2b and bradykinin**
- Hereditary angioedema typically presents in late childhood.
- Episodes usually follow an infection, dental procedure, or trauma.
- **C1q levels** are normal in hereditary angioedema and depressed in acquired forms, which usually present much later in life.
- **C4 levels** are depressed in all forms of angioedema.

ACQUIRED ANGIOEDEMA

- **Most common cause:** ACE inhibitors (aka kininase)
- **Mechanism:** ACE → breakdown of bradykinin. ACE inhibited by ACE inhibitor→ accumulation of bradykinin. Bradykinin is responsible for edema, inflammation and sensation of pain
- **C/F**: Patient presents with edema of face, mouth, tongue, lips, glottis and larynx. Laryngeal edema can cause airway obstruction and can be life threatening
- **Time of presentation:** typically within days to weeks of starting ACE inhibitors but can present at ANYTIME, not just within weeks of starting.
- **Management:**
  1. Check for airway compromise and vasomotor instability, which require subcutaneous epinephrine administration if present

2. If airway obstruction fails to respond to epinephrine, then emergency tracheostomy needs to be done
3. Stop ACE inhibitor immediately.

- **Other adverse effects of ACE inhibitors:**
  1. Cough
  2. Hyperkalemia
  3. Precipitation of acute renal failure in pt with B/L renal artery stenosis

PRIMARY HUMORAL DEFICIENCIES

Primary humoral deficiencies		
Diagnosis	**Clinical features**	**Laboratory findings**
X-linked agammaglobulinemia	Recurrent &/or severe sinopulmonary infections with viruses and encapsulated bacteria	↓ or absent B-cells ↓Immunoglobulins
Common variable immunodeficiency		Normal B cells ↓Immunoglobulins
IgA deficiency		Normal B cells ↓IgA
Hyper-IgM syndrome		Normal B cells ↓IgG & IgA ↑IgM
IgG subclass deficiency		Normal B cells ↓IgG

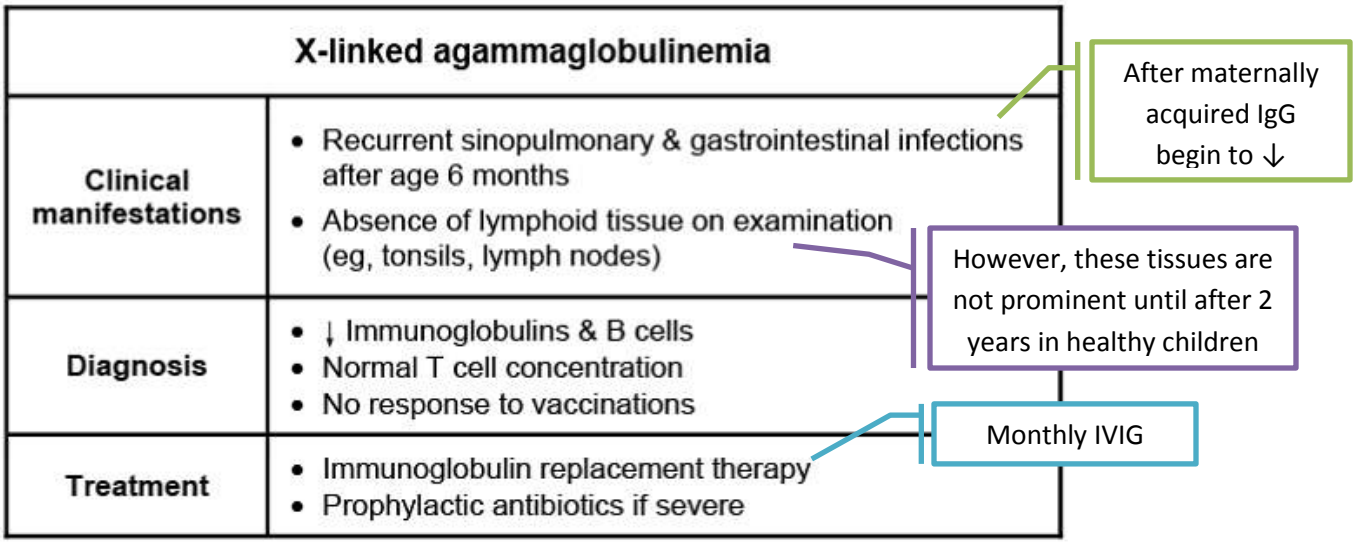
Humoral immunodeficiency syndromes					
Condition	**B cell count**	**IgG**	**IgA**	**IgM**	**IgE**
CD40 ligand deficiency (hyper-IgM syndrome)	Normal	↓	↓	↑	↓
Common variable immunodeficiency	Normal	↓	↓	↓	↓
Job syndrome (hyper-IgE syndrome)	Normal	Normal	Normal	Normal	↑
Selective IgA deficiency	Normal	Normal	↓	Normal	Normal
X-linked agammaglobulinemia	↓	↓	↓	↓	↓

- Mild resp. infections are common in childhood and can occur up to 10 times a year
- However severe and recurrent sinopulmonary infections (intubation, early tympanostomy tube placement, poor growth)→ raise concern for humoral deficiency
- **Important labs needed:** CBC with differential, lymphocyte T and B cell subsets, and serum immunoglobulins (Ig) G, A, and M are important screening tests. HIV infection should also be excluded.

HYPER-IgM SYNDROME

- X-linked genetic defect in CD40 ligand (normally binds CD40 on B cells and induce class switching and plasma cell formation)→ absent class switching, ↑ IgM and ↓ all Igs
- Absence of plasma cells→ poor response to infection and immunization
- Recurrent sinopulmonary infections with **encapsulated bacteria**, ↑ **viral** infections, ↑ risk of **opportunistic infections** e.g. PCP
- Growth impairment→ due to ↑ energy expenditure and poor oral intake during illness
- **Rx:** antibiotic prophylaxis and interval administration of IV immunoglobulin

X-LINKED AGAMMAGLOBULINEMIA or BRUTON AGAMMAGLOBULINEMIA



- Defect in tyrosine kinase that prevent the development of mature B cells from pre B cells in bone marrow (B lymphocytes= total lymphocytes- T lymphocytes)
- Predisposed to recurrent infections with encapsulated organisms like H. influenza, S. pneumoniae due to impaired humoral immunity
- Absence of IgA→GI infections like Giardia
- Live vaccine CI, others not CI but incapable of generating meaningful response

SELECTIVE IgA DEFICIENCY

Selective IgA deficiency	
Epidemiology	• Most common primary immune deficiency
Clinical features	• Usually asymptomatic • Recurrent sinopulmonary & gastrointestinal infections • Associated with autoimmune disease (eg, celiac) & atopy (eg, asthma, eczema) • Anaphylaxis during transfusions
Diagnosis	• Low or absent IgA • Normal IgG, IgM levels, B cells
Treatment	• Supportive care • Medical alert bracelet for transfusion reactions (for severe deficiency)

- Pts with selective IgA deficiency can develop IgE antibodies against IgA present in transfused blood and blood products like RBC, fresh frozen plasma, platelets etc.
- They can develop fatal anaphylactic shock if given blood with small amount of IgA
- These pts should receive blood from products that are washed of residual plasma or from an IgA deficient donor

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

- Characterized by decreased lgG, variable lgM, and normal lgA and B cell concentrations.
- Affected patients present with increased sinopulmonary and gastrointestinal infections that are usually mild rather than life-threatening.
- Immunoglobulin levels generally normalize by age 9-15 months

SEVERE COMBINED IMMUNODEFICIENCY

Severe combined immunodeficiency	
Etiology	• Gene defect leading to failure of T cell development • B cell dysfunction due to absent T cells
Inheritance	• X-linked recessive • Autosomal recessive
Clinical features	• Recurrent, severe viral, fungal, or opportunistic (ie, *Pneumocystis*) infections • Failure to thrive • Chronic diarrhea
Treatment	• Stem cell transplant

- Recurrent sinopulmonary infections due to B cell dysfunction
- **Laboratory findings:** lymphopenia and hypogammaglobulinemia
- Fatal in early childhood unless transplant is performed.
- SCID is included in **routine newborn screening** in the United States and is detected by the **absence of T cell receptor excision circles** (circular DNA excreted by developing T cells in the thymus) in dried blood
- Broad spectrum antibiotic and IVIG are short term treatment options for SCID while awaiting transplantation
- Live vaccines CI. Others are not CI but do not generate sufficient Ab response

WISKOT ALDRICH SYNDROME

- X-linked recessive disease
- Characterized by eczema, thrombocytopenia leading to bleeding in early infancy. T cell dysfunction and Hypogammaglobulinemia worsen with age and leads to recurrent infections.

LEUKOCYTE ADHESION DEFICIENCY

Features of leukocyte adhesion deficiency

• Recurrent skin & mucosal bacterial infections (eg, omphalitis, periodontitis)
  ○ No pus (lack of neutrophils at inflammation site)
  ○ Poor wound healing
• Delayed umbilical cord separation (>21 days)
• Marked peripheral leukocytosis with neutrophilia

Esp. during the time of infection

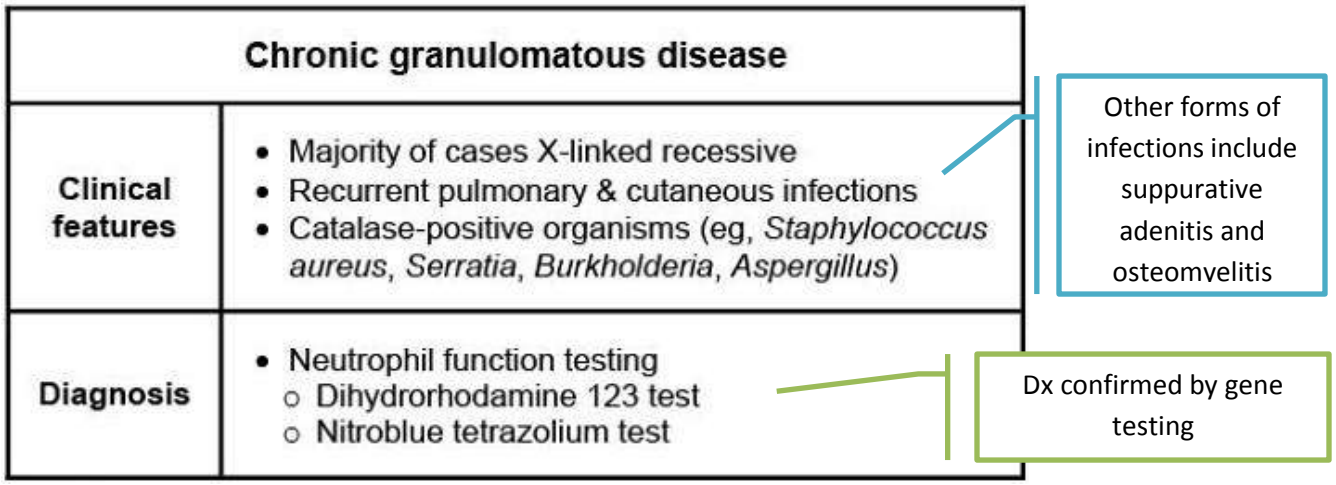
- Caused by defective integrins on leukocyte surface, which allow neutrophils to adhere to vascular endothelium, exit the vasculature and migrate to the areas of infection or inflammation

- Biopsy of infected tissue is devoid of neutrophils and culture often grows Staphylococcus aureus, S. pyogenes or Gram-negative bacilli.

CHEDIAK-HIGASHI SYNDROME

- Autosomal recessive disorder
- Characterized by partial oculocutaneous albinism and recurrent cutaneous infections.
- Staphylococcus aureus and Streptococcus pyogenes are common.

CHRONIC GRANULOMATOUS DISEASE



- Caused by a gene defect in the NADPH oxidase enzyme complex, leading to an inability to form hydrogen peroxide and impaired intracellular killing in phagocytes
- Leukocyte, platelet, B and T cell concentrations are normal
- Phagocytic cells filled with organism are common finding on gram stain
- **Management:**
  - Pt should receive antimicrobial prophylaxis with TMP-SMX and itraconazole—lifelong
  - Pts with severe phenotype may benefit from IFN-ɣ injections

PHARMACOLOGY

SIDE EFFECTS OF CYCLOSPORINE

Cyclosporine is a commonly used immunosuppressant. It acts by *inhibiting the transcription of interleukin-2* and several other cytokines, mainly the T-helper lymphocytes.
Some of the most common side effects of cyclosporine are:

1. **Nephrotoxicity**: This is the most common and serious side effect. It may manifest as reversible acute azotemia or irreversible progressive renal disease. Hyperuricemia with accelerated gout, hyperkalemia, hypophosphatemia, and hypomagnesemia can be seen as manifestations of renal-induced dysfunction. Rarely, hemolytic uremic syndrome (HUS) may be seen.
2. **Hypertension:** This is due to renal vasoconstriction and sodium retention. It is generally seen in the first few weeks of therapy. Calcium channel blockers are the drugs of choice for treatment.
3. **Neurotoxicity:** This is often reversible. It manifests as headache, visual disturbances, seizure, mild tremors, akinetic mutism, etc.
4. **Glucose intolerance**: This is fairly common. Patients who are concurrently taking prednisone (steroids) might develop significant hyperglycemia.
5. **Infection**: Chronic therapy with cyclosporine is associated with infection in 40% of patients.

6. **Malignancy**: There is an increased risk of squamous cell carcinoma of the skin and lymphoproliferative diseases.
7. **Gingival hypertrophy** and **hirsutism**.
8. **GI manifestations**, such as anorexia, nausea, vomiting, and diarrhea. These are fairly common but mild.

TACROLIMUS

Tacrolimus is a macrolide antibiotic produced by fungi. It has the same mechanism of action as cyclosporine and has a similar toxicity profile (including nephrotoxicity and hyperkalemia); however, in contrast to cyclosporine, tacrolimus does not cause hirsutism or gum hypertrophy, and has a higher incidence of neurotoxicity, diarrhea, and glucose intolerance.

AZATHIOPRINE

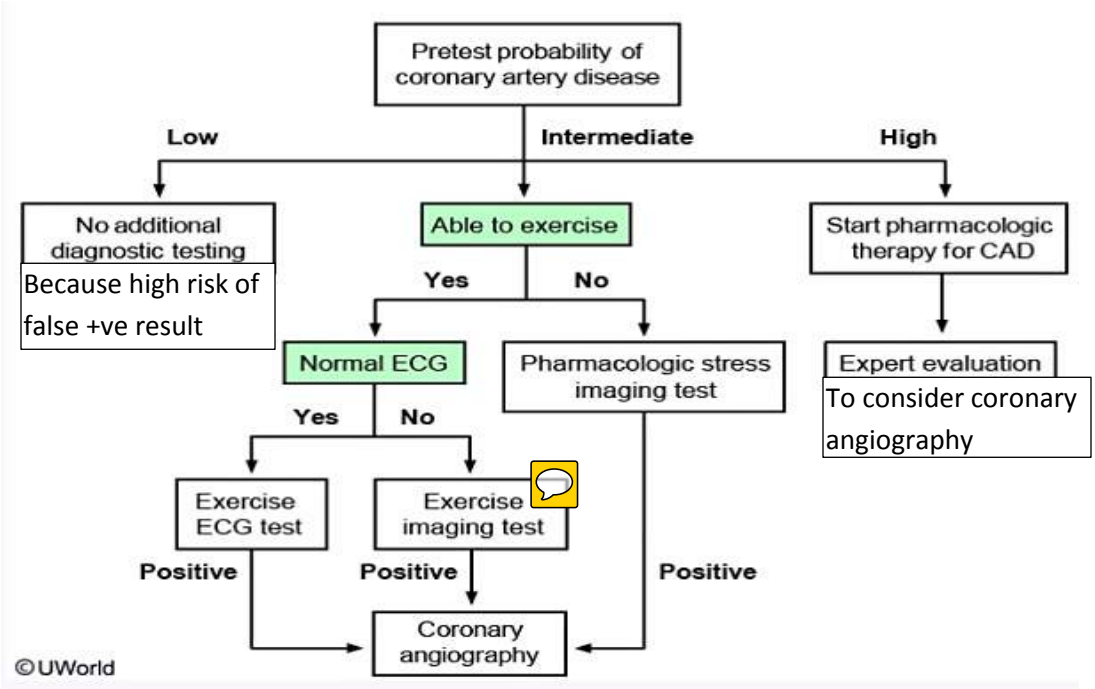
Azathioprine is a purine analog that is enzymatically converted to 6-mercaptopurine. It acts primarily by inhibiting purine synthesis. The major toxicity of azathioprine is dose-related diarrhea, leukopenia, and hepatotoxicity.

MYCOPHENOLATE

Mycophenolate is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is the rate-limiting enzyme in de novo purine synthesis. The major toxicity of mycophenolate is bone marrow suppression.

Contents

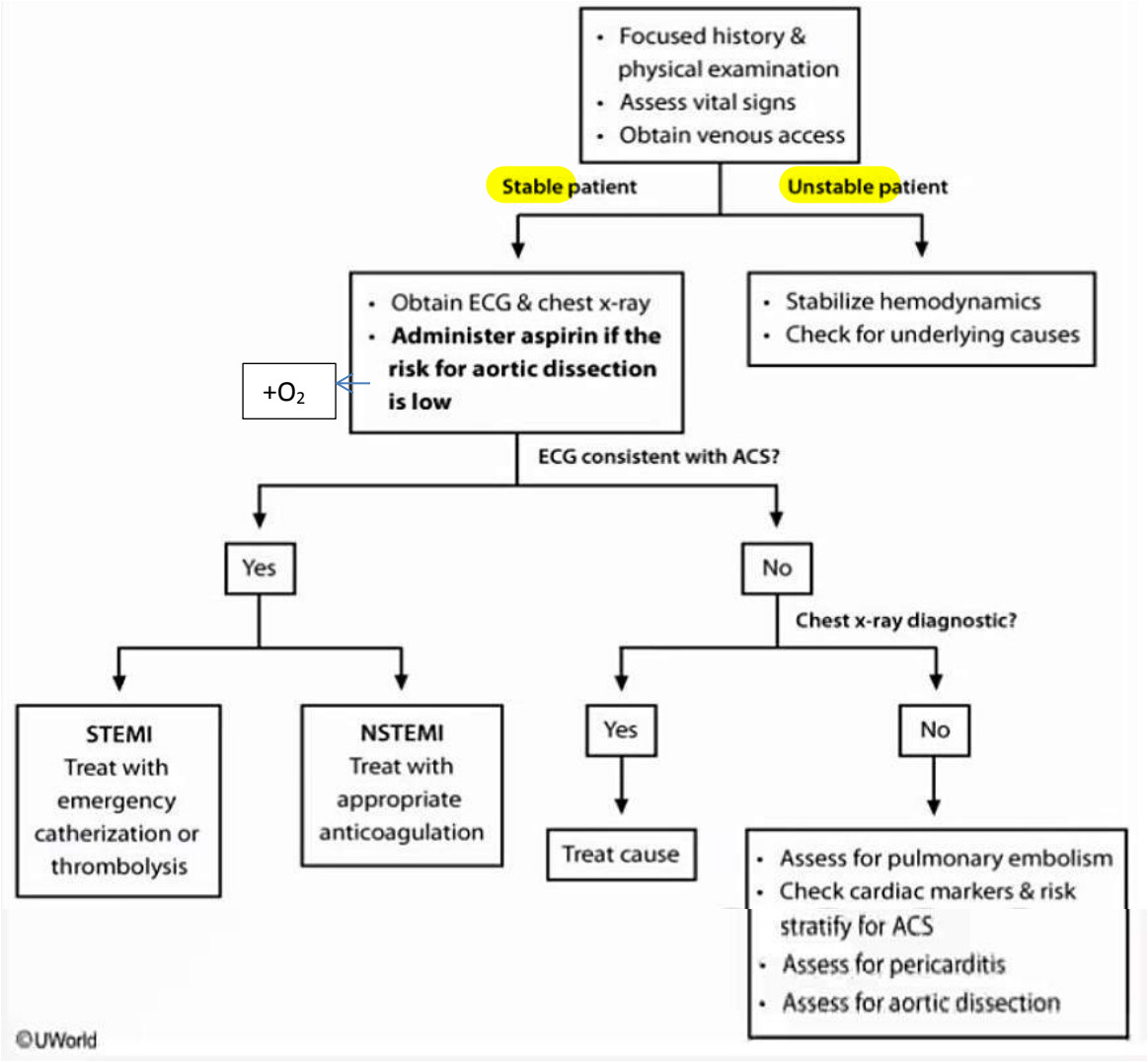
EVALUATION OF CHEST PAIN



Pretest probability of coronary artery disease	
Low (<10%)	• Asymptomatic people of all ages • Atypical chest pain in women age <50
Intermediate (20%-80%)	• Atypical angina in men of all ages • Atypical angina in women age ≥50 • Typical angina in women age 30-50
High (>90%)	• Typical angina in men age ≥40 • Typical angina in women age ≥60

Classification of angina	
Classic angina characteristics	• Typical quality (eg, pressure or crushing) & duration (usually >20 minutes) • Provoked by exercise/emotional upheaval • Relieved with nitroglycerin or rest
Atypical angina	• Chest pain with 2 of the classic angina characteristics
Non-anginal chest pain	• Chest pain with 0-1 of the classic angina characteristics

EVALUATION OF CHEST PAIN IN EMERGENCY DEPARTMENT



- **Aspirin** is given before heparin in ACS. Aspirin significantly reduce the rate of MI, stroke and overall mortality in ACS

ATYPICAL SYMPTOMS IN ACUTE CORONARY SYNDROME

Relative frequency of selected presenting symptoms in acute coronary syndrome	
Chest pain	80%-85%
Dyspnea	70%-75%
Nausea	40%-55%
Vomiting	15%-20%
Epigastric pain	10%-15%

- **Women, elderly and pts with diabetes** are more likely to develop atypical symptoms; up to 20% do not report chest pain at the time of presentation→delay diagnosis and under-treatment

MEDICATION TO WITHOLD PRIOR TO CARDIAC STRESS TESTING

Medications to withhold prior to cardiac stress testing	
Hold for 48 hours	Beta blockers, calcium channel blockers, nitrates
Hold for 48 hours prior to vasodilator stress test	Dipyridamole
Hold for 12 hours prior to vasodilator stress test	Caffeine-containing food or drinks
Continue	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, digoxin, statins, diuretics

- These medicines should be continued with those with known CAD to assess efficacy of antianginal therapy
- Decision to withhold meds should also be carefully tailored to the individuals to minimize the risk of rebound HTN or arrhythmias

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

Differential diagnosis & features of chest pain	
Coronary artery disease	• Substernal • Radiation to arm, shoulder, or jaw • Precipitated by **exertion** • Relieved by **rest or nitroglycerin**
Pulmonary/pleuritic (pleurisy, pneumonia, pericarditis, PE)	• Sharp/stabbing pain • Worse with inspiration • **Pericarditis:** Worse when lying flat • **PE**, **pneumothorax:** Respiratory distress, hypoxia
Aortic (dissection, intramural hematoma)	• **Sudden**, **severe** "tearing" pain • Radiates to **back** • Elderly men • Hypertension & risk factors for atherosclerosis
Gastrointestinal/ esophageal	• Nonexertional, relieved by antacids • Upper abdominal & substernal • Associated with regurgitation, nausea, dysphagia • **Nocturnal pain**
Chest wall/ musculoskeletal	• Persistent &/or prolonged pain • Worse with movement or change in position • Often follows **repetitive activity**

- **Features suggesting esophageal disease:** prolonged pain lasting >1 hour, postprandial symptoms, associated heart burn, dysphagia and relief of pain by antireflux therapy

TREATMENT FOR STABLE CHRONIC ANGINA

Treatment for stable chronic angina	
Antianginal	**Beta blocker** • **1st-line therapy** for anginal symptoms, improves exercise tolerance • Relieves angina by decreasing myocardial contractility & heart rate • Improves survival in those with myocardial infarction **Calcium channel blocker** • Can combine with beta blocker if angina persists or as alternate therapy • Improves angina by causing peripheral & coronary vasodilation **Nitrates** • Short-acting form is used in the **acute** setting • Long-acting form is an add-on therapy for persistent angina
Preventive	• Aspirin • Statin • Smoking cessation • Regular exercise & weight loss • Control of blood pressure & diabetes

- NGT is venodilator > arteriodilator

- Their primary anti-ischemic effect is mediated by systemic **vasodilation** and ↓ **in preload.** This, in turn, leads to a **reduction** in left ventricular end-diastolic volume and systolic **wall stress**, resulting in decreased myocardial oxygen demand.

- Although nitrates act as coronary vasodilators (via direct relaxation of coronary vascular smooth muscle cells), the beneficial effect of this mechanism is uncertain

VARIANT/PRINZMETAL ANGINA

- Common in young women, greatest risk factor is smoking. Atherosclerotic risk factors usually absent
- Episodes common at night (12am to 8am), after exercise, hyperventilation, emotional stress, cold exposure or cocaine use
- Transient ST elevation and then return to baseline (unlike ST depression in unstable angina and longer duration of ST elevation in MI)
- Rx: CCB or nitrates

- Prinzmetal's angina is caused by temporary spasm of the coronary arteries, as opposed to atherosclerotic narrowing which is seen in myocardial infarction.

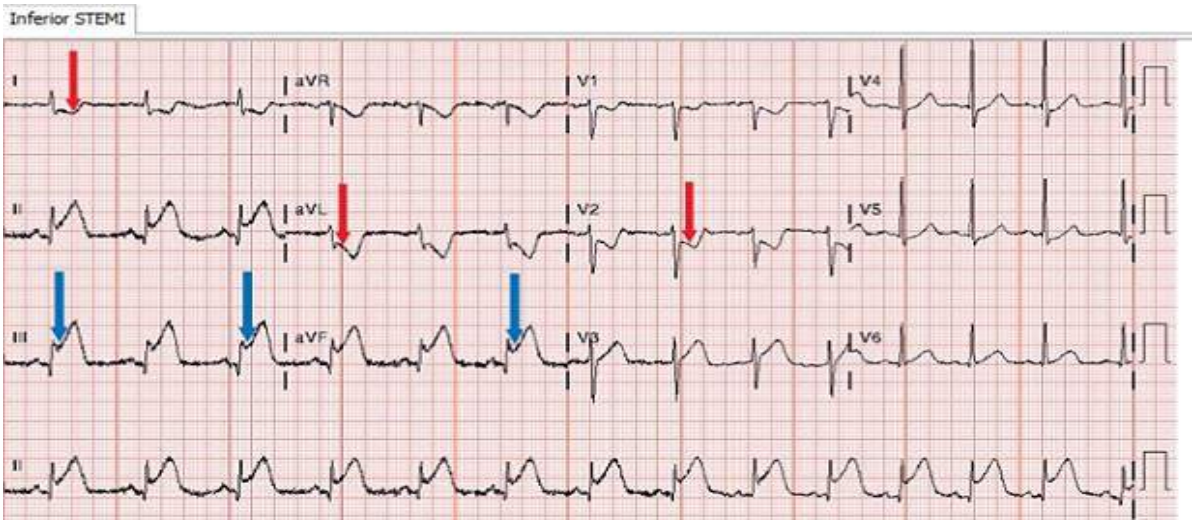
- Variant angina is associated with other vasospastic disorders, such as **Raynaud's** phenomenon and **migraine** headaches.

MYOCARDIAL INFARCTION

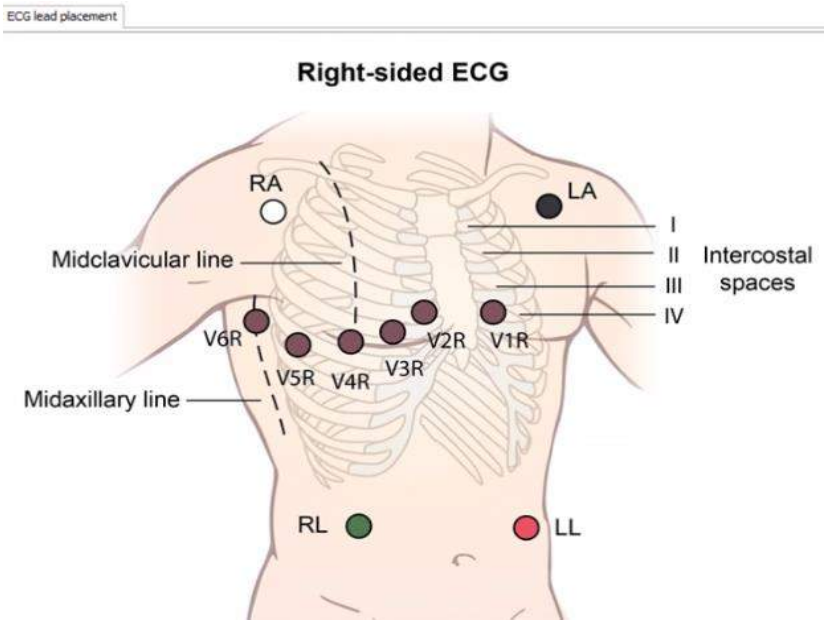
Myocardial infarction location based on coronary vessel involvement		
Involved myocardium	**Blocked vessel**	**ECG leads involved**
Anterior MI	LAD	• Some or all of leads V1-V6
Inferior MI	RCA or LCX	• ST elevation in leads II, III & aVF
Posterior MI	LCX or RCA	• ST depression in leads V1-V3 • ST elevation in leads I & aVL (LCX) • ST depression in leads I & aVL (RCA)
Lateral MI	LCX, diagonal	• ST elevation in leads I, aVL, V5 & V6 • ST depression in leads II, III & aVF
Right ventricle MI (occurs in ½ of inferior MI)	RCA	• ST elevation in leads V4-V6R

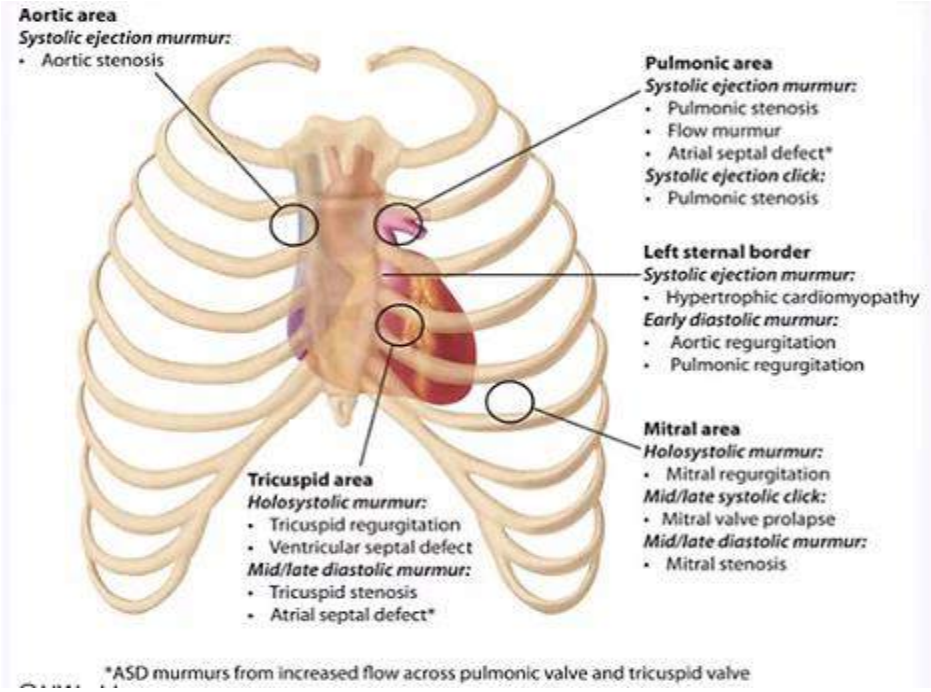
Right ventricular MI:

- Seen in 30-50% pts with acute inferior wall MI due to occlusion of RCA proximal to origin of RV branches
- **ST segment elevation in inferior leads II, III and avF**. Transient bradycardia or AV block can also occur with acute inferior wall MI due to enhanced vagal tone**.** JVD, Kussmaul sign, and clear lungs are signs of RHF.
  - ➔ **Massive pulmonary embolism** can present similar to RV infarction however, ECG will show tachycardia, non-specific ST segment or T wave changes (rather than ST segment elevation), new onset RBBB or S1Q3T3 pattern



- **Dx of RVMI is confirmed with**: >/= 1mm ST segment elevation in right **precordial leads V4R-V6R**. RV failure leads to dec. preload and resultant **hypotension** (worsen with nitroglycerin, diuretics and opioids that dec. preload-avoid). Drugs that slow HR like beta blockers and that dec. contractility like CCB should be used with caution

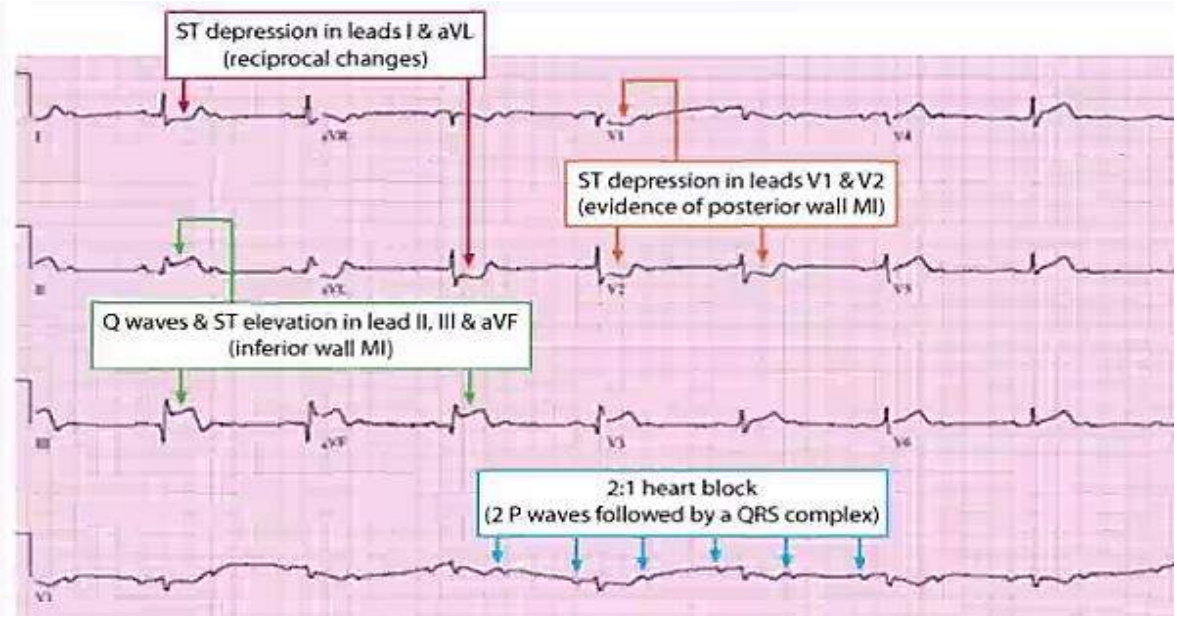




- **In addition to standard MI therapy,** such pts (without pulmonary congestion, low/normal JVP) are typically treated with high flow IV fluids (isotonic saline) to improve RV preload and facilitate left ventricular filling. IV fluids are less likely to help in these pts if JVP is elevated

Inferior and posterior wall MI (RCA in ECG):

- RCA also supplies AV node and hence, occlusion can cause AV block. Inferior wall MI is most commonly associated with sinus bradycardia due to increased vagal tone in first 24 hours after infarction and dec. RCA blood flow to SA node. Also lead RV infarction/dysfunction→hypotension



Acute inferior wall MI→papillary muscle dysfunction (rupture can occur in 2-7 days post MI)→ acute MR→excessive diastolic volume overload → **elevated left ventricular end diastolic pressure (LVEDP, LV filling pressure)**→reflected back to left atrium → pulmonary circulation→S/S of congestive heart failure. Unlike chronic MR, acute MR does not cause any significant change if left atrial or ventricular size and/or compliance

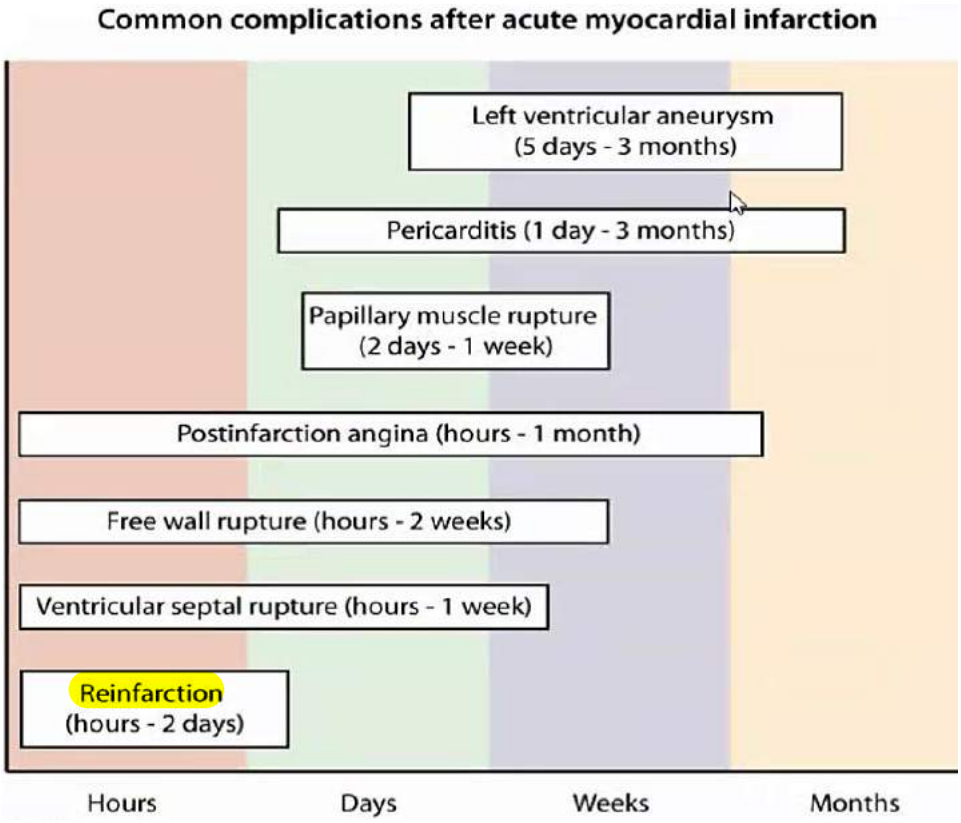
- **ST elevation in lead I, aVL and V2-V6 and reciprocal depression in II, III and aVF**→ acute anterolateral MI due to occlusion of LAD
- **LAD** supply anterior walls of left ventricle and ant. 2/3rd of septum and hence, occlusion can cause 2nd degree AV block

POST-MI COMPLICATIONS

Mechanical complication of acute MI	Time course	Coronary artery typically involved	Clinical findings	Echocardiography
Right ventricular failure	Acute	RCA	• Hypotension and clear lungs • Kussmaul sign	• Hypokinetic RV
Papillary muscle rupture	Acute and within 3-5 days	RCA	• Acute, severe pulmonary edema • New holosystolic murmur	• Severe mitral regurgitation with flail leaflet
Interventricular septum rupture/defect	Acute and within 3-5 days	• LAD → apical septal rupture • RCA → basal septal rupture	• Shock and chest pain • New holosystolic murmur • Biventricular failure	• Left-to-right shunt at level of ventricle • Step-up oxygen level between right atrium and ventricle
Free wall rupture	Within first 5 days-2 weeks	LAD	• Shock and chest pain • Jugular venous distention	• Pericardial effusion with tamponade

→ Murmur heard at left lower border usually

Distant heart sounds



Ventricular arrhythmias:

- Ventricular arrhythmias , including ventricular premature beats, non-sustained or sustained ventricular tachy, and ventricular fibrillation—quite common in immediate post MI period
- **Ventricular fibrillation** – most common cause of sudden cardiac arrest in setting of acute MI; moore than 50% occur within **first hour** of symptom onset
- Reentry is the predominant mechanism responsible— though underlying mechanism depends on time elapsed since onset of MI
- Arrhythmia occurring within 10 min of coronary occlusion—**immediate or phase 1a ventricular arrhythmia**— MOA: reentrant arrhythmia
- Arrhythmia occurring within 10-60 min after acute infarction—**delayed or phase 1b arrhythmia**— MOA: abnormal automaticity

Ventricular free wall rupture:

- Majority of ventricular free wall rupture occur after anterior wall MI
- Abrupt LV rupture leads to hemopericardium and eventually cardiac tamponade→ compresses left ventricle and decrease stroke volume→compensatory sinus tachycardia
- Severe mechanical compromise can rapidly progress to pulseless electrical activity (PEA) with ECG showing low voltage electrical activity
- LV free wall rupture should be suspected in cases of recent MI and no signs of heart failure
- Rapid diagnosis with echo, supportive care, pericardiocentesis and possible surgical repair are needed to save pt. life.

Ventricular aneurysm:

- **Hallmark ECG findings:** persistent ST segment elevation after recent MI and deep Q waves in same leads

Usually, ST-segment elevations resolve within a few weeks of an MI, but here it does not.

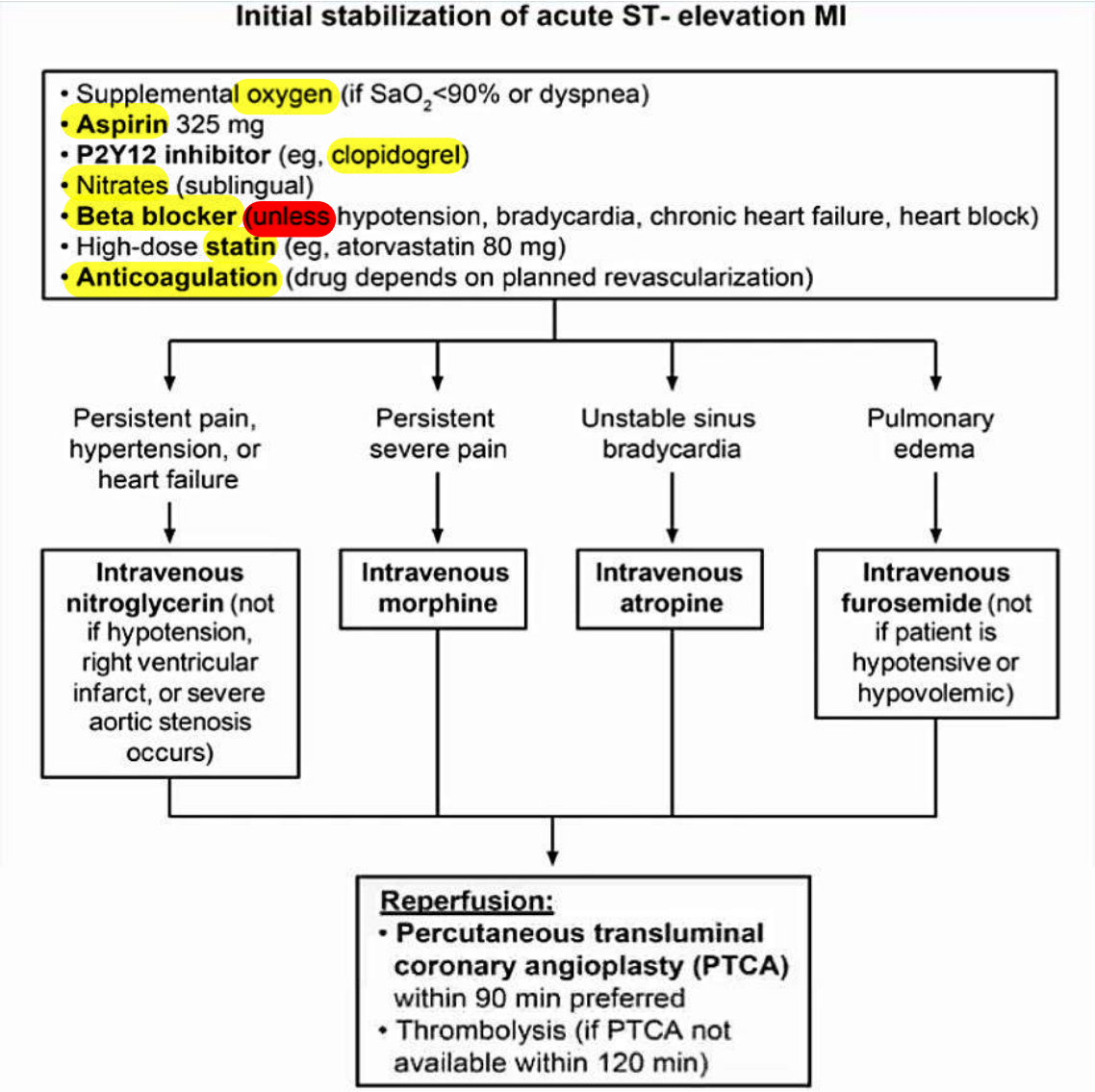
- **Large VA:** can lead to progressive left ventricular enlargement leading to heart failure, refractory angina, ventricular arrhythmia and mural thrombus leading to systemic embolization
- Progressive LV enlargement can lead to MR
- Confirmed with echo—showing dyskinetic wall motion of a portion of left ventricle

Papillary muscle rupture:

- Life-threatening complication due to surrounding tissue necrosis→severe acute MR→hypotension and pulmonary edema

Dressler syndrome: can occur weeks after MI. NSAIDs are the mainstay of therapy and corticosteroids can be used in refractory cases or when NSAIDs are contraindicated. Anticoagulants should be avoided to prevent development of hemorrhagic pericardial effusion

MANAGEMENT OF STEMI



- Beta blockers should not be used in case of pulmonary edema i.e. acute decompensation
- Morphine is anxiolytic +↓pre-load. Should not be routinely used co' of increased mortality
- Ischemic heart failure 2° to MI→acute pulmonary edema **("flash pulmonary edema")**

- **Stent thrombosis** is a potentially fatal complication of coronary artery stenting and long term dual antiplatelet therapy with aspirin and platelet P2Y12 rceptor blockers is recommended to reduce this complication. **Premature discontinuation** of these meds is the strongest predictor of stent thrombosis within 1st 12 months—screening and counseling regarding medicine compliance is needed

Management of ST-segment elevation myocardial infarction (STEMI)

- Oxygen for arterial saturation <90%
- Nitrates
  - Caution with hypotension, right ventricular infarction, or severe aortic stenosis
- Antiplatelet therapy
  - Aspirin + $P2Y_{12}$ receptor blocker
- Anticoagulation
  - Unfractionated heparin, low-molecular weight heparin, or bivalirudin
- Beta blockers
  - Contraindicated in overt heart failure
  - High risk for cardiogenic shock
  - Bradycardia
- Prompt reperfusion with PCI
  - Ideal first medical contact to PCI ≤90 minutes
- Statin therapy as soon as possible

PCI = percutaneous coronary intervention.

- Aspirin in full dose to be chewed for quick action
- **Morphine** can also be given for pain control if nitroglycerin insufficient. Nitroglycerin mainly cause dilation of capacitance vessels (veins)→dec. preload→dec. heart size→dec. O2 demand. Also dilate arteries i.e dec. afterload but this is not significant
- **Prompt coronary reperfusion with PCI or fibrinolytic therapy** restores flow, limit myocardial damage and reduce mortality→most important intervention to improve long term prognosis
- **Current guidelines for PCI for pts with acute STEMI**
  - ➔ Within 12 hours of symptom onset AND
  - ➔ Within 90 minutes from 1st medical contact to device time at PCI-capable facility
  - ➔ Within 120min from 1st medical contact to device time at a non-PCI capable facility (to allow time for transport to a PCI capable facility.
- **PCI** has better survival and less risk of MI and stroke as compared to fibrinolytic therapy which can be done if within 12 hours of symptom onset who cannot undergo PCI (e.g. PCI is nt available within the recommended time frame)
- **If fibrinolytics are being used** then "door to needle" time should ideally be 30 min.

MANAGEMENT OF NSTEMI

- Revascularization with drug eluting stent placement
- Long term therapy for 2* prevention

these are the drugs given after discharge of MI pts

1. **Dual antiplatelet therapy (DAPT)** with aspirin and P2y12 receptor blockers (eg clopidogrel, prasugrel, ticgrelor)→ significant reduction of recurrent MI and cardiovascular death compared to aspirin alone. Long term DAPT reduce stent thrombosis. Recommended for at least 12 months in all pts following drug eluting stent
2. **Beta blockers**
3. **ACEi or ARB**
4. **Statins**
5. **Aldosterone antagonist** if EF </=40% with HF symptoms or DM

- **ACEi** should be started in all pts with MI within 24 hours to prevent remodeling of heart i.e. dilation of left ventricle with thinning of ventricular wall which takes wks to months
  - ➔ **Apixaban (factor Xa inhibitor)** is used for anticoagulation in non valvlular atrial fibrillation and for management of DVT and pulmonary embolism
  - ➔ **Read qid 9648** 💬

CAUSES OF HEART FAILURE WITH PRESERVED LEFT VENTRICULAR FUNCTION

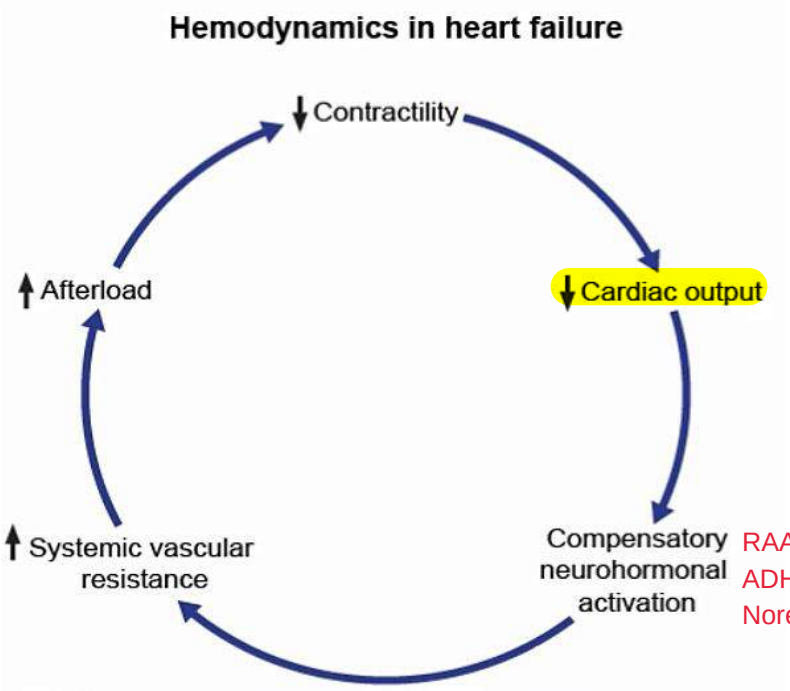
(DIASTOLIC DYSFUNCTION)

- Common cause of decompensated congestive heart failure. CHF signs with normal or near-normal EF (>50%). Exacerbated by **loss of atrial kick**

Causes of heart failure with preserved left ventricular function	
Diastolic heart failure	• Hypertension with left ventricular hypertrophy • Restrictive cardiomyopathy • Infiltrative cardiomyopathy (eg, sarcoidosis) • Hypertrophic cardiomyopathy • Occult coronary artery disease
Valvular heart disease	• Aortic stenosis or regurgitation • Mitral stenosis or regurgitation
Pericardial disease	• Constrictive pericarditis • Cardiac tamponade
Systemic disorders (high-output cardiac conditions)	• Thyrotoxicosis • Severe anemia beriberi, Paget disease, and arteriovenous fistulas

- Associated with S4
- S4 is an indicator of a stiff left ventricle

HEMODYNAMICS IN HEART FAILURE



RAAS
ADH
Norepinephrine

سؤال يوورلد

RAAS EFFECTS:

1. Vasoconstriction of both the afferent and efferent glomerular arterioles→ decrease in renal blood flow

2. Vasoconstriction of efferent renal arterioles→ inc. interglomerular pressure→ maintain GFR.

3. sodium resorption in the proximal tubules and increased secretion of aldosterone (decreased sodium delivery to the distal tubule)

Cardiac index= CO/body surface area

Cardiac index is also reduced in heart failure

ACUTE DECOMPENSATED HEART FAILURE

Clinical features of acute decompensated heart failure	
Clinical presentation	• Acute dyspnea, orthopnea, paroxysmal nocturnal dyspnea • Hypertension common; hypotension suggests severe disease • Accessory muscle use, tachycardia, tachypnea • Diffuse crackles with possible wheezes (cardiac asthma) • Possible S3, jugular venous distention, peripheral edema
Treatment	**Normal or elevated blood pressure with adequate end-organ perfusion** • Supplemental oxygen • Intravenous loop diuretic (eg, furosemide) • Consider intravenous vasodilator (eg, nitroglycerin) **Hypotension or signs of shock** • Supplemental oxygen • Intravenous loop diuretic (eg, furosemide) as appropriate • Intravenous vasopressor (eg, norepinephrine)

- Most common cause: LV systolic or diastolic dysfunction with or without additional cardiac dis. (e.g. acute MI, arrhythmia, acute severe MR or AR)
- Pulm. Edema can also occur in severe HTN, renal artery stenosis or severe renal dis. With fluid overload
- Nitroglycerin is of special benefit in pts with MR or symptomatic myocardial ischemia
- **Cardioselective beta blockers** contraindicated in acute case

❖ **Elevated BNP and S3 gallop** correlate with increased cardiac filling pressures and noted in pts with CHF due to **left ventricular systolic dysfunction.** proBNP produce active BNP and N-terminal proBNP—both of them correlate with severity of left ventricular systolic dysfunction. BNP has very high negative predictive value and if negative test result the look for other causes. Peripheral edema also does not correlate with BNP as much as S3

POOR PROGNOSTIC FACTORS IN SYSTOLIC HEART FAILURE

Poor prognostic factors in systolic heart failure	
Clinical	• Higher NYHA functional class • Resting tachycardia • Presence of S3 gallop • Elevated jugular venous pressure • Low blood pressure (< 100/60 mm Hg) • Moderate to severe mitral regurgitation • Low maximal oxygen consumption (peak VO_2)
Laboratory	• Hyponatremia • Elevated pro-BNP levels • Renal insufficiency
Electrocardiography	• QRS duration >120 msec • Left bundle branch block pattern
Echocardiography	• Severe LV dysfunction • Concomitant diastolic dysfunction • Reduced right ventricular function • Pulmonary hypertension
Associated conditions	• Anemia • Atrial fibrillation • Diabetes mellitus

LV = left ventricular; **NYHA** =New York Heart Association; **Pro-BNP**= N-terminal pro-brain natriuretic peptide; **VO_2**= oxygen consumption.

- **Hyponatremia** in pts with CHR usually parallel the severity of heart failure and is independent predictor of adverse clinical outcomes
- ↓perfusion at pressure at baroreceptors and renal afferent arterioles→neurohumoral activation and renin, NE and ADH secretion→ADH-promote free water absorption, renin and NE ↑proximal sodium and water absorption and limit water delivery to distal tubule→free water retention and dilutional hyponatremia
- **Restrict water intake, ACEi and loop diuretics**—initial therapy in hyponatremia in CHF pt. (salt tablets can be given in SIADH but not in edematous state)

Exacerbation of congestive heart failure (CHF)

RF: HTN , Smoking, CAD
PE: bibasilar crackles, Decreased breath sounds (due to pleural effusion), some whhezing (cardiac asthma).0
ABGs: hypoxia, hypocapnia, and respiratory alkalosis .
s3 ,↑BNP

qid: 4570 RESPIRATORY

COCAINE INDUCED STEMI

Clinical features of cocaine use	
Clinical features	• Sympathetic hyperactivity - tachycardia, hypertension, dilated pupils • Chest pain due to coronary vasoconstriction • Psychomotor agitation, seizures
Complications	• Acute myocardial ischemia • Aortic dissection • Intracranial hemorrhage
Management of chest pain	• **Benzodiazepines** for blood pressure & anxiety • Aspirin • Nitroglycerin & calcium channel blockers for pain • Beta blockers **contraindicated** • Fibrinolytics not preferred due to increased risk of intracranial hemorrhage • Immediate cardiac catheterization with reperfusion when indicated

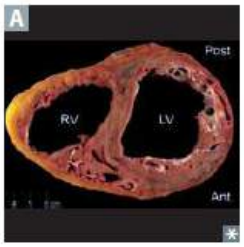
- Associated with pupil dilation and blood crusted nose
- Cocaine also enhance thrombus formation by enhancing platelet activation and aggregation
- Benzodiazepines ↓myocardial oxygen demand and alleviate cardiovascular symptoms as well. given in IV form along with supplemental oxygen
- Alpha blockers like phentolamine can also help reduce vasospasm

AORTIC VALVE ENDOCARDITIS AND AV BLOCK

- When AR is due to valvular disease→ murmur heard along left sternal border (3rd and 4th intercostal space.
- When AR is cox of aortic root dilation→ murmur best heard at right sternal border
- If new AV block is present in case of IV drug user alongwith AR murmur, suspect perivalvular abscess extending into adjacent cardiac conduction pathway (conduction defects not common in tricuspid endocarditis)
- Occurs in 30-40% pts of IE.
- Aside from aortic valve involvement, IVDU is also independent predictor of periannular extension of infection

Cardiomyopathies

Dilated cardiomyopathy



Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies include chronic Alcohol abuse, wet Beriberi, Coxsackie B viral myocarditis, chronic Cocaine use, Chagas disease, Doxorubicin toxicity, hemochromatosis, sarcoidosis, peripartum cardiomyopathy.

Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

Treatment: Na^+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.

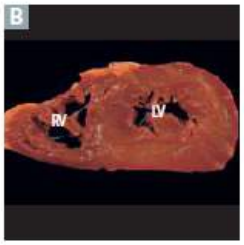
Systolic dysfunction ensues.

Eccentric hypertrophy A (sarcomeres added in series).

ABCCCD.

Takotsubo cardiomyopathy: "broken heart syndrome"—ventricular apical ballooning likely due to increased sympathetic stimulation (stressful situations).

Hypertrophic cardiomyopathy



60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Can be associated with Friedreich ataxia. Causes syncope during exercise and may lead to sudden death in young athletes due to ventricular arrhythmia.

Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

Treatment: cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca^{2+} channel blockers (eg, verapamil). ICD if patient is high risk.

Diastolic dysfunction ensues.

Marked ventricular concentric hypertrophy (sarcomeres added in parallel) B, often septal predominance. Myofibrillar disarray and fibrosis.

Hypertrophic obstructive cardiomyopathy (subset)—asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.

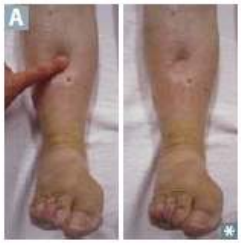
Restrictive/infiltrative cardiomyopathy

Postradiation fibrosis, Loffler syndrome, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common) (Puppy LEASH).

Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially amyloid).

~~Loffler syndrome—endomyocardial fibrosis with a prominent eosinophilic infiltrate.~~

Heart failure



Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema A.

Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

- **Dilated cardiomyopathy**
  - echocardiogram with reduced ejection fraction
  - progressive heart failure
  - S3
- **Restrictive cardiomyopathy**
  - Kussmaul sign on physical exam
  - ECG with **low voltages**
  - S3
- **Hypertrophic cardiomyopathy**
  - echocardiogram with normal ejection fraction
  - S4 gallop on physical exam

HYPERTROPHIC CARDIOMYOPATHY

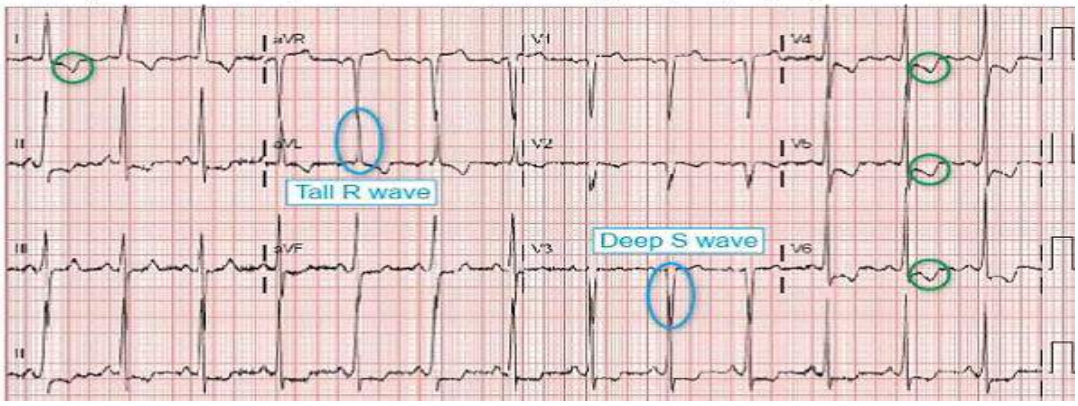
Effect of maneuvers on hypertrophic cardiomyopathy		
	Physiologic effect	**Change in murmur intensity**
Valsalva (straining phase)	↓ Preload	↑
Abrupt standing (from sitting or supine position)		
Nitroglycerin administration		
Sustained hand grip	↑ Afterload	↓
Squatting (from standing position)	↑ Afterload & ↑ preload	
Passive leg raise	↑ Preload	

- HCM common in African American population and is autosomal dominant
- 2 most common mutations responsible for about 70% cases are: (1) cardiac myosin binding protein C gene (2) cardiac beta myosin heavy chain gene
- Pt. may be asymptomatic or present with dyspnea on exertion, chest pain, palpitations or presyncope/syncope. Up to half of the pts who die suddenly from HCM don't have any prior symptoms
- Myocardial hypertrophy and fibrosis peak during puberty and exertion can precipitate acute LV outflow tract obstruction or ventricular fib.
- Physical exam: carotid pulse with dual upstroke due to mid-systolic obstruction during cardiac contraction
- HCM with significant LVOT obstruction causes systolic ejection murmur along left sternal border with a strong apical impulse
- All athletes should undergo pre-participation evaluation before being cleared for sports as it is preventable.
- FH of sudden unexplained death should prompt echo and ecg and pt should refrain from exertion till nothing is found on these tests.
- Athletes without prior cardiac condition can develop fatal ventricular fib after sudden blunt chest trauma, also known as commotio cordis

Major causes of sudden cardiac death
• Coronary artery disease • Cardiomyopathy (eg, hypertrophic cardiomyopathy) • Arrhythmia (eg, long QT syndrome) • Congenital heart defect

Hypertrophic cardiomyopathy

- Left ventricular hypertrophy: Tall R wave in aVL + Deep S wave in V3 (Cornell criteria)
- Repolarization changes in anterolateral leads (I, aVL, V4, V5, V6)



RESTRICTIVE CARDIOMYOPATHY

- Less common than dilated and HCM
- **Caused by**: infiltrative dis. (sarcoidosis, amyloidosis), storage dis. (hemochromatosis), endomyocardial fibrosis, or it may be idiopathic. Hemochromatosis is the only one which is reversible with treatment i.e. phlebotomy
- Primarily cause diastolic dysfunction with minimally affected systolic function.
- Left ventricular volume is normal and wall thickness is either normal or **symmetrically** thickened (distinguishes from HCM)
- Right heart failure signs are more prominent but can also cause signs of left HF.

Amyloidosis:

Amyloidosis	
Etiology	• Extracellular deposition of insoluble polymeric protein fibrils in tissues & organs • Can be primary (AL type) or secondary (AA) to chronic inflammatory conditions such as: ○ **Inflammatory arthritis** (eg, rheumatoid arthritis) ○ **Chronic infections** (eg, bronchiectasis, tuberculosis, osteomyelitis) ○ **Inflammatory bowel disease** (eg, Crohn's disease) ○ **Malignancy** (eg, lymphoma) ○ **Vasculitis**
Clinical presentation	• Asymptomatic proteinuria or nephrotic syndrome • Restrictive cardiomyopathy • Hepatomegaly • Peripheral neuropathy &/or autonomic neuropathy • Visible organ enlargement (eg, macroglossia) • Bleeding diathesis • Waxy thickening, easy bruising of skin
Diagnosis	• Abdominal fat pad aspiration biopsy

- Predominantly diastolic dysfunction. Pt may develop syncope or presyncope due to conduction abnormalities
- ECG: low voltage
- Echo: Increased ventricular wall thickness with normal ventricular cavity dimensions (esp in ots without HTN)
- Tissue biopsy (eg **abdominal fat pad,** bone marrow, rectum, kidney, endomyocardial biopsys) can confirm diagnosis by showing amyloid deposits

Sarcoidosis:

- Can cause granulomatous infiltration of myocardium and HF with both systolic and/or diastolic dysfunction
- Affects young adults, involve lungs, skin, eyes

causes

DILATED CARDIOMYOPATHY

- **As** a result of toxic (alcohol), metabolic (hemochromatosis) or infectious agents

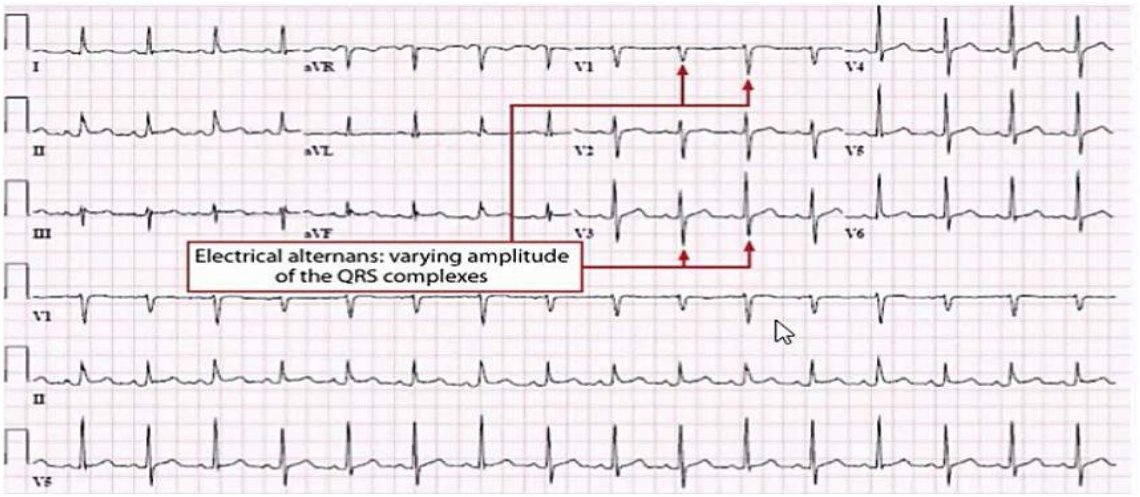
VIRAL MYOCARDITIS

- **Viral myocarditis:** h/o recent upper resp. tract infection
- **Most common cause:** Coxsackievirus B
  Other viral causes: parvovirus B19, HHV 6, adenovirus and enterovirus
- **MOA:** direct viral damage and as a result of humoral or cellular immune responses to persistent viral infections
- **Dx:** echo shows dilated ventricles with diffuse hypokinesia resulting in a low ejection fraction (i.e. systolic dysfunction)
- **Rx:** largely supportive, mainly management of CHF symptoms

CARDIAC TAMPONADE

- **Cardiac tamponade** vs dilated cardiomyopathy: in tamponade there will be clear lung fields whereas in dilated cardiomyopathy bibasilar crackles will be heard with pulmonary venous congestion on CXR. S3 will be heard in DCM. Cardiac tamponade can be idiopathic (usually viral), can be bacterial, fungal, neoplastic (primary or metastatic), post MI, trauma, uremia, autoimmune, hypothyroidism.
- Enlarged globular cardiac silhouette (water bottle heart shape). Mainly affects right side of heart
- Inability to palpate point of maximal impulse. Beat to beat variation in QRS amplitude and axis. Electrical alternans with sinus tachy is highly specific for large pericardial effusion→emergency pericardiocentesis

مهم عليه كذا سؤال



Auscultation of heart sounds

Ausculation of cardiac murmurs			
Maneuver	**What it does**	**Murmurs that get louder**	**Murmurs that get softer**
Valsalva	• **Early (Strain)** ↓ Venous return ↓ All murmurs except HCM & MVP • **Late (Release)** ↑ Venous return ↑ Right-sided murmurs	• **HCM** ↓ LV volume ↑ Gradient • **MVP** ↓ LV volume ↑ Leaflet prolapse	• **All others** ↓ Flow through stenotic or regurgitant valve during strain phase
Standing	• ↓ Venous return • Similar to the strain phase of Valsalva	• **HCM** ↓ LV volume ↑ Gradient • **MVP** ↓ LV volume ↑ Leaflet prolapse	• **All others** ↓ Flow through stenotic or regurgitant valve during strain phase
Squatting	• ↑ Venous return • ↑ Afterload by kinking of femoral arteries • ↑ Reverse flow	• AR • MR • VSD	• **HCM** ↑ Preload ↓ Gradient across outflow obstruction ↓ Obstruction • **MVP** ↑ LV size ↓ Leaflet prolapse
Handgrip	• ↑ Afterload • ↑ Blood pressure • ↑ Reverse flow across valve	• AR • MR • VSD	• **HCM** (↑ LV volume) • **AS** (↓ transvalvular pressure gradient)

AR = aortic regurgitation; **HCM** = hypertrophic cardiomyopathy; **LV** = left ventricular; **MR** = mitral regurgitation; **MVP** = mitral valve prolapse; **VSD** = ventricular septal defect; **AS** = aortic stenosis

Gallop heart sounds			
	Features	**Normal**	**Abnormal/associated conditions**
Third heart sound (S3)	• Ventricular gallop sound (after S2) • Heard during rapid filling of ventricles in diastole • Turbulent blood flow to the ventricles due to increased volume	• Children • **Young** adults • Pregnancy	• Age >40 • Heart failure • Restrictive cardiomyopathy • High-output states
Fourth heart sound (S4)	• Atrial gallop sound (before S1) • Heard immediately after atrial contraction phase as blood is forced into a stiff ventricle	• Healthy **older** adults	• Younger adults, children • Ventricular hypertrophy • Acute myocardial infarction

S4 is heard in acute MI because of ischemia induced myocardial dysfunction

Benign versus pathologic murmurs		
	Benign	**Pathologic**
History	• Normal appetite, energy, activities & growth • No significant family history	• Diaphoresis & fatigue with feeding or exercise, poor weight gain, chest pain, dizziness, syncope, shortness of breath • Family history of sudden cardiac death, heart defects, etc.
Murmur features	• Early or mid-systolic • Grade I or II intensity that decreases on standing & Valsalva maneuver • Low-pitched, musical, pure, or squeaky tone at LLSB (Still's murmur) or high-pitched at LUSB (pulmonary flow murmur)	• Harsh, holosystolic, diastolic • Grade III intensity or higher • Increases with standing & Valsalva maneuver
Other findings	• None	• Loud, fixed split, or single S2 • Decreased or absent femoral pulses
Workup	• None indicated	• ECG (to assess for hypertrophy) • Echocardiogram (to assess for structural abnormalities) • Cardiology referral

- Key distinguishing feature of benign vs pathological murmur is change in instensity with change in position. Position that dec. venous return to heart, dec intensity of innocent murmur.
- **Management:** reassurance and observation in benign murmurs.

HEPATOJUGULAR REFLUX

- Used to differentiate btw cardiac and liver dis.
- Elevation of JVP >3cm during abdominal compression
- Sign of failing right heart.
- Common in constrictive pericarditis, right ventricular infarction and restrictive cardiomyopathy

CONSTRICTIVE PERICARDITIS

- Major cause of right heart failure
- Hepatic congestion with hepatomegaly and eventual progression to cirrhosis (cardiac cirrhosis)
- ↑JVP with hepatojugular reflux, Kussmaul's sign (lack of ↓ or an ↑ in JVP on inspiration), pericardial knock and pericardial calcifications on CXR

Features of constrictive pericarditis	
Etiology	• Idiopathic or viral pericarditis 40% • Cardiac surgery or radiation therapy 30% • Tuberculous pericarditis (in endemic areas) → Africa, India, China.
Clinical presentation	• Fatigue & dyspnea on exertion • Peripheral edema & ascites • ↑ Jugular venous pressure • Pericardial knock may be heard → sound directly after the second heart sound in (early/ mid) diastole... sth like an early s3 • Pulsus paradoxus • Kussmaul's sign
Diagnostic findings	• ECG may be nonspecific or show atrial fibrillation or low-voltage QRS complex • Imaging shows pericardial thickening & calcification • Jugular venous pulse tracing shows prominent x & y descents

- **Echo confirms diagnosis. S**how: ↑ pericardial thickness, abnormal septal motion and biatrial enlargement.
- **Rx**: Diuretics—temporary relief, pericardiectomy—definitive treatment for refractory cases
- Survivors of Hodgkin lymphoma can present as much as 10-20 yrs after mediastinal irradiation and/or anthracycline therapy. Cardiac complications of Hodgkin lymphoma include: acute or delayed pericardial disease, myocardial ischemia/infarction, restrictive cardiomyopathy, CHF, valvular abnormalities and conduction defects

PERICARDITIS

Etiologies of pericarditis	
Infection	Viral (most common), bacterial
Iatrogenic	Surgery, trauma, radiation & drug-related
Connective tissue disease	Rheumatoid arthritis, systemic lupus erythematosus
Cardiac	Dressler syndrome (post-myocardial pericarditis), usually 1-6 weeks after myocardial infarction
Uremic	Serum BUN usually >60 mg/dL, but degree of pericarditis does not always correlate with degree of elevation
Malignancy	Can be due to cancer (eg, lung & breast, Hodgkin lymphoma) or treatment (eg, radiation, chemotherapy)

Uremic pericarditis:

- Occur in 1-6% pts of renal failure
- Involve visceral and perietal membranes of pericardium
- Does not present with classic ECG findings of pericarditis as inflammatory cells do not penetrate the myocardium and lack of involvement of epicardium
- **Dialysis** is the most effective treatment for UP and can resolve symptoms and decrease the size of any pericardial effusion
  - ➔ NSAIDS and/or colchicine—1st line for idiopathic or acute viral pericarditis. In UP, used if not responding to dialysis
- Avoid anticoagulants→ hemorrhage into pericardial sac

→**Acute pericarditis:** can cause diffuse ST segment elevation on EKG often accompanied with PR depression in limb and left precordial leads

INDICATIONS FOR URGENT DIALYSIS

Indications for urgent dialysis (AEIOU)	
Acidosis	• Metabolic acidosis ◦ pH <7.1 refractory to medical therapy

Electrolyte abnormalities	• Symptomatic hyperkalemia
	  ◦ ECG changes or ventricular arrhythmias
	• Severe hyperkalemia
	  ◦ K >6.5 mEq/L refractory to medical therapy

Ingestion	• Toxic alcohols (methanol, ethylene glycol) • Salicylate • Lithium • Sodium valproate, carbamazepine
Overload	Volume overload refractory to diuretics

Uremia	• Symptomatic:
	  ◦ Encephalopathy
	  ◦ Pericarditis
	  ◦ Bleeding

HEART BLOCK

FIRST DEGREE AV BLOCK:

- Due to delayed impulse transmission from atria to ventricles at a number of possible locations including atria, AV node, bundle of His or infra-Hisian conduction system (bundle branches or fascicles)→prolonged PR interval >0.20 sec
- PR interval remains constant
- Most first degree AV block with **normal QRS** are due to conduction delay in AV node→ no further evaluation needed. Benign but 1st degree block is associated with higher risk of heart failure, a. fib, and overall mortality

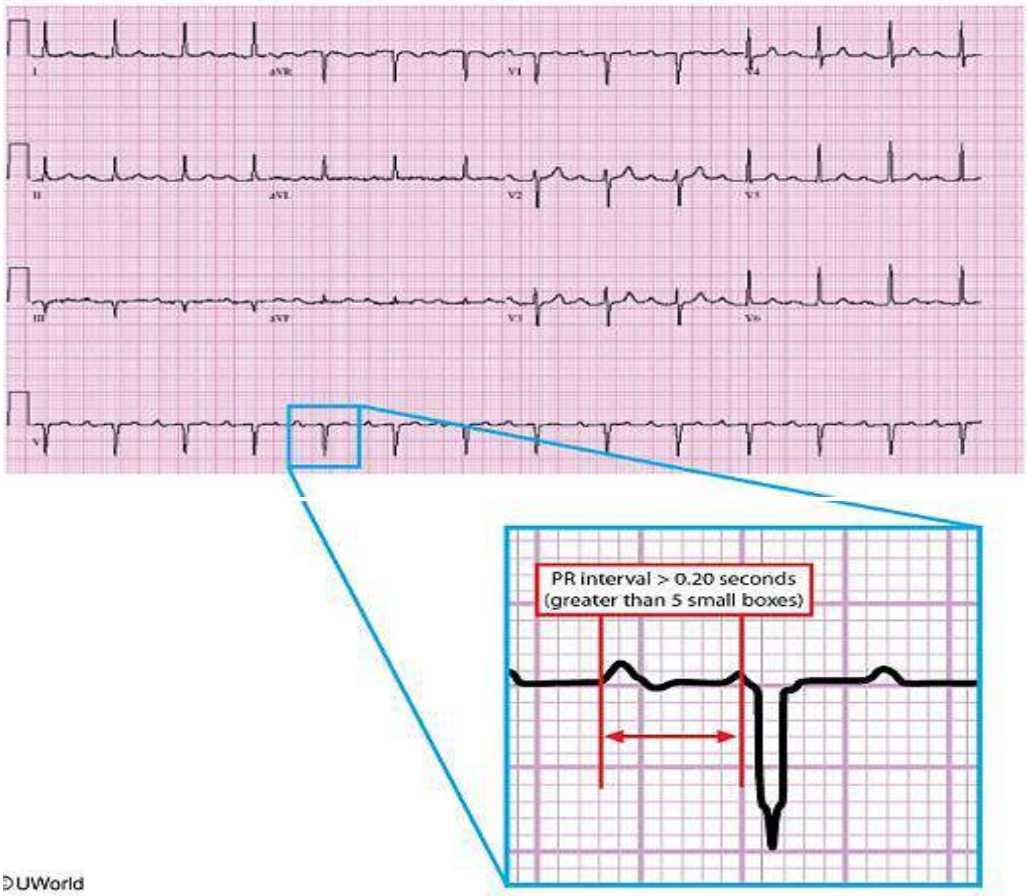
observation

- First degree AV block with **wide QRS** (>120msec)—conduction delay below AV node, mostly bundle branches—can have unpredictable progression to 2nd and 3rd degree block and should have **electrophysiologic testing** to determine the site of conduction delay

electrophysiologic study

- Some pts with 1st degree AV with marked prolongation of PR interval can develop **"pacemaker syndrome"**—uncomfortable sensation of awareness of heart beat due to atrial contraction against close mitral valve during ventricular systole. Such symptomatic pts are potential candidates for pacemaker explantation

First degree heart block:
Occurs due to slowed conduction through the AV node
- Prolonged PR interval
- P wave always follows QRS, unlike other heart blocks



SECOND DEGREE AV BLOCK:

Second-degree AV block: Distinguishing features of Mobitz type I & type II AV block		
	Mobitz type I	**Mobitz type II**
Level of block	Usually AV node	Below the level of AV node (eg, bundle of His)
ECG findings	Progressive prolonged PR interval leads to a nonconducted P wave **("group beating")**	PR interval remains constant with intermittent nonconducted P waves
QRS complex	Narrow	Narrow or wide
Exercise or atropine	Improves type I AV block	Worsens type II AV block
Vagal maneuvers (carotid sinus massage)	Worsens type I AV block	Paradoxically improves type II AV block
Risk of complete heart block	Low risk	Higher risk, indication for pacemaker

- **Mobitz type 1:** due to delay of break in cardiac electrical signal pathway from atria to ventricles

➔ Can occur in healthy people, athletes, older pts, those with heart dis., and those who are on drugs that block AV node (e.g digoxin, beta blockers, calcium channel blockers)

➔ Constant P-P interval

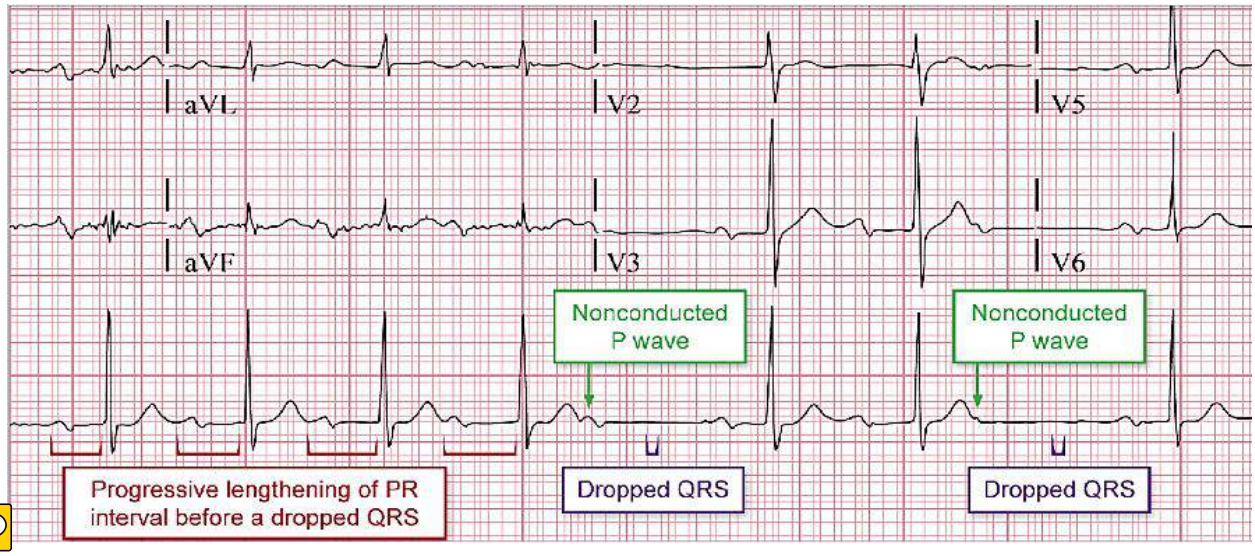
➔ Increasing PR interval

➔ Decreasing R-R interval

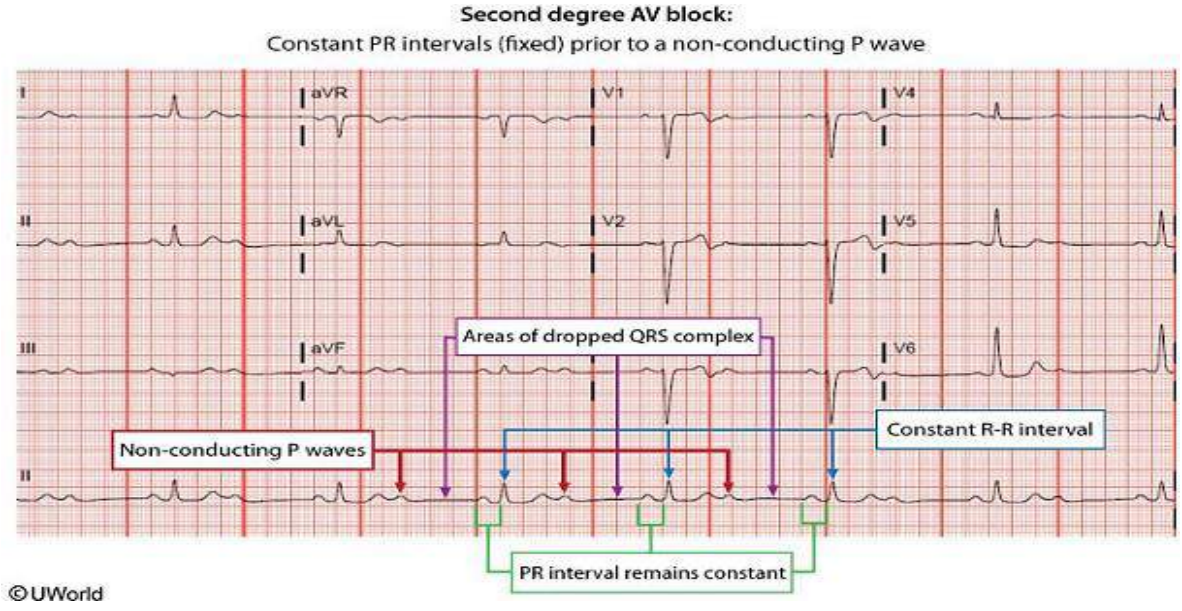
➔ There can be a predictable grouping between P-QRS complexes before dropped QRS complex (e.g. after every 3 P-QRS complexes, there is a drop). This is called "**group beating"**

➔ **Rx:** observe in asymptomatic pts as it is benign (esp in young with good ventricular function) and correct correctable causes like meds.

➔ Can rarely cause significant bradycardia with sx of inadequate cardiac output (eg fatigue, lightheadedness, angina, syncope, heart failure) esp in older pt withacute ischemia or additional cardiac comorbidity

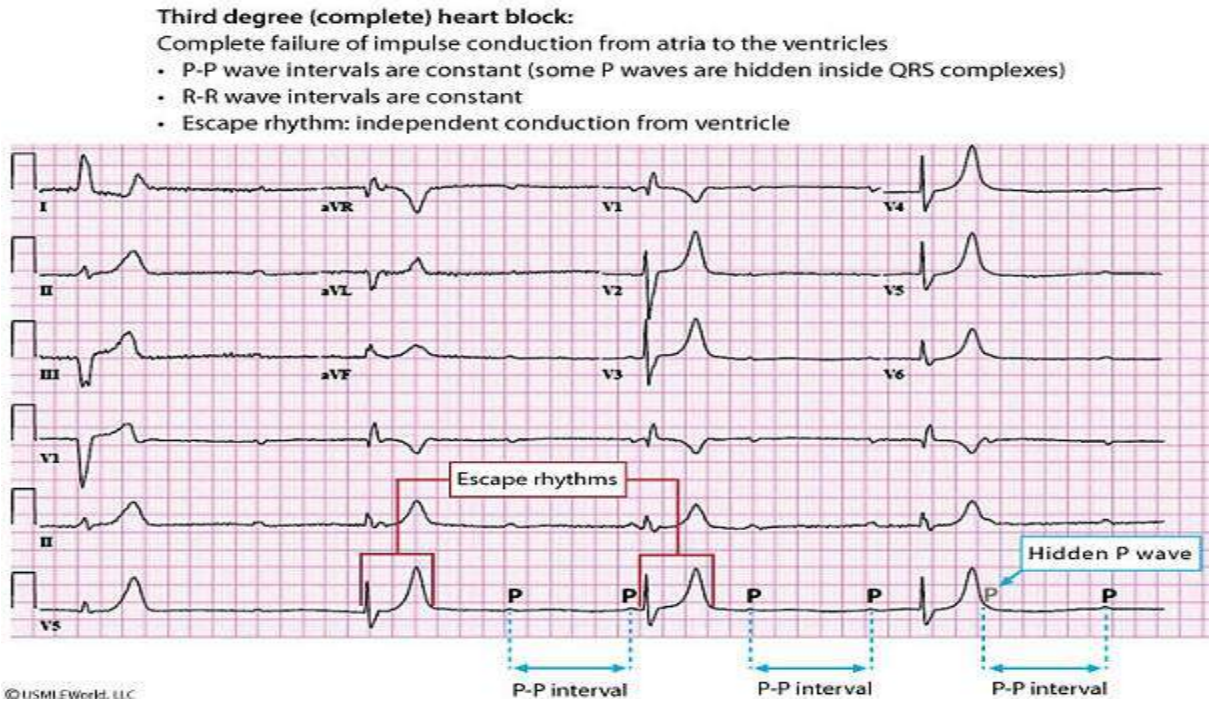


- **Mobitz type 2:** episodic and unpredictable absence of conduction



THIRD DEGREE/COMPLETE AV BLOCK:

- Complete failure of impulse conduction between atria and ventricles



EKG findings in complete AV block
• There is a complete failure of atrial impulses (p waves) to capture the ventricles (QRS)
• Unless an escape rhythm is initiated, ventricular asystole (syncope/death) will occur
• The escape rhythm (QRS) can be narrow (junctional escape) or wide (ventricular escape)
• The p waves have no relation to QRS complexes (complete AV dissociation)
• Ventricular rate is always slower than the atrial rate and is usually < 50

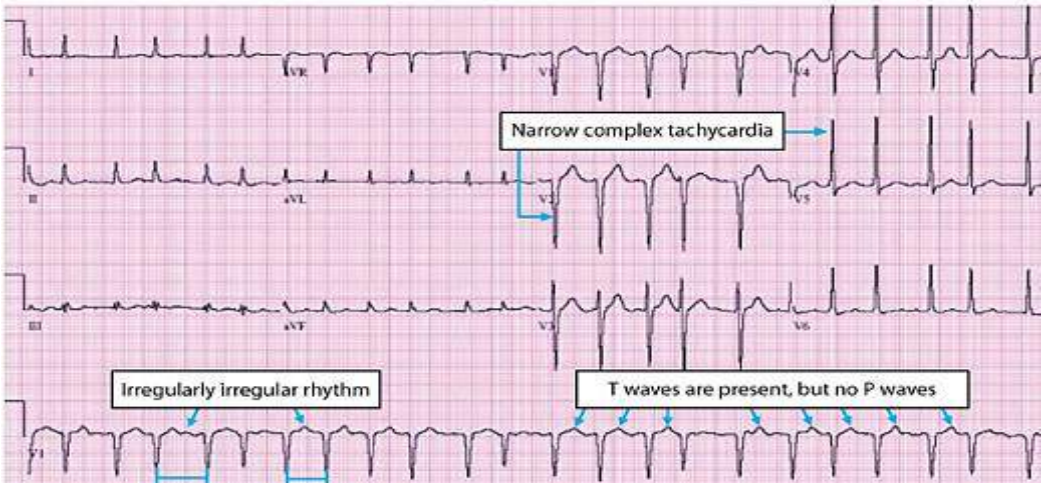
- Sx: dizziness and worsening angina
- Left untreated→ ventricular arrythmia or asystole
- **Sympotmatic pts** should be referred immediately for temporary pacemaker insertion while detailed evaluation for potential causes is performed.
- **Reversible causes:** MI, increased vagal tone (e.g during sleep or due to pain), metabolic disturbnace (eg hyperkalemia), and AV nodal blocking agents (like beta blockers, CCB e.g verapamil)
- **Permanent pacemaker** is indicated in absence of reversible causes.
- **Contraindications:** beta blockers, digoxin→ worsen complete block

ATRIAL FIBRILLATION

- The **pulmonary veins (PV)** are the most frequent location of ectopic foci that cause AF.
- Cardiac tissue (myocardial sleeves) extends into PVs and normally functions like a sphincter to reduce reflux of blood into PV during atrial systole. This tissue has different electrical properties than the surrounding atrial myocytes and is prone to ectopic foci and/or aberrant conduction, which can initiate

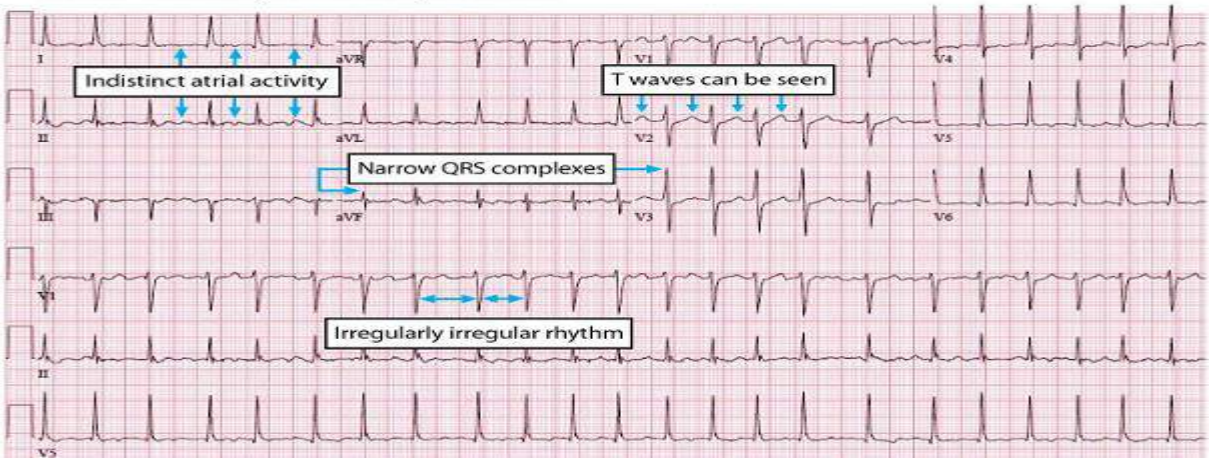
AF—this tissue can be disrupted by catheter-based radiofrequency ablation in those who are unable to achieve adequate rate and rhythm control with standard medical therapy, thereby disconnecting PVs from left atrium

- No organized atrial activity and impulses are conducted in a random and unpredictable manner. This leads to absence of any discernable P waves and irregularly irregular rhythm with varying R-R interval
- **Atrial fibrillation with rapid ventricular response:** irreglularly irregular rhythm with narrow complex tachy and no organized P waves. Ventricular rates can be as high as 150/min. symptoms are due to fast ventricular rate rather than arrythmia itself.



Atrial fibrillation

- No distinct p waves in AF
- Irregularly, irregular R-R intervals
- Narrow QRS complexes typically seen
- Atrial rate is usually ≥ 350 beats per minute

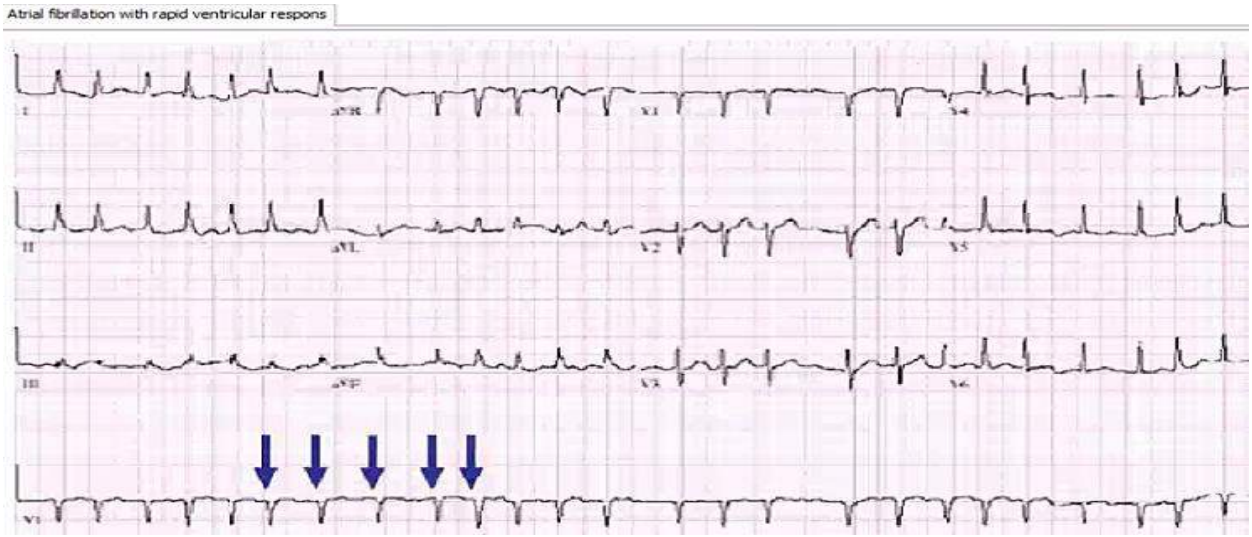


Tachycardia-mediated cardiomyopathy - Qid: 4238

- tachyarrhythmias with prolonged periods of rapid ventricular rates can lead to this cardiomyopathy these include **AF**, **atrial flutter**, **ventricular tachycardia,** incessant atrial/junctional tachycardia, and atrioventricular nodal reentrant tachycardia.

- Initial treatment is aimed at restoration of sinus **rhythm** or aggressive control of ventricular **rate** and can lead to significant improvement in left ventricular function.

- Therapeutic options include AV nodal blocking agents, antiarrhythmic drugs, and catheter ablation of arrhythmia.



Conditions associated with atrial fibrillation	
Cardiac	• Hypertensive heart disease (most common) • Coronary artery disease • Rheumatic/Valvular heart disease (eg, mitral stenosis, mitral regurgitation) • Congestive heart failure • Hypertrophic cardiomyopathy • Congenital heart disease (eg, atrial septal defect) • Post cardiac surgery
Pulmonary	• Obstructive sleep apnea • Pulmonary embolism • Chronic obstructive pulmonary disease • Acute hypoxia (eg, pneumonia)
Miscellaneous	• Obesity • Endocrine (eg, hyperthyroidism, diabetes) • Alcohol abuse • Drugs (eg, amphetamines, cocaine, theophylline)

- Pts with new onset AF should be screened for occult hyperthyroidism by TSH and free T4 levels checked
- Two issues that need to be addressed in all pts with new onset AF include choice between **rate or rhythm control strategy** and risk stratification for prevention of **systemic embolization.** There is no significant difference in morbidity and mortality between rate and rhythm control strategy.
- **Rate control** is preferred over rhythm control in hemodynamically stable pts. Rate control is achieved by **beta blockers (**metoprolol), **calcium channel blockers (**diltiazem) **or digoxin** to control ventricular rates
- **Rhythm control** (immediate synchronized cardioversion) is needed in hemodynamically unstable pts with rapid AF. It should be considered in those who do not achieve adequate rate control or recurrent symptomatic episodes (eg, palpitations, lightheadedness, dyspnea, angina) or heart failure symptoms in setting of underlying left ventricular systolic dysfunction. Attempting cardioversion for an unknown duration or >48 hours without adequate anticoagulation inc. risk of systemic thromboembolism

- **CHA2DS2-VASc score** is used to identify which pt is at highest risk of thromboembolic complication and will benefit from **antithrombotic therapy.** All pts with a.fib should be assessed for this.

CHA_2-DS_2-VASc score		
Risk criteria		**Score**
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75*	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65-74*	1
Sc	Sex category (ie, female)	1
	Maximum score	**9**

*pt assigned to one of these two categories

Anticoagulation in atrial fibrillation		
Nonvalvular atrial fibrillation		
CHA_2DS_2VASc score	**Stroke risk**	**Anticoagulant therapy**
0	Low	None
1	Intermediate	None or aspirin or oral anticoagulant*
>2	High	Oral anticoagulant*
Valvular atrial fibrillation or mechanical/prosthetic valve • Warfarin		

*Warfarin or target-specific oral anticoagulants

- all pts with paroxysmal or persistent AF should have risk stratification with CHADS2 score to assess need of long term anticoagulation

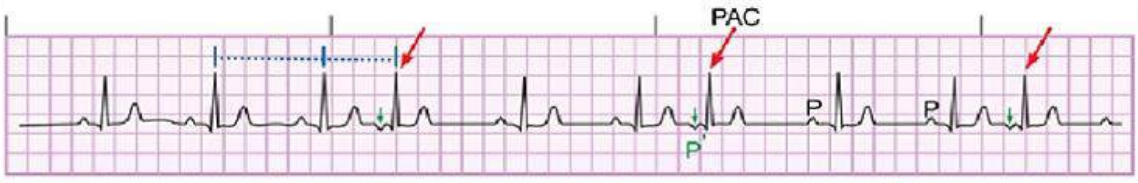
Anticoagulation in atrial fibrillation		
$CHADS_2$ score	Stroke risk	Antithrombotic therapy
0	Low	No anticoagulation (preferred) or Aspirin
1	Intermediate	Anticoagulation (preferred) or Aspirin
2-6	High	Anticoagulation

- "**Lone AF":** presence of paroxysmal, persistent or permanent atrial fibrillation with no evidence of cardiopulmonary or structural heart disease. Pts with lone AF are usually <60 and by definition, have CHA2-DS2-VASc scor of 0 and need no treatment.

ATRIAL PREMATURE BEATS

- Indicate depolarization of the atria originating in a focus outside SA node. They are seen on ECG as a P wave with abnormal morphology, often occuring earlier in a cardiac cycle than a normal P wave

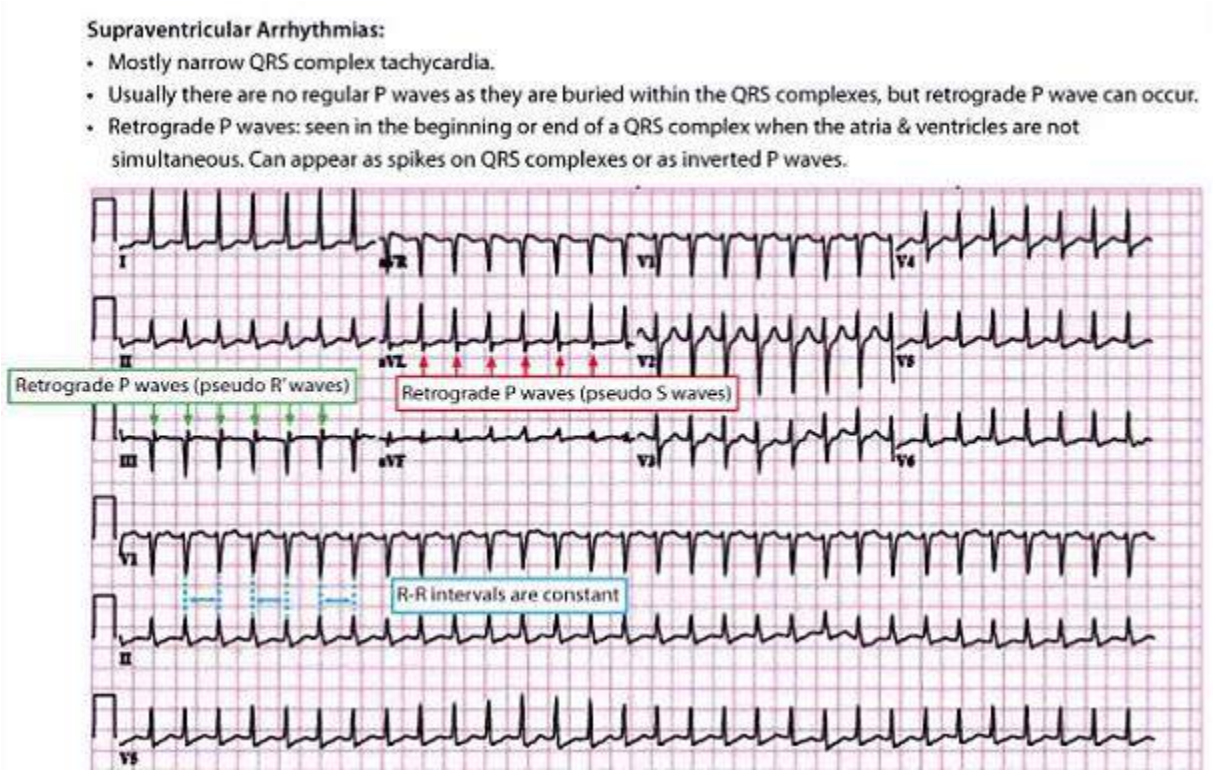
Premature atrial contractions (PACs)



Rate	Rhythm	P wave	QRS
60-100	Irregular	P wave of the PAC often has a different shape from the one originating in the SA node	Normal

- Benign—can occur in healthy people and those with diseased heart
- Usually asymptomatic but can cause symptoms of "skipped" beats or palpitations
- Can precede a. fib
- Rx: only when symptoms cause distress or when there is SVT—persistent PACs with symptoms can be treated with low dose beta blockers
- Even in asymptomatic pts, **precipitating factors** like tobacco, alcohol, caffeine, and stress should be identified and avoided
- In the absence of precipitating factors, transthoracic echo should be performed to look for cardiac/valvular structural/functional abnormality

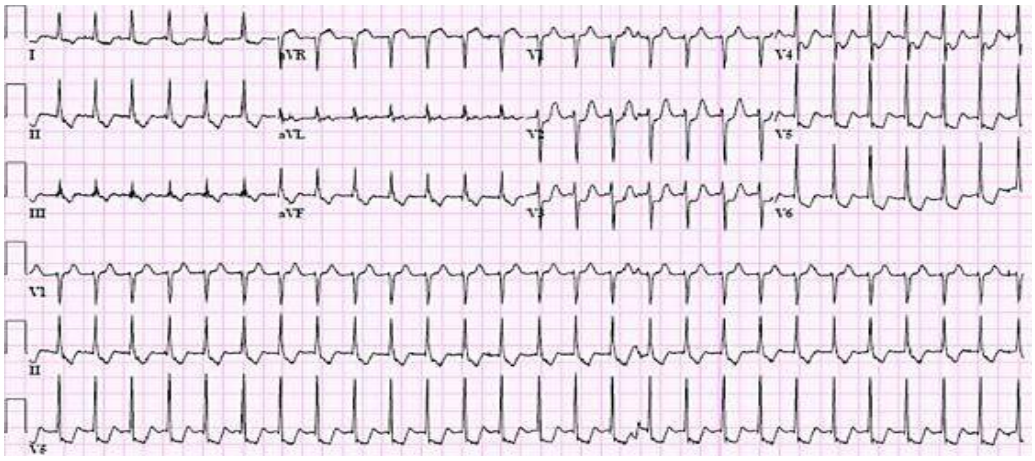
SUPRAVENTRICULAR TACHYCARDIA



- **ECG:** shows a **regular and narrow complex tachycardia** (QRS duration <120ms) at a rate of approx 160 beats/min
- **SVT:** any tachycardia originating above the His-bundle and includes sinus tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), and junctional tachycardia
- **AVNRT**—it is because of reentrant circuit formed by 2 separate conducting pathways (one fast and one slow) within AV node
- **AVRT**— due to reentrant circuit involving accessory AV bypass tract
- **C/F:** palpitations, dizziness, lightheadedness, SOB, diaphoresis, chest pain, presyncope, or syncope
- **Paroxysmal supraventricular tachycardia (PSVTs):** type of SVT with abrupt onset and offset; they include AVNRT, AVRT, atrial tachycardia, and junctional tachycardia. Sudden onset, regular, narrow complex tachycardia. MOA: re-entry into AV node
- In pts who are **hemodynamically stable,** the next step in evaluation is to **identify the type of SVT** with the use of **vagal maneuvers** (eg. carotid sinus massage, Valsalva, eyeball pressure, inserting face in cold water) or **IV adenosine**. Adenosine or vagal maneuvers **temporarily slow conduction via AV node** and can aid in diagnosis by unmasking "hidden" P waves in pts with atrial flutter or atrial tachycardia. They can also cause a transient AV nodal block and terminate AV node-dependent arrythmias, including AVNRT and orthodromic AVRT. IV beta blockers and CCB can be occasionally given to those who do not respond to vagal maneuver and/or IV adenosine uworld Qs
- In **hemodynamically unstable patients with persistent tachyarrhthmia (narrow or wide QRS)--** hypotension and signs of poor perfusion (cool extremities), signs of shock, ischemic chest discomfort, mental status change, acute pulmonary edema—**immediate synchronized direct current cardioversion** due to risk of rapid clinical deterioration. It involves delivery of low-energy electric shock synchronized to QRS complex. If possible, provide adequate sedation and analgesia prior to cardioversion

(unsynchronized cardioversion given in ventricular fib, pulseless ventricular tachy (pulseless cardiac arrest)

Paroxysmal SVT



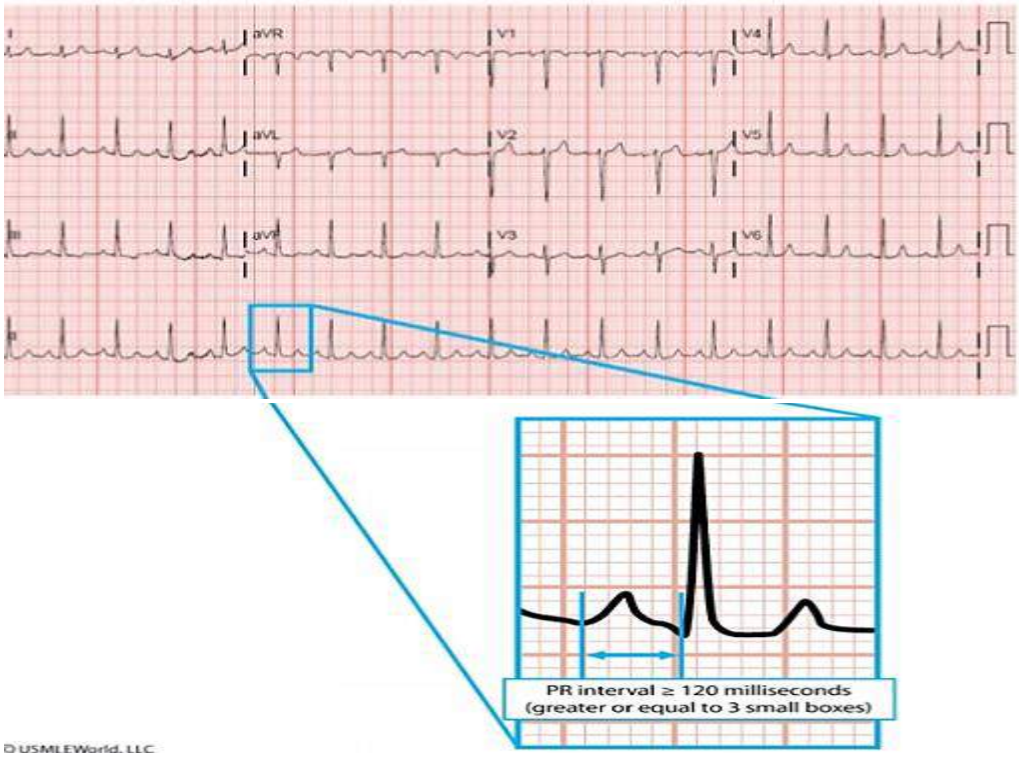
Atrial flutter:

- The most common cause of atrial flutter is a reentrant circuit around tricuspid annulus, with slowing of the impulse through a region known as the cavotricuspid isthmus.
- Rapid "sawtooth" flutter waves are characteristic ECF features of a. flutter

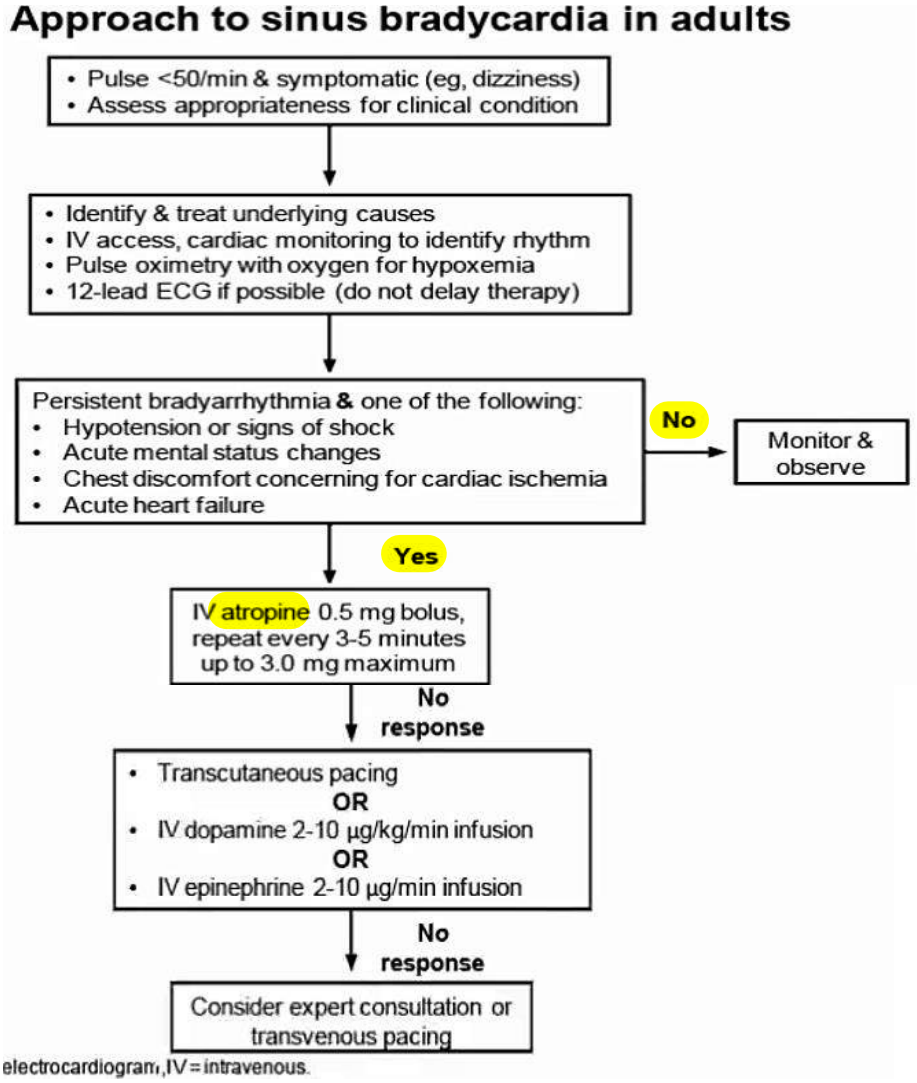
SINUS TACHYCARDIA

Sinus Tachycardia

- P waves usually before QRS complex
- Ventricular rate ≥ 100 beats/min
- P waves are usually upright in leads I, II, aVF, V3-V6
- Maximal heart rate in sinus tachycardia can be determined (beats/min = 220 – age)

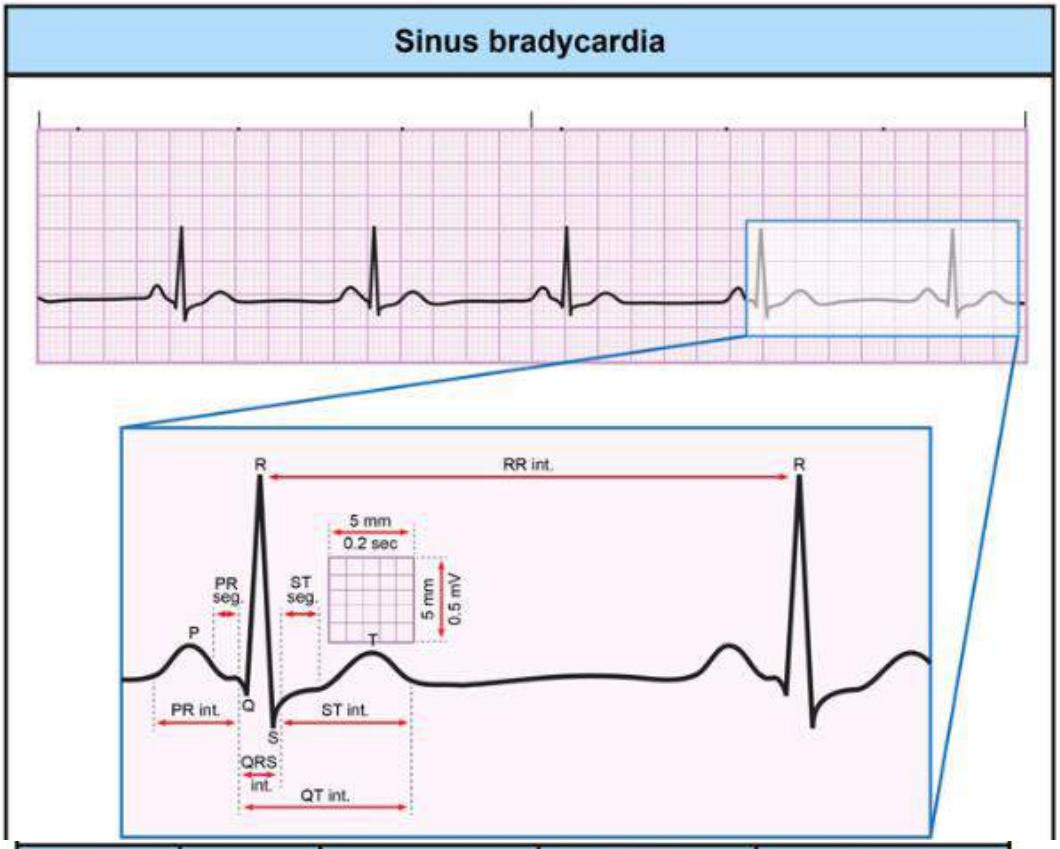


SINUS BRADYARRHYTHMIA



- Normal heatr rate: 60-100/min. Sinus brady: HR <60/min, regular rhythm, and constant PR interval
- Can occur normally in adolescents, young adults, well-conditioned athletes, and some elderly esp during sleep
- **Pathologic causes:** sick sinus syndrome, MI or ischemia, OSA, hypothyroidism, ↑ intracranial pressure and meds
- **Sx:** usually asymptomatic, but some may develop fatigue, dizziness, light-headedness, hypotension, syncope angina, and/or CHF
- **NE** is indicated to treat severe hypotension and shock (eg. septic shock) but not bradyarrhythmia

Sinus bradycardia

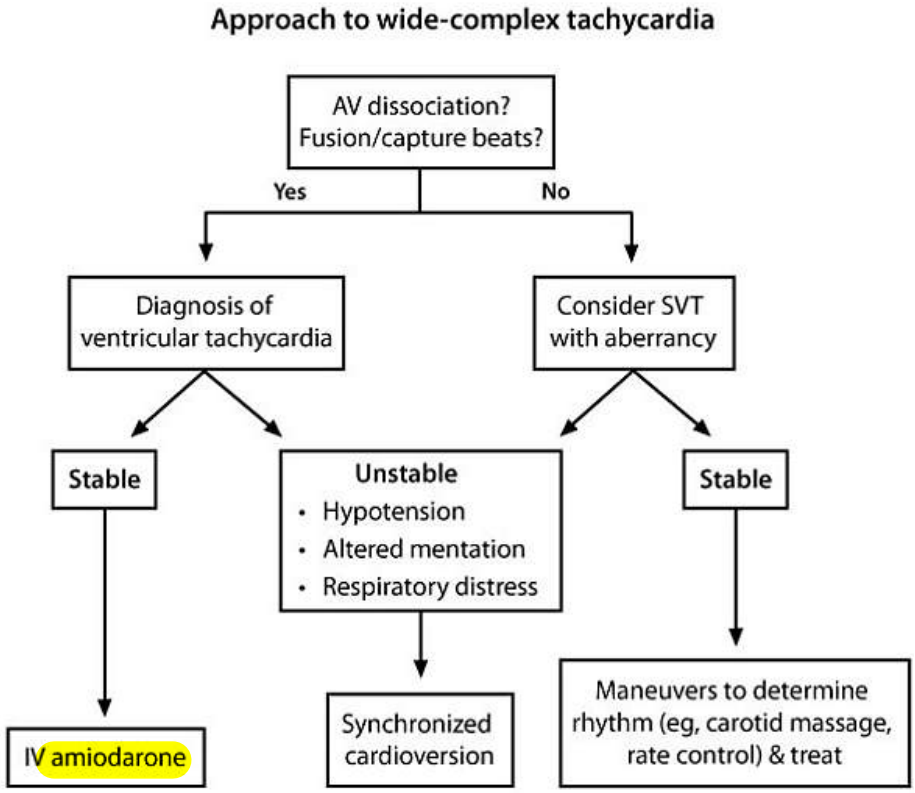


Heart rate	Rhythm	P wave	PR interval (in second)	QRS (in second)
< 60 bpm	Regular	Present before each QRS, identical	Normal duration (0.12 to 0.20)	Normal duration (< 0.12) Normal shape

ECG Interpretation

- Heart rate = number of RR intervals within 6 seconds X 10 (for irregular rhythm, count RR intervals for a full 60 seconds for accuracy)
- Measure RR intervals to determine regularity
- Evaluate the P waves: Are P waves present? Is there a P wave for every QRS? Are P waves identical?
- Measure and evaluate the PR interval
- Measure the QRS and examine it configuration

APPROACH TO WIDE COMPLEX TACHYCARDIA

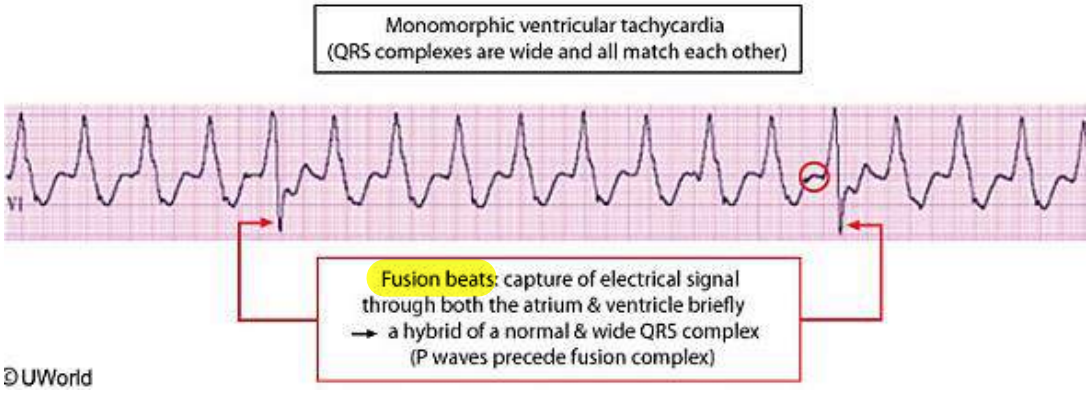


- the first thing to do for **V tach is satbilize** then **look for the underlying cause by serum electrolytes.**

- Loop diuretics cause **hypokalemia** and **hypomagnesemia.** These electrolyte abnormalities can cause ventricular tachycardia, and also potentiate the side effects of digoxin causin V tach.

UW: 2164

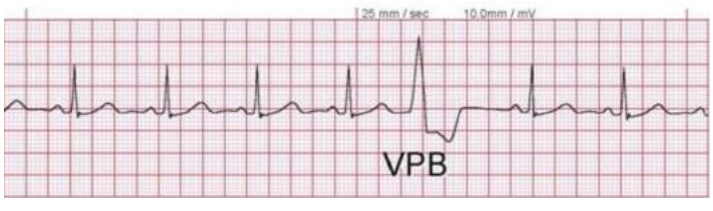
MONOMORPHIC VENTRICULAR TACHYCARDIA:



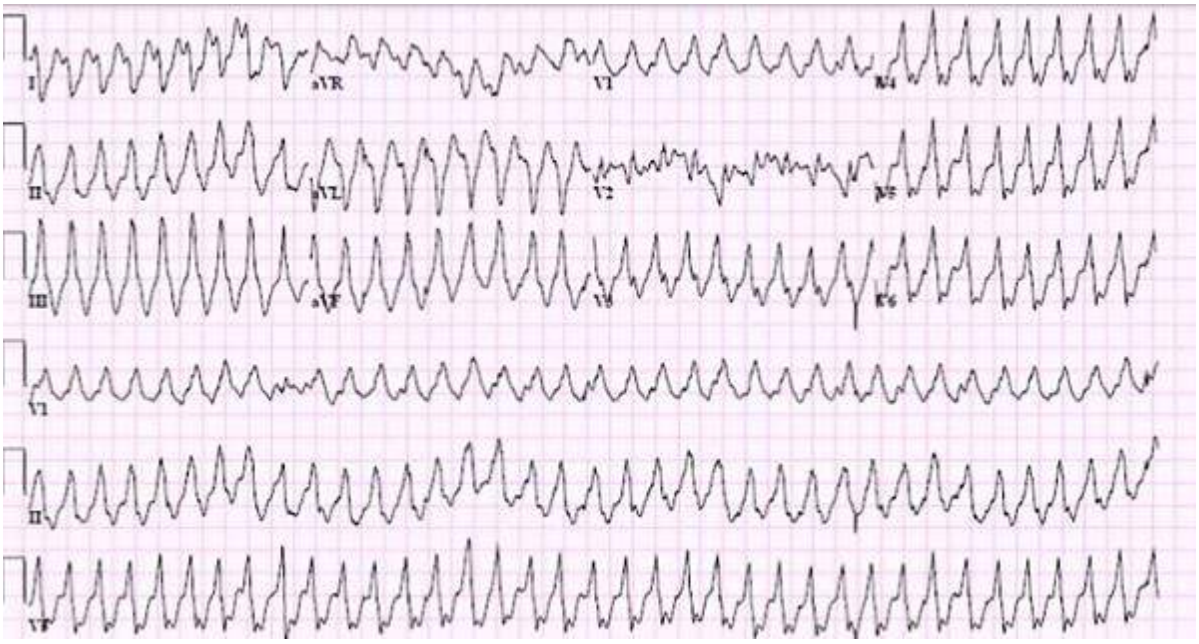
- Sustained wide complex tachycardia + fusion beats→**sustained monomorphic VT (SMVT)**
- Presence of AV dissociation is also diagnostic of VT
- SMVT occuring early (6-48 hours) during MI is associated with increased risk of in-hospital mortality
- Among anti-arrhythmics that can be used for this condition like amiodarone, lidocaine, procainamide, IV Amiodarone is the preferred one.

VENTRICULAR PREMATURE BEAT "VPB"

- Wide QRS with abnormal morphology
- benign & asymptomatic
-reassurance + B blocker



VENTRICULAR TACHYCARDIA



- **A**miodarone and lidocaine is often used in treatment of hemodynamically stable patient with wide-QRS-complex tachycardia. Amiodarone is also used in the treatment of atrial fib but not PSVT

SICK SINUS SYNDROME

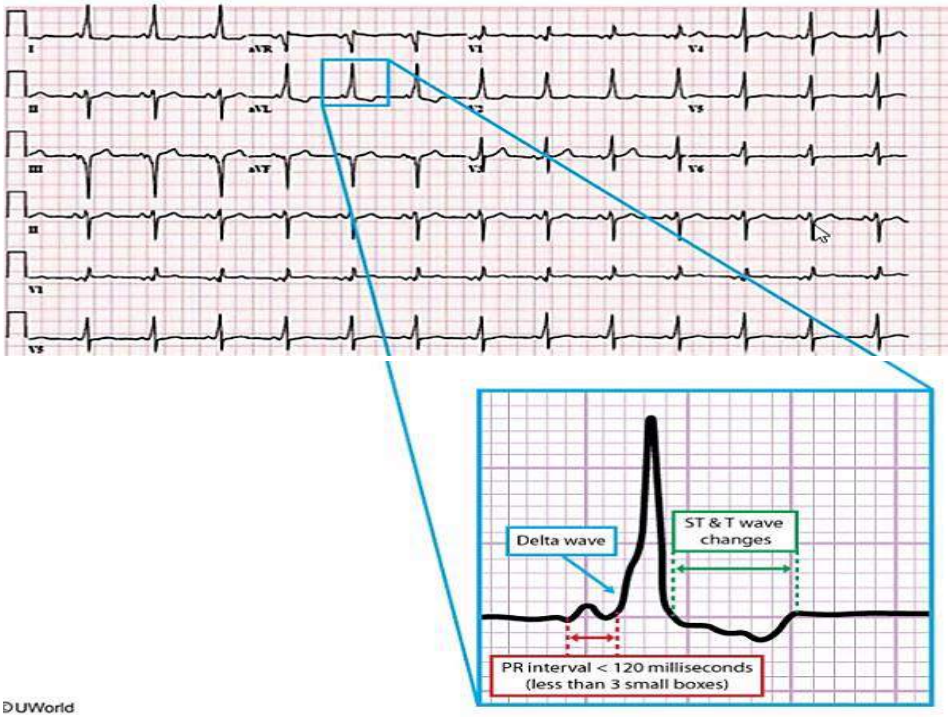
- Impaired SA node automaticity because of fibrosis and/or degeneration of SA node and surrounding myocardium
- **C/F:** fatigue, lightheadedness, palpitations, presyncope or syncope.
- **ECG:** bradycardia, sinus pauses/arrest, SA exit block, or alternating bradycardia and atrial tachyarrhythmias (tacharrhythmia-bradyarrhythmia syndrome)

WOLFF PARKINSON WHITE SYNDROME

- Accessory pathway conducts depolarization directly from atria to ventricle without travering AV node.
- A. fib occurs in 10-30% individual with WPW—potentially life threatening in these pts
- AF in these pts can bypass usual rate limiting function of AV node, leading to very **rapid ventricular response** rates.
- Persistent AF with rapid ventricular response in pts with WPW can ultimately deteriorate into **ventricular fibrillation**
- Acute treatment—prompt control of ventricular response and termination of AF as follows:
  1. **Hemodynamically unstable pts:** immediate **electrical cardioversion**
  2. **Stable pts:** rhythm control with anti-arrhythmic drugs such as IV ibutilide or **procainamide** is preferred
- **Contraindications:** AV blocking agents such as adenosine, beta blockers, calcium channel blockersesp verapamil and digoxin—as they can promote conduction across accessory pathway and degenerate AF into VF

Wolff-Parkinson-White Syndrome

Preexcitation of the ventricles via an abnormal bypass tract
- Short PR interval
- Presence of initial slow upstroke of the QRS complex (delta wave)
- ST and T wave abnormalities



- **PR** interval <0.12 sec, widened QRS complex

LONG QT SYNDROME

Causes of QT prolongation		
Acquired	**Electrolyte derangements**	• Hypocalcemia • Hypokalemia • Hypomagnesemia

	Medication-induced	• Macrolide antibiotics
		• Fluoroquinolone antibiotics
		• Psychotropic medications:
		  ○ Antipsychotics
		  ○ Tricyclic antidepressants
		  ○ Selective serotonin reuptake inhibitors
		• Opioids
		  ○ Methadone
		  ○ Oxycodone
		• Antiemetics
		  ○ Ondansetron
		  ○ Granisetron
		• Antiarrhythmics
		  ○ Quinidine
		  ○ Procainamide
		  ○ Flecainide
		  ○ Amiodarone
		  ○ Sotalol

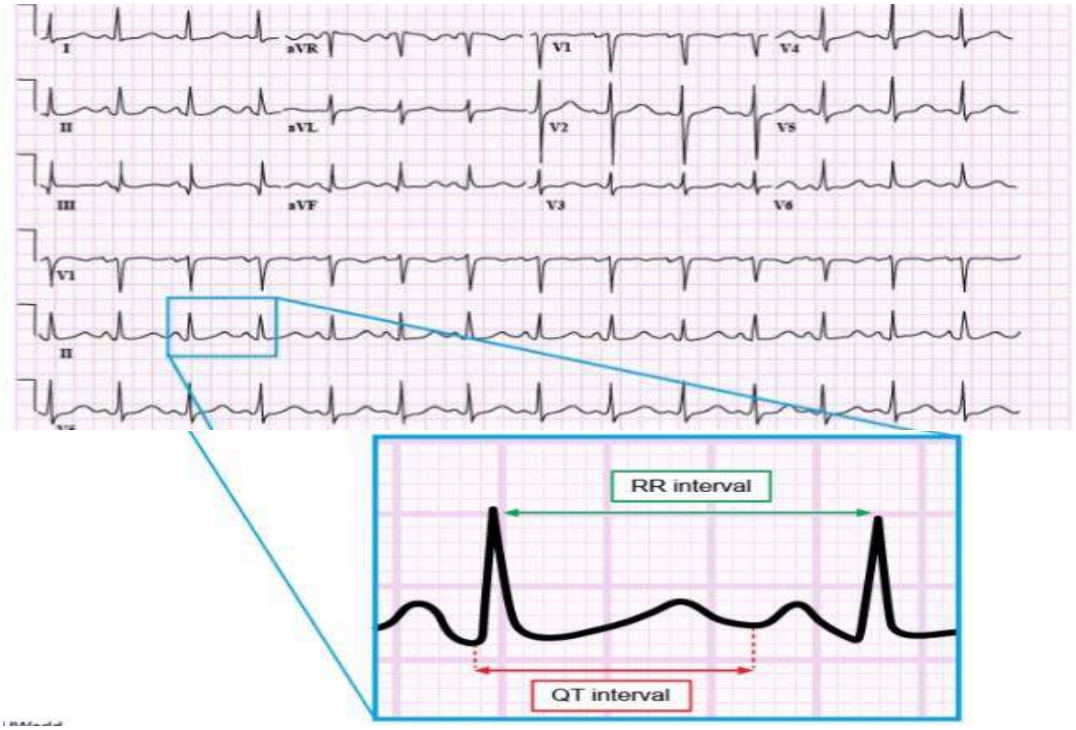
Inherited	• Jervell-Lange-Nielsen syndrome (autosomal recessive) • Romano-Ward syndrome (autosomal dominant)	

- **QT interval:** depolarization and repolarization of ventricles.
- **Normal duration:** variable but <440ms in males and <460ms in females
- **Jervell-Lange-Nielsen syndrome:**

1. FH of sudden death, congenital sensorineural hearing loss, QT ~600ms
2. high risk of syncope, life-threatening ventrcular arryhthmia like torsades and sudden death
3. Rx: refrain from vigorous exercise, avoid meds that prolong QT, maintain normal level of calcium, magnesium and potassium and pharmacotherapy. Beta blockers (class II antiarrhythmics) except sotalol blunt exertional heart rate and shorten QT interval and is the class of choice. Symptomatic pts (lightheadedness or palpitations) or those with h/o syncope require **beta blockers plus long term pacemaker placement**

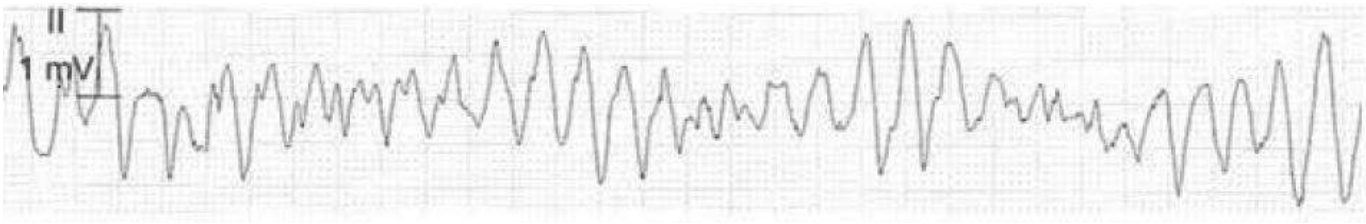
Causes of acquired long QT syndrome	
Medications	• Diuretics (due to electrolyte imbalances) • Antiemetics (eg, ondansetron) • Antipsychotics (eg, haloperidol, quetiapine, risperidone) • Tricyclic antidepressants • Selective serotonin reuptake inhibitors (eg, citalopram) • Antiarrhythmics (eg, amiodarone, sotalol, flecainide) • Antianginal drugs (eg, ranolazine) • Anti-infective drugs (eg, macrolides, fluoroquinolones, antifungals)
Metabolic disorders	• Electrolyte imbalances (↓K, ↓Mg, ↓Ca) • Starvation • Hypothyroidism
Bradyarrhythmias	• Sinus node dysfunction • Atrioventricular block (2nd or 3rd degree)
Others	• Hypothermia • Myocardial ischemia/infarction • Intracranial disease • HIV infection

- drugs (ABCDE)
  - class IA Antiarrhythmics (quinidine, procainamide, and disopyramide) due to ↑ QT interval
  - class III Antiarrhythmics (sotalol and ibutilide)
  - antiBiotics
  - antipsyChotics
  - antiDepressants
  - antiEmetics



TORSADES DE POINTES

1. Palpitations, pre-syncope, syncope, may resolve spontaneously or degenerate into ventricular fibrillation and sudden death
2. Rx: immediate defibrillation in hemodynamically unstable pt.
3. **Intravenous magnesium sulfate** is 1st line treatment for conscious and stable pt even if magnesium levels are normal; followed by identification and removal/correction of offending cause
4. If cause of Torsades de Pointes (TdP) is quinidine use→treat with sodium bicarb. Sodium bicarb is also used for cardiac arrest due to metabolic acidosis, hyperkalemia or TCAs overdose

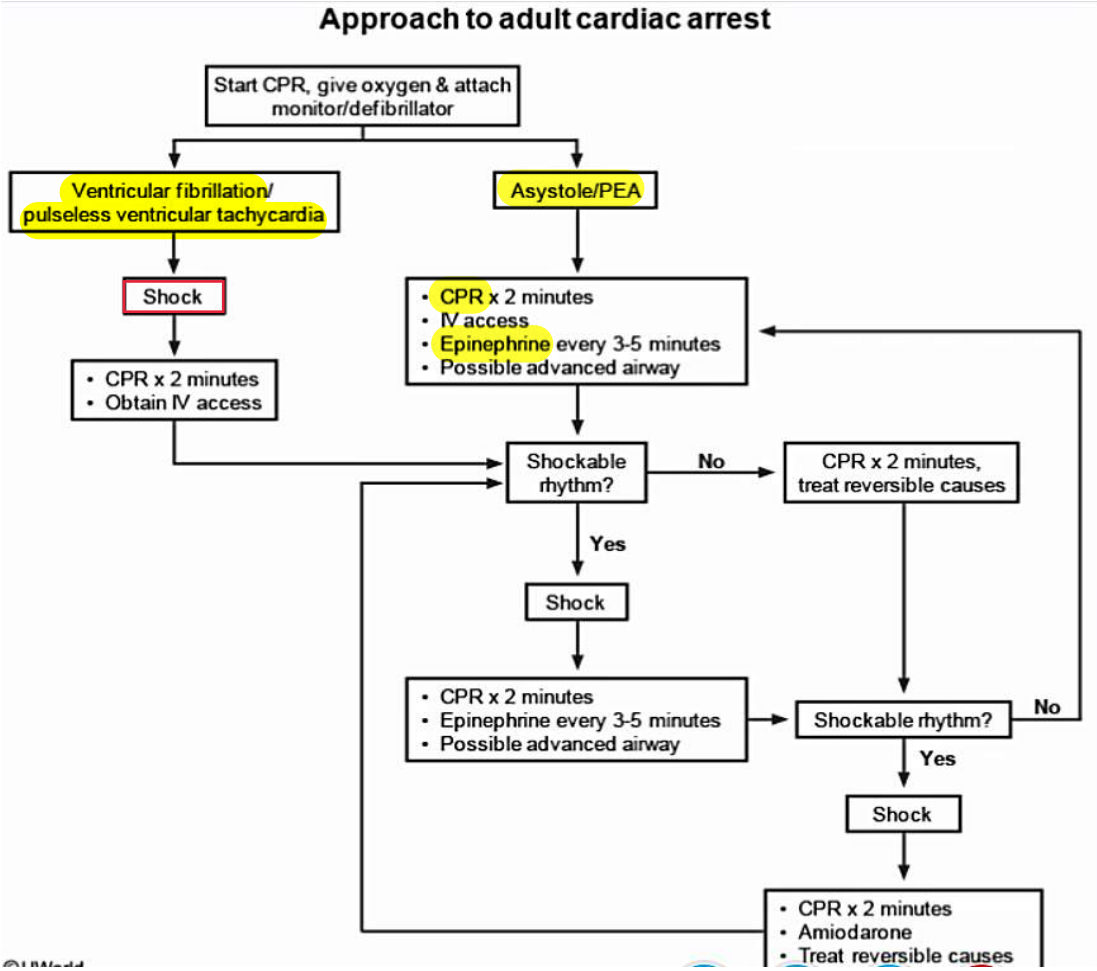


UW 2659

. polymorphic ventricular tachycardia in the setting of a prolonged QT interval

cyclic or sinusoidal alteration of QRS axis or morphology ("twisting of the points")
. around the isoelectric line

CARDIAC ARREST



- **Pulseless electrical activity (PEA)**

  → presence of organized rhythm on cardiac monitor ~~without measurable BP or~~ palpable pulse in cardiac arrest pt. →CPR and vasopressor (IV epinephrine 1mg/3-5min or a single dose vasopressin) to maintain adequate coronary and cerebral perfusion

  →**CPR** should be continued while attempts are made to identify and treat reversible causes of PEA (5Hs and Ts)

- **VF and sustained VT**—feared complication after MI, electrolyte imbalance, myocarditis, cardiomyopathy, drug side effect. ACLS algorithm for VF and pulseless VT, stresses the importance of early defibrillation. Energy required may be 200-360 joules. Greater the time after onset of VF and use of effective bystandard CPR, rhythm analysis and early defibrillator, lower the survival. In witnessed arrest <5min, defib should be performed immediately. If unwitnessed or witnessed arrest > 5min before arrival of defibrillator, a cycle of CPR should precede defibrillation. Studies in sudden cardiac arrest has shown better outcomes and improved survival to discharge with **compression only CPR** than standard CPR prior to arrival of emergency personnel

Reversible causes of asystole/pulseless electrical activity	
5 Hs	**5 Ts**
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade, cardiac
Hydrogen ions (acidosis)	Toxins (narcotics, benzodiazepines)
Hypo- or hyperkalemia	Thrombosis (pulmonary or coronary)
Hypothermia	Trauma

- **No role of synchronized cardioversion and defibrillation in PEA &/or asystole:**

➔ Synchronized cardioversion delivers energy synchronized to QRS complex—used in symptomatic or sustained monomorphic VT (unresponsive to antiarrhythmics) and hemodynamically unstable atrial fibrillation with rapid ventricular response.

➔ Defibrillation delivers energy randomly during cardiac cycle without synchronization to QRS complex. Needed for pulseless ventricular tachycardia and ventricular fibrillation

FACTORS ASSOCIATED WITH POOR OUTCOME AFTER WITNESSED OUT-OF-HOSPITAL SUDDEN CARDIAC ARREST

Factors associated with poor outcome after witnessed out-of-hospital sudden cardiac arrest
• Time elapsed prior to effective resuscitation (delayed bystander CPR, delayed defibrillation) • Initial rhythm of pulseless electrical activity or asystole • Prolonged CPR (>5 minutes) • Absence of vital signs • Advanced age • Prior history of cardiac disease • ≥2 Chronic illnesses • Persistent coma after CPR • Need for intubation or vasopressors • Pneumonia or renal failure after CPR • Sepsis, cerebrovascular accident, or class III or IV heart failure

CENTRAL VENOUS CATHETER

- Commonly used in pts with difficult vascular access and for long-term administration of medications

- **Complications:** occur in 1-5% cases and include: arterial puncture, pneumothorax, hemothorax, thrombosis, air embolism, sepsis, vascular perforation and myocardial perforation leading to tamponade.
- **CXR** should be obtained to confirm proper placement of catheter and absence of complications
- **To avoid myocardial perforation**, catheter tip should be located proximal to either cardiac silhouette or the angle between the trachea and the right mainstem bronchus. Ideally catheter tip should lie in superior vena cava. Tip placement in smaller vessels can cause perforation.

PULMONARY HYPERTENSION

- Defined as mean pulmonary arterial pressure of >/= 25mmHg at rest (normal <20mmHg)

WHO classification	• **Group 1 (PAH)**
	  ○ Due to idiopathic PAH
	• **Group 2**
	  ○ Due to left heart disease
	• **Group 3**
	  ○ Due to chronic lung disease (eg, COPD, ILD, chronic hypoxemia)
	• **Group 4**
	  ○ Due to thromboembolic occlusion of the pulmonary vasculature
	• **Group 5**
	  ○ Due to hematologic disorders (eg, myeloproliferative disorders), systemic conditions (eg, sarcoidosis), metabolic disorders (eg, glycogen storage disease), or miscellaneous causes

Symptoms	• Dyspnea, fatigue/weakness • Exertional angina • Syncope • Abdominal distention/pain
Signs signs similar to right sided heart failure	• Left parasternal lift or prominent right ventricular heave • Jugular venous distension • Loud P_2 in 2nd heart sound • Pansystolic murmur of tricuspid regurgitation • Right-sided 3rd heart sound (S_3) • Ascites and/or peripheral edema • Hepatomegaly • Cool extremities

Rx: endothelin receptor antagonist (eg bosentan), PDE5 inhibitor (eg sildenafil) and/or prostanoids (eg epoprostenol)

Rx: loop diuretics and ACEi or ARB, often with beta blockers and in some cases aldosterone antagonists

Rx: oxygen &/or bronchodilators

Rx: long term anticoagulation due to chronic thromboembolic occlusion

COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; WHO = World Health Organization;

- **Path:** hyperplasia of the intimal smooth muscle layer of the pulmonary arteries leading to increased pulmonary vascular resistance.
- The lung parenchyma is generally unaffected in PAH, which is evidenced by the absence of infiltrates on chest x-ray and **normal FEV1** and **FEV1/FVC** ratio on PFT.

ACUTE DYSPNEA IN HOSPITALIZED PATIENT

Acute dyspnea in the hospitalized patient		
Mechanism	**Risk factors**	**Clinical features**
Arrhythmia	• Cardiac disease • Electrolyte abnormalities	• Dizziness, palpitations • Tachycardia or bradycardia
Bronchoconstriction	• Asthma • Medications (eg, aspirin, beta blockers)	• Wheezing • Prolonged expiration
Congestive heart failure/hypervolemia	• Cardiac disease • Chronic kidney disease • Iatrogenic (fluids, blood products)	• Crackles • Elevated jugular venous pressure (>8 cm H2O) • Lower-extremity edema
Infection/pneumonia/ aspiration	• Chronic lung disease • Immunosuppression • Impaired mental status • Stroke/dysphagia	• Fever • Leukocytosis
Pleural effusion	• Congestive heart failure • Chronic kidney disease • Malignancy	• Decreased breath sounds • Dullness to percussion
Pulmonary embolism	• Prolonged immobility • Surgery (eg, hip/knee replacements)	• Tachycardia, tachypnea • Hypoxemia • Signs of deep venous thrombosis
Anxiety	• Dementia • Chronic mental illness • Sleep deprivation	• Tachycardia, tachypnea • Normal oxygenation/lung examination

- Aspirin is a common trigger for bronchoconstriction in pts with asthma, especially those with a concurrent chronic rhinitis and nasal polyps
- Cardioselective beta blockers→considered safe in pts with mild-moderate asthma but all can trigger bronchoconstriction at higher doses and should be used cautiously in asthmatics. Nebivolol is cardioselective
- In pleural effusion, there can be dec. movement of ipsilateral chest wall as well

THORACIC AORTA ANEURYSM Qid: 4129

- Asymtomatic or chest pain, back pain, flank pain or abdominal pain depending on location.
- 60% **Ascending aorta aneurysm:** arise anywhere from aortic valve to innominate artery (brachiocephalic a.). Cause: cystic medial degeneration (cox of aging) or connective tissue disease (eg Marfan and Ehler Danlos)

40% - **Descending aorta aneurysm:** distal to left subclavian—due to atherosclerosis; risk factor: HTN, hypercholestrolemia and smoking
- **CXR in TAA:** widened mediastinal silhoutte, ↑ aortic knob and tracheal deviaton. CXR cannot distinguish TAA from tortuous aorta—confirm with CT with contrast

ABDOMINAL AORTIC ANEURYSM

- **Normal diameter of AA= 1-3 cm** AAA=>3cm. unlike thoracic aortic aneurysm, it does not form false lumen and an intimal flap and is composed of all 3 layers
- Usually found incidentally and needs close follow up because rupture is life-threatening
- Imaging modality of choice: **abdominal ultrasound** (100% sensitivity and specificity, no need of contrast, inexpensive), facilitates measurement of aneurysm size and show presence of thrombus
- Screening: **men aged 65-75** who have **smoked cigarettes** have greatest benefit from screening—1 time abdominal USG in such pts is recommended
- **Risk factors for developing AAA:** older age (>60 yrs), cig. Smoking, FH of AAA, white race and atherosclerosis
- The **risk of AAA rupture increases** in pts with large aneurysm diameter (>/=5.5cm), aortic expansion rate >0.5cm/6mo and >1cm/year, female gender, current ongoing smoking and HTN (HTN has weak association with AAA formation and expansion and rupture)
- **Rupture of AAA present with:** profound hypotension, abdominal or back pain followed by syncope and examination may show pulsatile mass at or above level of umblicus. AAA can rupture in retroperitoneal space→form aortocaval fistula→venous congestion→ fragile and distended veins in bladder can rupture→gross hematuria
- screening and surgical repair of >/=5.5 cm aneurysm has shown to decrease mortality
- **indications for surgical repair or endovascular repair:** size >5.5cm, rapid rate of expansion >0.5cm/6mo and >1cm/year and presence of symtoms (abdominal, back or flank pain; limb ischemia) regardless of size
- risk of AAA formation and expansion is lower in diabetics than non-diabetics

➔ **Peripheral artery aneurysm:** popliteal AA-most common followed by femoral AA (located below inguinal ligament). Compress adjacent structures (nerves and veins) and can cause thrombosis and ischemia. Frequently associated with AAA

PERIPHERAL ARTERY DISEASE (PAD)

Clinical features of peripheral artery disease	
Etiologies	• Atherosclerosis due to risk factors (eg, diabetes, hyperlipidemia, hypertension, smoking, age >70) • Thromboangiitis obliterans (Buerger's disease)
Clinical presentation	**Asymptomatic (20%-50%)** **Physical examination findings** • ↓ or absent pulses below the level of stenosis • Occasional bruits over stenotic lesions • Poor wound healing in areas of diminished perfusion • Cool extremity with prolonged venous filling time • Shiny, atrophied skin with nail changes • Foot pallor with leg elevation (Buerger's test) **Specific pain patterns** • Buttock & hip pain (aortoiliac disease) ◦ Bilateral diminished or absent groin pulses, occasional bruits over iliac & femoral arteries, muscle atrophy & slow wound healing in legs ◦ Leriche's syndrome: Triad of erectile dysfunction, buttock & hip pain, absent femoral pulses on examination • Thigh pain (aortoiliac or common femoral disease): Normal groin pulses but decreased distal pulses • Calf pain (most common): Increasing pain with exertion & decreased with rest ◦ Upper 2/3 of calf (superficial femoral artery disease) ◦ Lower 1/3 of calf (popliteal artery disease) • Foot pain (tibial or peroneal artery disease)

- **Dx:** ankle-brachial index→abnormal→arterial duplex USG who are being considered for surgery
- **a supervised graded exercise** is the most useful intervention to improve functional capacity and reduce caludication- include minimum of 12 wks, with 30-45 min at least 3 times a wk. Goal: reproduction of claudication symptoms during each session
- **antiplatelet therapy (low dose asprin)** reduce risk of CAD
- **other measures for treating PAD:** smoking cessation, aggressive DM control (A1C <7%), and blood pressure control and **statins** as per recommendation
- **Cilostazol** should be considered in those with persistent symptoms despite anti-platelet therapy and supervised exercise programs
- **Percutaneous or surgical revascularization** is reserved for pts with limb threatening complications, significant limitation in activities of daily living, or failure to respond to exercise and pharmacologic therapy

Pt wiht PAD = start aspirin + lipid lowering therapy
then control other risk factors + excercise

cilostazol and percutaneous or surgical revascularization should be reserved for those with persistent symptoms despite adequate supervised exercise therapy

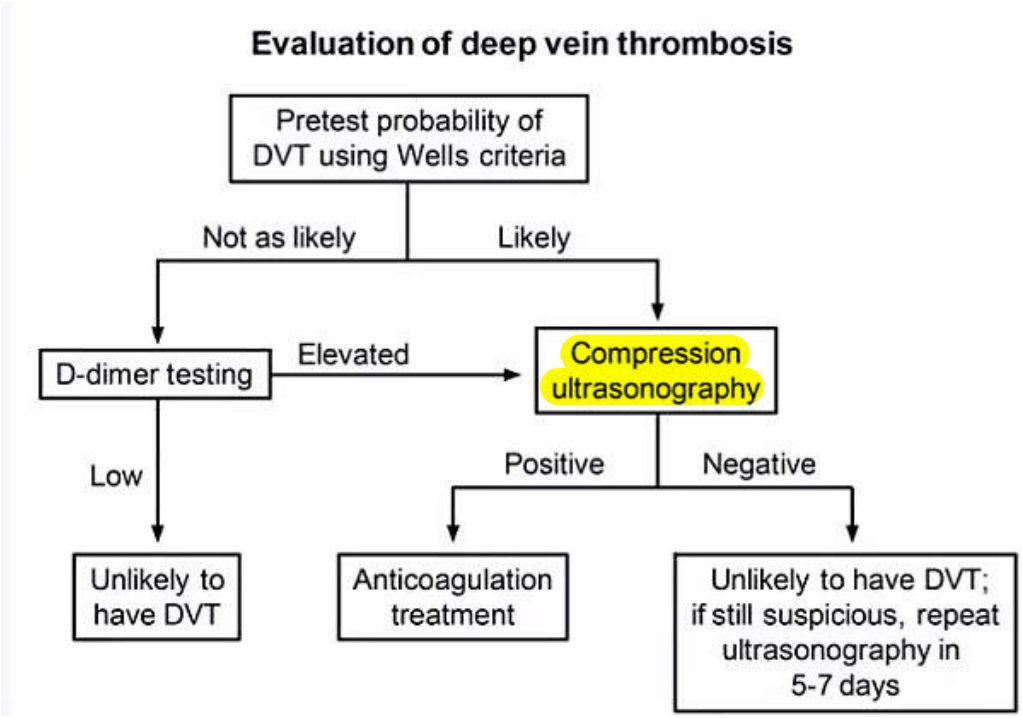
Ankle-brachial index interpretation	
Ankle-brachial index is calculated by dividing the higher ankle (dorsalis pedis or posterior tibial) systolic pressure in each lower extremity by the higher brachial artery (left or right) systolic pressure.	
ABI	**Interpretation**
≤0.90	Abnormal
0.91-1.30	Normal
≥1.30	Suggestive of calcified & uncompressible vessels; additional vascular studies should be considered

ABI = ankle-brachial index.

AORTOILIAC SYNDROME (LERICHE SYNDROME)

- Arterial occlusion at bifurcation of aorta into common iliac arteries
- Triad of: B/L hip, thigh and buttock claudication, impotence and symmetric atrophy of B/L lower extremities due to chronic ischemia. Impotence is almost always present in men and absence should lead to other diagnosis.
- Pulse is soft or absent B/L from groin distally and in the absence of thorough vascular examination, diagnosis can be missed
- Men with predisposition to atherosclerosis such as smoker are at greatest risk for this condition

DVT



- C/F: pain, swelling, discoloration of leg
- D/D: venous insufficiency, ruptured Baker's cyst, post-thrombotic syndrome, and cellulitis
- Rx: pt. with clinical evidence of PE (pleuritic chest pain, dyspnea, tachypnea, tachy cardia)→ begin anticoagulant therapy while undergoing diagnostic evaluation
- Pt. without PE and only DVT suspected →confirm diagnosis before anticoagulants
- Compression USG is the preffered initial test
- Proved DVT: begin anticoagulation with Heparin followed by warfarin, rivaroxaban or apixaban

Modified Wells criteria for pretest probability of DVT	
Score +1 points	• Previously documented DVT • Active cancer • Recent immobilization of the legs • Recently bedridden >3 days • Localized tenderness along vein distribution • Swollen leg • Calf swelling >3 cm compared to other leg • Pitting edema • Collateral superficial nonvaricose veins • Alternate diagnosis more likely (-2 points)
Total score for clinical probability	≤1: DVT unlikely ≥2: DVT likely

PULMONARY EMBOLISM

- **C/F:** pleuritic chest pain-does not improve with leaning forward, dyspnea, tachypnea, tachycardia, cough, hemoptysis, and/or lower extremity pain/swelling (suggesting DVT), prolonged immobility
- **CXR:** frequently abnormal in PE but has poor sensitivity and specificity. Atelectasis, infiltrates, pleural effusions, Westermark's sign (peripheral hyperlucency due to oligemia), Hampton's hump (peripheral wedge of lung opacity due to pulmonary infarction) and Fleishner's sign (enlarged pulmonary artery)

Modified Wells criteria for pretest probability of PE
Score +3 points • Clinical signs of DVT • Alternate diagnosis less likely than PE **Score +1.5 points** • Previous PE or DVT • Heart rate >100 • Recent surgery or immobilization **Score +1 point** • Hemoptysis • Cancer **Total score for clinical probability** ≤ 4 = PE unlikely > 4 = PE likely

Heparin is given if there is high probability of having PE

GUIDELINES FOR LIPID LOWERING THERAPY

Guidelines for lipid-lowering therapy	
Indication	**Recommended therapy**
Clinically significant atherosclerotic disease • ACS, MI • Stable or unstable angina • Coronary or other arterial revascularization • Stroke, TIA, PAD	• **Age ≤75:** High-intensity statin • **Age >75:** Moderate-intensity statin
LDL ≥190 mg/dL	**High-intensity statin**
Age 40-75 with diabetes	• **10-year ASCVD risk ≥7.5%:** High-intensity statin • **10-year ASCVD risk <7.5%:** Moderate-intensity statin
Estimated 10-year ASCVD risk ≥7.5% (Pooled Cohort Equations)	Moderate- to high-intensity statin*

ACS = Acute coronary syndrome; **ASCVD** = atherosclerotic cardiovascular disease; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **TIA** = transient ischemic attack.

* High-intensity statins include atorvastatin 40-80 mg, rosuvastatin 20-40 mg; moderate-intensity statins include atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg.

- there is no recommended LDL level, but it should be checked after starting statins to assess response and pt adherence

Cholesterol, serum	
Total	150-240 mg/dL
HDL	30-70 mg/dL
LDL	<160 mg/dL

DYSLIPIDEMIA / HYPERLIPIDEMIA

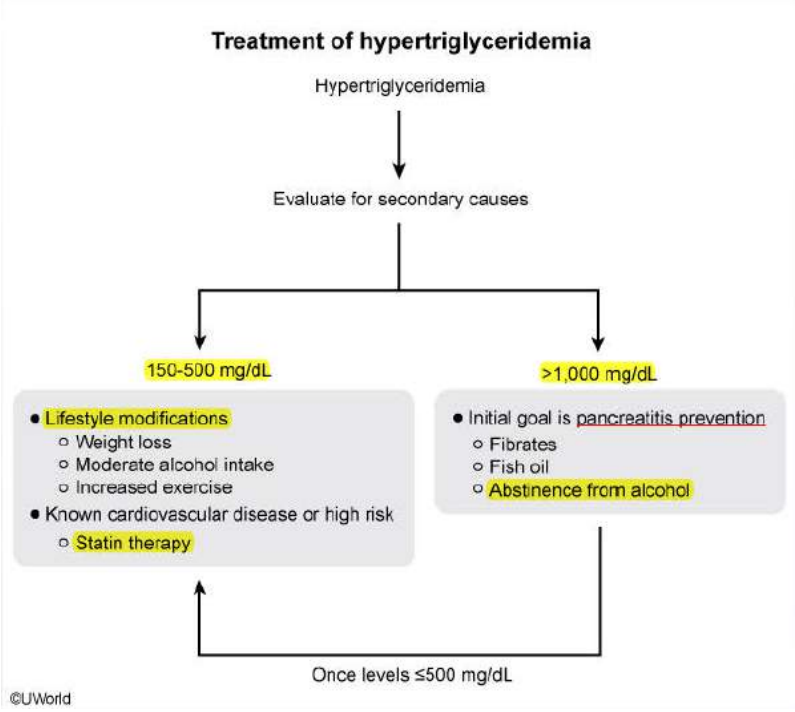
Drug	*Effect*	*Mechanism*	*Side Effect*
Statins	↓LDL ↓TG	HMG-CoA reductase	**Myositis LFT ↑**
Fibrates	↓TG ↑HDL	Lipoprotein Lipase	**Myositis LFT ↑**
Ezetimibe	↓LDL	Cholesterol Absorption	**Diarrhea**
Niacin	↑HDL ↓LDL	↓ Fatty Acid Release ↓ LDL Synthesis	Flushing (treat with ASA)
Bile Acid Resins	↓LDL	Bile Acid Reabsorption	**Diarrhea**

Look in a vignette for signs of hepatotoxicity or myositis as a reason to STOP a statin. Get a **CK** for **Myositis**.

- Niacin therapy to treat lipid abnormalities frequently produces cutaneous flushing and pruritus. This side effect is explained by **prostaglandin**-induced peripheral **vasodilatation** and can be reduced by low-dose aspirin. (niacin is never the answer in dyslipidemia Qs)

HYPERTRIGLYCERIDEMIA

Triglycerides, serum	35-160 mg/dL



CHOLESTEROL CRYSTAL EMBOLISM

Cholesterol crystal embolism (atheroembolism)	
Risk factors	• Comorbid conditions (hypercholesterolemia, hypertension, type 2 diabetes mellitus) • **Cardiac catheterization** or vascular procedure
Clinical features	• Dermatologic (**livedo reticularis**, ulcers, gangrene, **blue toe syndrome**) • Renal (**acute or subacute kidney injury**) • Central nervous system (stroke, amaurosis fugax) • Ocular involvement (**Hollenhorst plaques**) • Gastrointestinal (intestinal ischemia, pancreatitis)
Diagnosis	• **Laboratory findings** ◦ Elevated serum creatinine, **eosinophilia**, hypocomplementemia ◦ Urinalysis – typically benign with few cells or casts, may have **eosinophiluria** • **Skin or renal biopsy** ◦ Biconvex, needle-shaped clefts within occluded vessels ◦ Perivascular inflammation with eosinophils

- Can be immediate or delayed (>/= 30 days after inciting event)
- Advanced age, smoking and obesity are also risk factors
- Skin manifestations are most common. **Blue toe syndrome**: cyanotic toes with intact pulses. **Livedo reticularis:** blanches with pressure application
- Hollenhost spots: bright, yellow, refractile plaques in retinal artery
- Some may have persistent renal failure >2wks in contrast to dye induced renal injury which usually resolves in <1wk
- Rx: supportive and reinforces the use of statin therapy

ACUTE LIMB ISCHEMIA

- Occurs from arterial occlusion caused by cardiac emboli, thrombosis (eg vascular stents, hypercoagulable state) or trauma. Major cardiac sources of arterial emboli:
  1. LV thrombus
  2. Thrombus (usually left atrial) fromation due to a. fib
  3. Aortic atherosclerosis
- Pts with **large anterior ST- elevation MI (STEMI)** are at highest risk of LV thrombus and anteroapical anuerysm formation
- Acute arterial occlusion of extremity leads to **6Ps**: pain, pallor, poikilothermia (cool extremity), paresthesia, pulselessness and paralysis
- Immediately start on **anticoagulation** and vascular surgery evaluation while further diagnostic procedures are performed. IV heparin prevent further thrombus propagation and thrombosis is distal

arterial and venous circulation. **Transthoracic echocardiogram** with echo contrast must be performed to screen LV thrombus and evaluate LV function

CAROTID ENDARTERECTOMY

- lesion <50% are typically monitored with annual Duplex USG. They are medically managed at this stage with pharmacotherapy (eg antiplatelet agents and statins) and risk factor optimization (eg. tobacco cessation, DM and HTN control)
- asymptomatic carotid artery stenosis can progress to TIA or embolic stroke
- Symptomatic means: occurence within past 6 months of sudden onset focal neurological symptoms corresponding to a carotid artery lesion

Indications for carotid endarterectomy	
Men	**Asymptomatic:** • 60-99% stenosis **Symptomatic:** • 50-69% stenosis (Grade IIA) • 70-99% stenosis (Grade IA)
Women	**Both symptomatic & asymptomatic:** • 70-99% stenosis

Carotid endarterectomy **(CEA)** is recommended for men and women with **symptomatic** carotid stenosis of **70%-99%** and is also beneficial for men with **asymptomatic** carotid stenosis of **60%-99%.**

NEW GUIDELINES

1. <70% **or** asymptomatic = medical ttt

2. >70% + Sx **or** >80% = Endartectomy

SYNCOPE

Syncope	
Likely etiology	**Clinical clues to diagnosis**
Vasovagal or neurally mediated syncope	Triggers: Prolonged standing or emotional distress, painful stimuli Prodromal symptoms: nausea, warmth, diaphoresis
Situational syncope	Triggers: Cough, micturition, defecation
Orthostatic syncope	Postural changes in heart rate/blood pressure after standing suddenly
Aortic stenosis, HCM, anomalous coronary arteries	Syncope with exertion or during exercise
Ventricular arrhythmias	Prior history of CAD, MI, cardiomyopathy, or ↓ EF
Sick sinus syndrome, bradyarrhythmias, atrioventricular block	Sinus pauses, ↑ PR or ↑ QRS duration
Torsades de pointes (acquired long QT syndrome)	Hypokalemia, hypomagnesemia, medications causing ↑ QT interval
Congenital long QT syndrome	Family history of sudden death, ↑ QT interval, syncope with triggers (eg, exercise, startle, sleeping)

- Syncope is defined as a **transient** loss of consciousness accompanied by loss of postural or motor tone with a **spontaneous return** to baseline neurologic function.
(It is usually benign and self-limiting)

- Clonic jerks can occur during any syncopal episode that is prolonged and associated with cerebral hypoxia, regardless of etiology.

- Transient ischemic attacks (TIAs) are an infrequent cause of syncope, as the TIA must affect the posterior circulation and brainstem to cause syncope.

VASOVAGAL SYNCOPE

Overview of vasovagal syncope	
Inciting events	**Age <60 years:** • Emotional/orthostatic stress (eg, venipuncture, prolonged standing, heat exposure, exertion) **Age >60 years:** • May also be triggered by micturition, cough & defecation
Symptoms	• Prodrome of pallor, dizziness, nausea & diaphoresis • Short duration of syncope (seconds to few minutes) • Symptoms improve with supine position
Diagnosis	• Mainly clinical diagnosis • Upright tilt table testing in uncertain cases
Treatment	Preventive measures to avoid triggering activities (eg, prolonged standing)

- most common due to excessive vagal tone. Also known s neurocardiogenic syncope.
- Particularly common in young women
- Beingn and self-limited in most cases
- diagnosis is usually clinical and needs no further testing if history and physical exam point strongly toward the diagnosis and resting ECG is normal.
- During upright tilt table test, pt lies down, strapped on an examination table. Continuous ECG and BP monitoring are used throughout the test. Exam table moves passively from a supine to a head-up position between 60* to 90*. Pt is held in this position for 20-45 min. If there are signs of unconsciousness (e.g syncope, inability to maintain posture due to fall in BP or pulse), diagnosis is confirmed and test is stopped. Test has limited sensitivity and specificity

CAROTID SINUS HYPERSENSITIVITY SYNDROME

- Syncopal episodes triggered by neck movement or pressure on carotid sinus by tight neck collars.
- This is a cause of unexplained falls in older adults (>40yrs).
- Carotid sinus massage is considered diagnostic if pt develops asystole >3 seconds, a fall in systolic BP >50 mmHg, and/or reproduction of symptoms (eg, syncope)

SITUATIONAL SYNCOPE

- Specific situation like micturition or coughing fit can lead to syncope commonly in middle age or older male.
- **MOA**: autonomic dysregulation which can partially be explained by straining and rapid bladder emptying. Cardioinhibitory and/or vasodepressor mechanisms may be involved

ORTHOSTATIC HYPOTENSION

- Drop in systolic BP >20mmHg and diastolic >10mmHg on standing from sitting position within 2-5min of standing from supine position

• Reasons for the increased incidence of orthostatic hypotension in the **elderly.**

- Due to **decreased baroreceptor sensitivity** leading to decreased constriction of resistance and capacitance vessels, **dec. intravscular volume/hypovolemia, meds,** dec. catecholamines in nerve endings, decreased myocardial sensitivity to sympathetic stimulation. Autonomic neuropathy (e.g diabetes and Parkinson disease), elderly and prolonged recumbence increases risk.
- People often note pre-syncopal lightheadedness sensation
- ↑BUN and BUN/creatinine ratio is a sensitive but not specific indicator of hypovolemia. It is because of ↓ GFR and ↑ urea reabsorption. BUN/creatinine ratio ↑ with increasing severity of hypovolemia
- Urine Na+ (esp if pt is on diuretic as well), blood K+, lactic acidosis are not sensitive indicators of hypovolemia.

sensitive for hypovolemia: 1.BUN
2. urnie Na (unless taking diuretic)

AORTIC STENOSIS

- Syncope, fatigue, ↓ pulse pressure, pulsus parvus et tardus, crescendo-decrescendo murmur at right upper sternal border, soft and single S2 due to delayed A2 and reaching P2, hence a single, soft murmur is heard
- Early peaking systolic murmur—mild to moderate stenosis
- Late peaking systolic murmur—severe AS

PULSUS PARVUS ET TARDUS

- Arterial pulse with decreased amplitude and delayed peak
- Common in severe aortic stenosis

AORTIC REGURGITATION

Aortic regurgitation	
Common causes	• Aortic root dilation (eg, Marfan syndrome, syphilis) • Post-inflammatory (eg, rheumatic heart disease, endocarditis) • Congenital bicuspid aortic valve
Pathophysiology	• Backflow from aorta into LV → **↑ LVEDV** Compensatory myocardial hypertrophy & ventricular enlargement initially maintain stroke volume & cardiac output • Excessive LV stretching later leads to ↓ stroke volume, ↓ forward blood flow & systolic heart failure • **↑ Left ventricular end diastolic pressure** → pulmonary congestion
Clinical features	• **Diastolic decrescendo murmur** • **Widened pulse pressure** (↑systolic blood pressure, ↓diastolic blood pressure) • Collapsing/water hammer pulse • Heart failure signs/symptoms

- Murmur is high pitched, blowing, and best heard along left lower sternal border

- May be soft and heard in some patients only by applying firm pressure with the diaphragm while pt is sitting up, leaning forward and holding breath in full expiration
- Left ventricular enlargement brings apex close to chest wall and causes uncomfortable sensation of heart beat and pounding sensation esp. in left lateral decubitus position
- Water hammer pulse is also called Corrigan pulse
- **Developed countries** most common cause: bicuspid aortic valve or aortic root dilation
- **Developing countries**: rheumatic fever

PULSUS BISFERIENS (OR BIPHASIC PULSE)

- Two strong systolic peaks or aortc pulse from left ventricular ejection separated by a midsystolic dip.
- Can be palpated in pts with significant aotic regurg. with or without stenosis, HOCM, and occasionally large PDA

Common causes of aortic regurgitation	
Aortic valve leaflet disease	• Rheumatic heart disease • Endocarditis • Bicuspid aortic valve • Trauma • Myxomatous degeneration • Ankylosing spondylitis • Acromegaly • Medications (e.g., fenfluramine-phentermine)
Ascending aorta or aortic root disease	• Hypertension • Aortitis (e.g., syphilis) • Ankylosing spondylitis • Dissecting aneurysm • Ehlers-Danlos • Inflammatory bowel disease • Reactive arthritis • Marfan syndrome

INFECTIVE ENDOCARDITIS

Vascular & immunologic manifestations of infective endocarditis	
Vascular phenomena	• Systemic emboli (cerebral, pulmonary, or splenic infarcts) • Mycotic aneurysm • Janeway lesions – Macular, erythematous, **nontender** lesions on the palms & soles
Immunologic phenomena	• Osler nodes – **Painful**, violaceous nodules seen on the fingertips & toes • Roth spots – Edematous & hemorrhagic lesions of the retina

- Abnormal urine (proteinuria and/or hematuria) and swollen interphalangeal joints (arthritis)
- Extensive evaluation is needed for definitive diagnosis

- Empiric treatment with **vancomycin** after obtaining blood cultures (cover staph, strep and enterococci)
- Most **viridans group streptococci** are highly susceptible to penicillin with minimum inhibitory conc. </= 0.12µg/ml.
- Penicillin susceptible strains should be treated with **IV aqueous penicillin G (**every 4-6 hours or 24 hours continuous infusion) or IV **ceftriaxone** (once daily) for **4 weeks.** Ceftriaxone is easier to administer at home due to once-daily dosing
- Oral antibiotics are generally not recommended as initial therapy in patients with IE. Can be considered in some patients but then combination therapy is given rather than monotherapy

COMPLICATIONS OF INFECTIVE ENDOCARDITIS

Complications of infective endocarditis	
Cardiac	• Valvular insufficiency – common cause of death • Perivalvular abscess • Conduction abnormalities • Mycotic aneurysm
Neurologic	• Embolic stroke • Cerebral hemorrhage • Brain abscess • Acute encephalopathy or meningoencephalitis
Renal	• Renal infarction • Glomerulonephritis • Drug-induced acute interstitial nephritis from therapy
Musculoskeletal	• Vertebral osteomyelitis • Septic arthritis • Musculoskeletal abscess

RHEUMATIC FEVER

Antibiotic prophylaxis for rheumatic fever	
The preferred antibiotic for prophylaxis is intramuscular benzathine penicillin G every 4 weeks.	
Associated condition	**Duration of antibiotic therapy**
Rheumatic fever without carditis	5 years or until 21 years old (whichever is longer)
Rheumatic fever with carditis but no residual heart or valvular disease by clinical or echocardiographic criteria	10 years or until 21 years old (whichever is longer)
Rheumatic fever with carditis & persistent heart or valvular disease	10 years or until 40 years old (whichever is longer)

- All pts with initial diagnosis of rheumatic fever should be treated with antibiotic therapy to eradicate GAS regardless of presence or absence of pharyngitis at the time of diagnosis
- Pts with h/o RF are at increased risk of recurrence and progression of RHD with repeat episodes of GAS pharyngitis
- Mitral stenosis is almost always due to RF. Pts with symptomatic MS need preload reduction with diuretcs or nitrates and not afterload reduction with ACEi etc

MARFAN SYNDROME

Clinical features of Marfan syndrome	
Skeletal	• Arachnodactyly • ↓ Upper-to-lower body segment ratio, ↑ arm-to-height ratio • Pectus deformity, scoliosis, or kyphosis • Joint hypermobility
Ocular	• Ectopia lentis
Cardiovascular	• Aortic dilation, regurgitation, or dissection • Mitral valve prolapse
Pulmonary	• Spontaneous pneumothorax from apical blebs
Skin	• Recurrent or incisional hernia • Skin striae

AORTIC DISSECTION

Clinical features of aortic dissection	
Risk factors/ associations	• Hypertension (most common) • Marfan syndrome • Cocaine use
Clinical features	• Severe, sharp, tearing chest or back pain • >20 mm Hg variation in systolic blood pressure between arms
Complications (involved structure)	• Stroke (carotid arteries) • Acute aortic regurgitation (aortic valves) • Horner's syndrome (superior cervical sympathetic ganglion) • Acute myocardial ischemia/infarction (coronary artery) • Pericardial effusion/cardiac tamponade (pericardial cavity) • Hemothorax (pleural cavity) • Lower-extremity weakness or ischemia (spinal or common iliac arteries) • Abdominal pain (mesenteric artery)

- 50% cases in ppl <40 years are due to Marfan syndrome but HTN is most common risk factor seen in 75% patients
- Pts with aortic dissection &/or progressive aortic root dilation can develop aortic regurgitation murmur heard best at left lower sternal border with pt sitting up and leaning forward and holding breath after full expiration—aortic dissection murmur is heard better on **right** sternal border compared to left for primary valvular disease.
- Pain can also radiate to neck
- **Stanford type A**: involve ascending aorta
- **Stanford type B**: involve only descending aorta
- Acute, type A aortic dissection can occasionally cause occlusion of right coronary artery by dissection flap, leading to inferior MI. aortic dissection can extend into renal arteries leading to acute renal failure
- **Rx:**

➔ **Type A:** acute lowering of BP with **Labetalol** + surgery

➔ **Type B:** usually managed with Labetalol alone

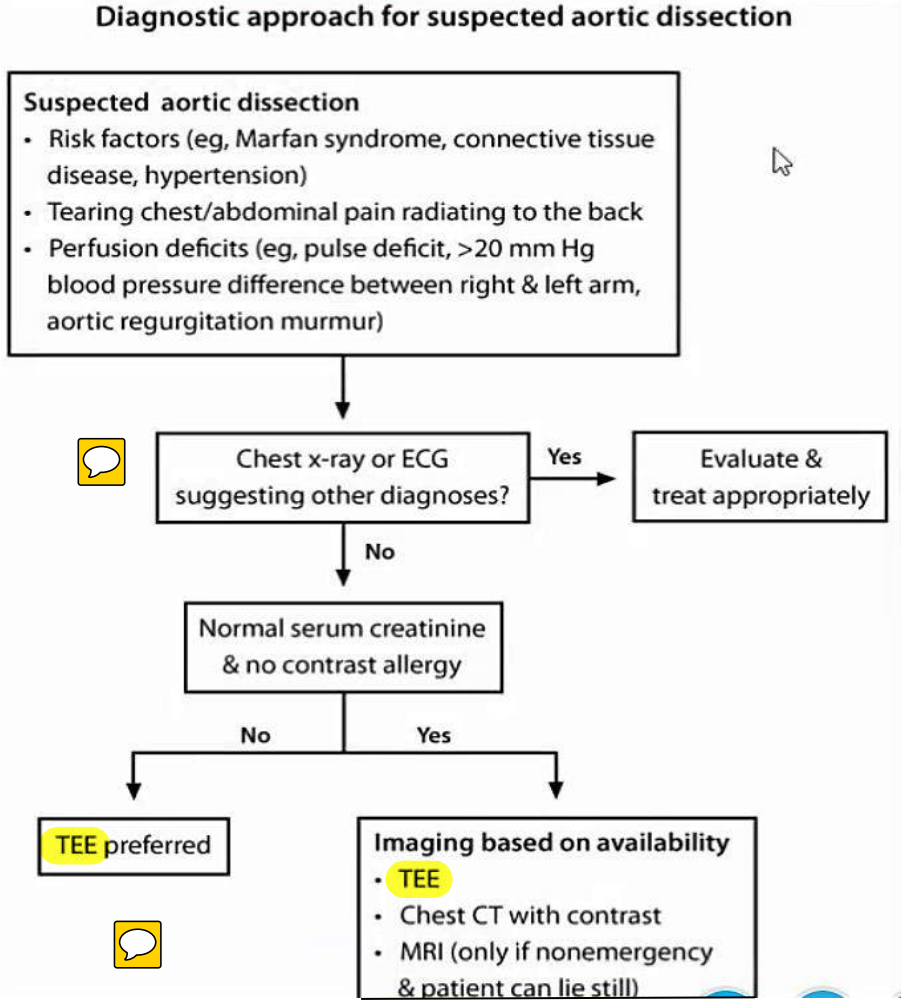
- **MANAGEMENT:**

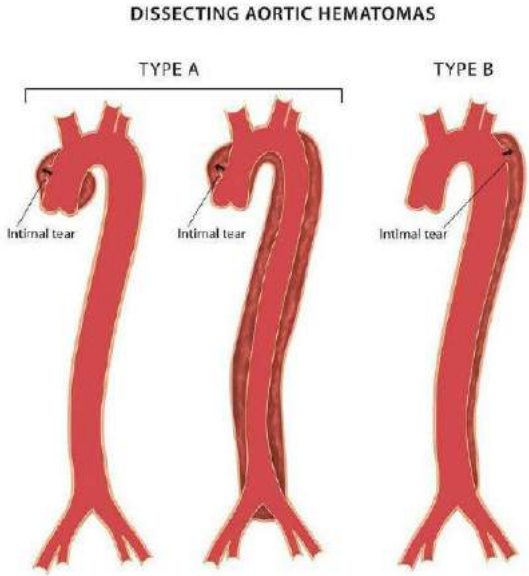
1. Even if transthoracic echo has been performed, transesophageal echo is performed in emergency room to confirm the diagnosis as it is more sensitive and specific and help visualize ascending, transverse and descending aorta. CT and MRI are alternatives if emergency TEE is not available
2. **Beta blockers** are used as they decrease heart rate and BP , minimizing stress on aortic wall

- **Vasodilators** should not be used as they can cause reflex tachy further increasing stress on walls. Only use if further BP is to be lowered after beta blockers already given
- **Anticoagulants and fibrinolytics** should never be used

3. Emergency pericardiocentesis is needed in those who are not hemodynamically stable

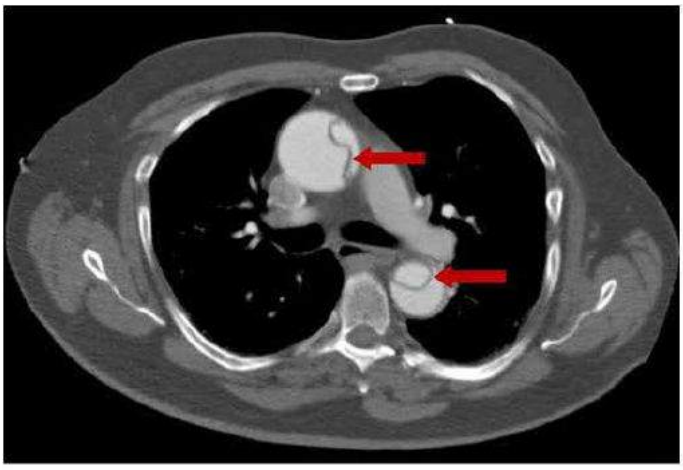
Diagnostic approach for suspected aortic dissection





Management of patients with acute aortic dissection

- Pain relief with morphine
- Intravenous beta blockers for a target systolic blood pressure of 100-120 mm Hg
- Transfer to intensive care unit
- Initiate additional vasodilator (eg, sodium nitroprusside) if systolic blood pressure remains elevated
- Surgery for acute ascending aortic dissections & complicated descending aortic dissections



HOLT-ORAM SYNDROME (HEART HAND SYNDROME)

- Both upper limb defects (e.g. deformities of radius and carpal bone) and atrial septal defect

ALCOHOL WITHDRAWAL

Alcohol withdrawal syndrome		
Manifestations	**Symptoms/signs**	**Onset since last drink (hours)**
Mild withdrawal	Anxiety, insomnia, tremors, diaphoresis, palpitations, gastrointestinal upset, intact orientation	6-24
Seizures	Single or multiple generalized tonic-clonic	12-48
Alcoholic hallucinosis	Visual, auditory, or tactile; intact orientation; stable vital signs	12-48
Delirium tremens	Confusion, agitation, fever, tachycardia, hypertension, diaphoresis, hallucinations	48-96

HYPERTENSION

Hypertensive complications	
Hypertensive urgency	• Severe hypertension (usually ≥180/120 mm Hg) with no symptoms or acute end-organ damage
Hypertensive emergency	Severe hypertension with acute, life-threatening, end-organ complications • **Malignant hypertension**: Severe hypertension with retinal hemorrhages, exudates, or **papilledema** • **Hypertensive encephalopathy**: Severe hypertension with cerebral edema & non-localizing neurologic symptoms & signs

- Malignant HTN common in long standing and uncontrolled HTN.
- In malignant HTN, there can also be malignant nephrosclerosis (ARF, hematuria and proteinuria). However, these are not always present and not diagnostic criteria

HYPERTENSIVE EMERGENCY

- Severe HTN +end organ failure
- BP should be lowered 10-20% in 1st hour and 5-15% in next 23 hours
- Excessive drop in BP→ cerebral ischemia e' altered mental status and/or generalized seizures

HYPERTENSIVE ENCEPHALOPATHY

- Inc BP with signs and symptoms of cerebral edema
- C/f: headache, nausea, vomiting, nonlocalizing neurological symptoms, restlessness, confusion, agitation, seizures and coma. Pt can also develop intracerebral or subarachnoid hemorrhage

WORK-UP OF HYPERTENSION

- Most people have essential HTN, but initial evaluation should assess possible secondary causes.
- Basic work up includes:

1. Investgating duration of HTN, extent of target organ damage and cardiovascular risk factors

2. Basic labs include:

➔ **Urinanalysis** (for occult hematuria and protein/creatinine ratio)

➔ **Chemistry panel**

➔ **Lipid profile** (risk stratification for coronary artery dis)

➔ **Baseline ECG(**to evaluate for coronary artery dis. Or left ventricular hypertrophy)

➔ Further evaluation is needed for those with signs/symptoms of possible 2° HTN

TREATMENT OF HYPERTENSION

JNC 8 recommendations for treating hypertension		
	Initiate Rx	**Goal BP**
Age ≥60	≥150 mm Hg systolic BP **or** >90 mm Hg diastolic BP	<150/90 mm Hg
Age <60, chronic kidney disease, diabetes	≥140 mm Hg systolic BP **or** >90 mm Hg diastolic BP	<140/90 mm Hg

Initial treatment choice	Black	Thiazide diuretic or CCB, alone or in combination (ACE/ARB not first-line)
	Other ethnicities	Thiazide diuretic, ACEI, ARB, or CCB alone or in combination
	All ethnicities with chronic kidney disease or diabetes	ACEI or ARB, alone or combined with other drug classes

➔ **Isolated systolic hypertension initial treatment:** monotherapy with low dose thiazide diuretic, ACEi or a long acting calcium channel blocker

➔ Systolic HTN can also occur in hyperthyroidism because of hyperdynamic state. Signs of hyperdynamic state: ventricular heave or dynamic precordium upon examination

➔ Most common features of mitral regurgitation are exertional dyspnea and fatigue 2* to decreased cardiac output annd inc. left atrial pressure. Dry cough can occur in case of LV dysfunction in more severe cases causing pulmonary congestion and edema

Treatment of hypertension		
Modification	**Recommended plan**	**Approximate ↓ systolic BP (mm Hg)**
Weight loss	Reduce BMI <25 kg/m^2	5-20 per 10 kg loss
DASH diet	Diet high in fruits and vegetables and low in saturated fat and total fat	8-14
Exercise	30 minutes/day for 5-6 days/week	4-9
Dietary sodium	<3 g/day	2-8
Alcohol intake	2 drinks/day in men and 1 drink/day in women	2-4

- Most effective method to control HTN is life-style modification
  1. reducing weight is most imp in obese pts
  2. DASH diet is most imp. In non-obese pts. This has more importance than low sodium diet to lower BP

ANTI-HYPERTENSIVES IN PREGNANCY

Antihypertensive medications in pregnancy		
First-line (safe)	**Second-line**	**Contraindicated**
• **Methyldopa** • Beta blockers **(labetalol)** • **Hydralazine** • Calcium channel blockers (nifedipine)	• Thiazide diuretics • Clonidine	• ACE inhibitors • Angiotensin receptor blockers • Aldosterone blockers • Direct renin inhibitors • Furosemide

CALCIUM CHANNEL BLOCKERS AND PERIPHERAL EDEMA

- CCB cause preferential dilation of pre-capillary vessels (arteriolar dilation)→increase hydrostatic pressure in capillaries→ edema
- Also cause headache, flushing and dizziness
- ACEi or ARBs cause dilation of post capillary venules and when used in combination with CCBs, there is lower risk of CCB associated peripheral edema, by normalizing capillary pressure.

CYANIDE TOXICITY

- Nitroprusside (quick onset and offset and used in hypertensive emergency) if given for longer time or in higher doses can cause this esp in renal insufficiency
- C/F: altered mental status, lactic acidosis, seizures and coma

BETA-BLOCKER TOXICITY

Qid: 2663

- Bradycardia, hypotension, AV block, cardiogenic shock, **wheezes** cox of bronchospasm, hypoglycemia, neurologic like delirium, seizures etc. AV block, hypotension and bradycardia can occur with CCB, anticholnergics and digoxin too
- **Management:**
  1. Secure airway
  2. **Give isotonic fluid boluses and IV atropine** for hypotension and bradycardia
  3. **IV glucagon** if refractory or profound hypotension→ ↑cAMP and effective in BB and CCB toxicity
  4. Other therapies that can be used simultaneously or in succession: IV calcium, vasopressor (epinephrine or NE), high dose insulin and glucose and IV lipid emulsion therapy

SECONDARY CAUSES OF HTN

Secondary causes of hypertension

Condition	Clinical clues/features
Renal parenchymal disease	• Elevated serum creatinine • Abnormal urinalysis (proteinuria, red blood cell casts)
Renovascular disease	• Severe hypertension (≥180 mm Hg systolic &/or 120 mm Hg diastolic) after age 55 • Possible recurrent flash pulmonary edema or resistant heart failure • Unexplained rise in serum creatinine • Abdominal bruit
Primary aldosteronism	• Easily provoked hypokalemia • Slight hypernatremia • Hypertension with adrenal incidentaloma
Pheochromocytoma	• Paroxysmal elevated blood pressure with tachycardia • Pounding headaches, palpitations, diaphoresis • Hypertension with an adrenal incidentaloma
Cushing syndrome	• Central obesity, facial plethora • Proximal muscle weakness, abdominal striae • Ecchymosis, amenorrhea/erectile dysfunction • Hypertension with adrenal incidentaloma
Hypothyroidism	• Fatigue, dry skin, cold intolerance • Constipation, weight gain, bradycardia
Primary hyperparathyroidism	• Hypercalcemia (polyuria, polydipsia) • Kidney stones • Neuropsychiatric presentations (confusion, depression, psychosis)
Coarctation of the aorta	• Differential hypertension with brachial-femoral pulse delay

- **All** pts with resistant HTN, severe or malignant HTN, sudden BP rise in a pt with previously controlled BP, age of onset <30 years without family h/o HTN should be screened for 2* causes of HTN
- **Resistant HTN:** persistant HTN despite using >/=3 antihypertensive agents of different classes (one being a diuretic)
- Significant HTN with primary hyperparathyroidism suggest possible evaluation of MEN2 with pheochromocytoma

RENOVASCULAR HTN/ RENAL ARTERY STENOSIS

- Most common and most correctable cause of 2° HTN
- Not responsive to antihypertensives
- **Should be suspected and evaluated in following cases + those in table above:**
  1. ↑serum creatinine **>30% from baseline** after starting ACEi or ARB
  2. Severe HTN in pts with diffuse atherosclerosis
  3. HTN in a pt with **asymmetric kidney size** or a small atrophic U/L kidney
- Esp. common in pts with h/o atherosclerotic dis. And abdominal bruit
- Systolic-diastolic bruit is heard in this case (only systolic bruit is heard in AAA)-99% specific and 40% sensitive

→ **Difference in BP in arms:**

- **>** in Left than right: subclavian atherosclosis
- **>** in right arm than left: coarctation proximal to left subclavian artery origin
- In case of aortic dissection but chest pain radiating to back is also present

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease	
Symptoms	• Most patients are asymptomatic • Hematuria • Flank pain (nephrolithiasis, infection, cyst rupture, hemorrhage)
Clinical signs	• Hypertension • Palpable abdominal masses (usually bilateral) • Proteinuria • Chronic kidney disease
Extrarenal features	• Cerebral aneurysms • Hepatic & pancreatic cysts • Cardiac valve disorders (mitral valve prolapse, aortic regurgitation) • Colonic diverticulosis • Ventral & inguinal hernias
Diagnosis	• Ultrasonography (alternate: computed tomography, magnetic resonance imaging) shows multiple renal cysts
Management	• Follow blood pressure & renal function • Aggressive control of cardiovascular risk factors, including hypertension • ACE inhibitors preferred for high blood pressure • End-stage renal disease: dialysis, renal transplant

- HTN usually precede decline in renal function

FIBROMUSCULAR DYSPLASIA

- Most common cause of 2* HTN in children—**fibromuscular dysplasia.** Usually women 15-50
- It is non-inflammatory and non-atherosclerotic condition—abnormal cell growth in arterial wall→vessel stenosis, aneurysm, or dissection
- **Physical examination:** hum or bruit in costovertebral angle due to well-developed collaterals. Right renal is more affected than left→ renin and angiotensin ↑ (2° hyperaldosteronism) but ratio remains <20. Carotid bruit can also be heard
- **Angiography: "string of beads"** pattern to renal artery

Fibromuscular dysplasia	

Clinical presentation	• 90% women (in adults)
	• Internal carotid artery stenosis
	  ○ Recurrent headache
	  ○ Pulsatile tinnitus
	  ○ Transient ischemic attack
	  ○ Stroke
	• Renal artery stenosis
	  ○ Secondary hypertension
	  ○ Flank pain

Physical examination	• Subauricular systolic bruit • Abdominal bruit
Diagnosis	• Imaging preferred (eg, duplex US, CTA, MRA) • Catheter-based arteriography
Treatment	• Antihypertensives (ACE inhibitors or ARBs 1st line) • PTA • Surgery (if PTA unsuccessful)
ARB = angiotensin II receptor blocker; **CTA** = CT angiography; **MRA** = MR angiography; **PTA** = percutaneous transluminal angiography; **US** = ultrasonography.	

!!! remember WOMEN WOMEN WOMEN

➔ **Stenosis of renal artery** is common in elderly (>50 yo and esp. in males). More common on left side. Bruit may be heard but is unrelated to stenosis.

➔ In primary hyperaldosteronism→ ↑aldosterone and ↓ renin→aldosterone:renin >20

FMD ratio is ~10 (<20)

COARCTATION OF AORTA

Coarctation of the aorta	
Pathology	• Thickening of tunica media of aortic arch near the ductus arteriosus

Clinical features	• Hypertension in upper extremities
	• ↓Perfusion to lower extremities
	  ○ ↓Post-ductal oxygen saturation
	  ○ ↓Femoral pulses
	  ○ Lower-extremity claudication (adults)
	• Heart failure (irritability, poor feeding, diaphoresis); cardiogenic shock (infants)
	• Palpable pulsations of intercostal vessels (adults)

Treatment	• Surgical repair

- Systolic ejection murmur at left interscapular area
- Pt may be at increased risk of shock, delayed capillary refill (>3sec), metabolic acidosis, ↓ renal perfusion (↓urine output)

Late presentation of aortic coarctation	
Presentation	• Asymptomatic hypertension most common • Chest pain, claudication, headache, epistaxis, heart failure, aortic dissection in severe cases
Examination	• Brachial-femoral delay • Upper-extremity hypertension, lower- extremity hypotension • Continuous cardiac murmur from large collaterals

Diagnostic studies	• ECG: Left ventricular hypertrophy → With increased voltage of QRS complexes and ST and T wave changes in left precordial leads V5 and V6.
	• Chest x-ray:
	  ○ Notching of the 3rd-8th ribs from enlarged intercostal arteries
	  ○ "3 sign" from aortic indentation
	• Echocardiography – diagnostic confirmation

Treatment	Balloon angioplasty +/- stent
Associated conditions	• Bicuspid aortic valve • Ventricular septal defect • Turner syndrome

- **A**ll pts esp. young with systemic HTN should be evaluated for coarctation of aorta with simultaneous palpation of brachial and femoral pulses to assess for "brachial-femoral" delay
- Check supine b/l arm (brachial) and prone right and left leg (popliteal) BP to assess for differential pressures

HEPARIN INDUCED THROMBOCYTOPENIA

There are two types:

Type 1 HIT: non immune direct effect of heparin on platelet activation and usually presents within 1st 2 days of heparin exposure. The platelet count then normalizes with continued heparin therapy and there are no clinical consequences.

Type 2 HIT: more serious, immune mediated due to antibodies to platelet factor 4 (PF4) complexed with heparin→platelet aggregation, thrombocytopenia, and thrombosis (both arterial and venous). Platelet count usually drops >/=50% from baseline, with a nadir of 30,000-60,000/uL. Presents 5-10 days after initiation of heparin therapy and may lead to life threatening consequences (eg limb ischemia, stroke)

CYTOCHROME P450 INDUCERS AND INHIBITORS

Qid: 4473

Drugs/supplements that affect warfarin metabolism (selected)	
CYP450 Inhibitors **↑ Warfarin effect** (↑ bleeding risk)	• Acetaminophen, NSAIDs • Antibiotics/antifungals (eg, metronidazole) • Amiodarone • Cimetidine • Cranberry juice, *Ginkgo biloba*, vitamin E • Omeprazole • Thyroid hormone • SSRIs (eg, fluoxetine)
CYP450 Inducers **↓ Warfarin effect** (↓ in efficacy)	• Carbamazepine • Ginseng • Green vegetables (eg, spinach) • Oral contraceptives • Phenobarbital • Rifampin • St. John's wort

NSAIDs = nonsteroidal anti-inflammatory drugs; **SSRIs** = selective serotonin reuptake inhibitors.

- Acetaminophen, if taken at significantly high doses (>2g/day) for >1 week can significantly enhance effect of warfarin

DIGITALIS TOXICITY

- Atrial tachycardia with AV block is arrythmia specific for digitalis toxicity
- Digitalis is responsible for increased ectopy in atria and ventricles→atrial tachy
- Atrial tachy can be differentiated from atrial flutter by heart rate (150-250 bpm as opposed to 250-350bpm)
- P- waves present but different from normal P-waves. Closer the ectopic focus to SA node, more is the resemblence of ectopic P-wave to normal p-wave
- Digitalis causes inc. in vagal tone→ AV block
- Multifocal atrial tachy is rarely associated with digitalis toxicity. It is more commonly a consequence of pulmonary dis.

Symptoms of digoxin toxicity	
Cardiac	• **Life-threatening arrhythmias**
Gastrointestinal	• Anorexia • Nausea & vomiting • Abdominal pain
Neurologic	• Fatigue • Confusion • Weakness • **Color vision alterations**

- Amiodarone or verapamil, quinidine, and propafenone increases the serum levels of digoxin and can lead to toxicity
- Acute toxicity has predominant GI symptoms and chronic has predominant CNS symptoms
- It is recommended that the digoxin dose be **decreased by 25%-50% when initiating amiodarone** therapy, with close monitoring of digoxin levels once weekly for the next several weeks.

AMIODARONE TOXICITY

Major side effects of amiodarone	
Cardiac	• Sinus bradycardia, heart block • Risk of proarrhythmias – QT prolongation & risk of torsades de pointes
Pulmonary	• **Chronic** interstitial pneumonitis (cough, fever, dyspnea, pulmonary infiltrates) most common
Endocrine	• Hypothyroidism • Hyperthyroidism
Gastrointestinal/ Hepatic	• Elevated transaminases, hepatitis
Ocular	• Corneal microdeposits • Optic neuropathy
Dermatologic	• Blue-gray skin discoloration
Neurologic	• Peripheral neuropathy

- **Use of amiodarone:** serious ventricular arrhythmia in pts with coronary artery disease and ischemic cardiomyopathy, rhythm control in atrial fibrillation and underlying left ventricular dysfunction
- **50% pts** on long term amiodarone will develop S/E.

- **Pulmonary toxicity**—serious adverse effect of long-term use. Can also present with ARDS. Correlates with **total cumulative dose** rather than serum drug level and usually occurs months to several years after initiation of drug therapy
- **Baseline CXR and pulmonary function testing**—prior to therapy initiation, and long term by development of signs and symptoms (cough, fever, dyspnea) suggestive of pulm. Toxicity
- **Abnormal LFTs:** discontinue if >2-fold are seen
- **Corneal deposits:** as drug is secreted in lacrimal glands. Vision usually unaffected. Does not require drug discontinuation
- **Routine monitoring:** TFT (before starting and 3-4 months interval) and LFTs
- **Suspicious pulm symptoms:** CXR and PFTs
- **Visual symtpms**: thorough ophthalmologic examination

SEROTONIN SYNDROME

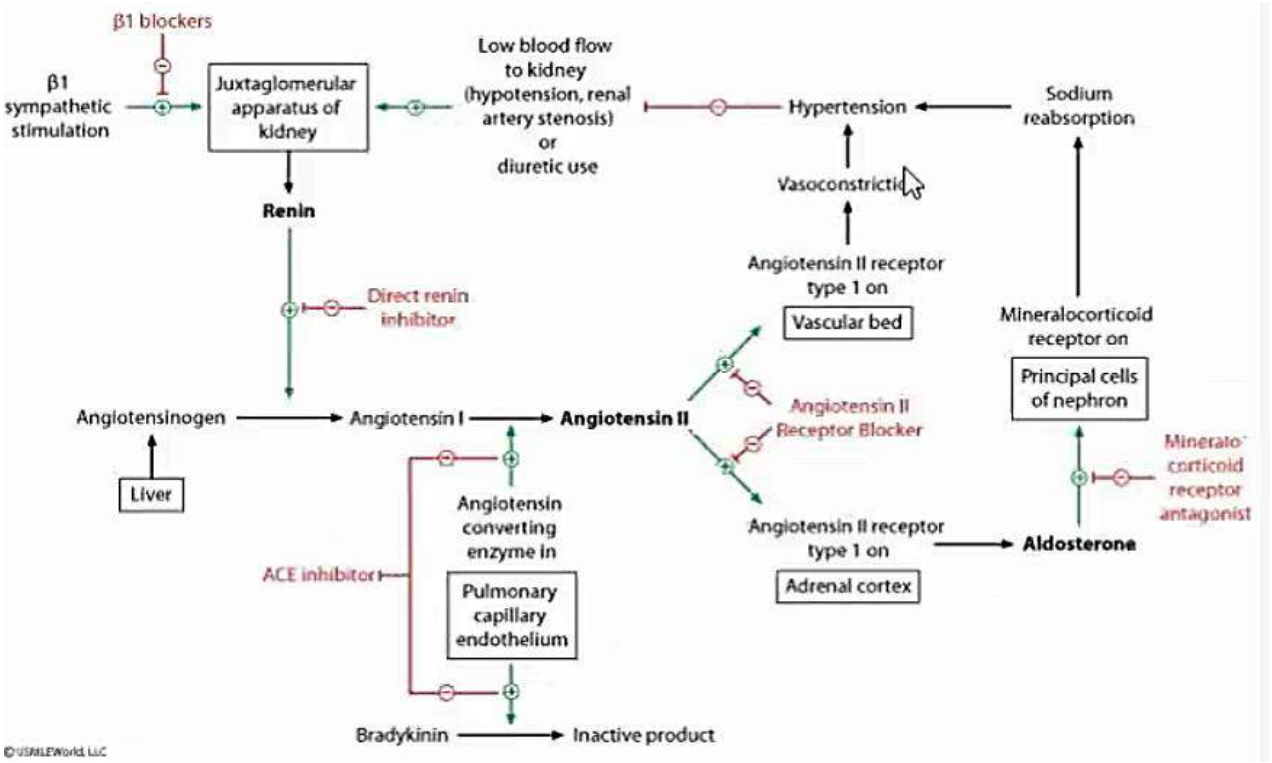
Clinical features of serotonin syndrome
Common drug interactions • Selective serotonin reuptake inhibitors • Serotonin-norepinephrine reuptake inhibitors • Monoamine oxidase inhibitors • Tricyclic antidepressants • Tramadol • Linezolid • 5-HT3 receptor antagonists (ondansetron) • Triptans (sumatriptan)
Signs/symptoms • Hyperthermia • Autonomic instability (tachycardia, hypertension) • Diaphoresis • Confusion • Agitation, tremor, hyperreflexia, akathisia • Muscle rigidity, inducible or spontaneous **clonus** (ocular or peripheral) • Dry mucous membranes, increased bowel sounds, flushed skin • Dilated pupils
Treatment • Discontinue serotonergic drugs • Benzodiazepines for sedation, agitation & blood pressure elevation • Supportive care (eg, oxygen, fluids) • Cyproheptadine is preferred when supportive measures fail • Critically ill require intubation in intensive care unit

ADVERSE EFFECTS OF PHOSPHODIESTERASE-5 INHIBITORS

Adverse effects of phosphodiesterase-5 inhibitors	
Cardiovascular	• **Hypotension** (especially with nitrates, alpha blockers)
Ocular	• Blue discoloration of vision • Nonarteritic anterior ischemic optic neuropathy
Genitourinary	• **Priapism**
Other	• Flushing • Headache • Hearing loss

- If alpha-blockers are to be used alongwith PDE-5i, then they should be used with caution. Minimum effective dose of both drugs should be given, with careful dose titration. Should be taken 4 hours apart. All antihypertensives should be used with caution with PDE-5i
- Diabetic retinopathy is not a CI for PDE-5i. PDE-5i cause temporary bluish discoloration due to cross-reactivity with PDE-6 inhibitors involved in color vision in retina.
- Non-arteritic optic neuropathy (NAION)- noted with PDE-5i use but relationship is unclear]
- PDE-5i have been found to dec symptoms of diabetic peripheral neuropathy and PAD

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



COR PULMONALE

Characteristic findings of cor pulmonale	
Common etiologies	• COPD (most common) • Interstitial lung disease • Pulmonary vascular disease (eg, thromboembolic) • Obstructive sleep apnea
Symptoms	• Dyspnea on exertion, fatigue, lethargy • Exertional syncope (due to ↓ cardiac output) • Exertional angina (due to ↑ myocardial demand)
Examination	• Peripheral edema • ↑ Jugular venous pressure with prominent *a* wave • Loud S2 • Right-sided heave • Pulsatile liver from congestion • Tricuspid regurgitation murmur
Imaging	• **Electrocardiogram (ECG)**: Partial or complete right bundle branch block, right axis deviation, right ventricular hypertrophy, right atrial enlargement • **Echocardiogram**: Pulmonary hypertension, dilated right ventricle, tricuspid regurgitation • **Right heart catheterization**: Gold standard for diagnosis showing right ventricular dysfunction, pulmonary hypertension & no left heart disease

- **Sx:** Occassionally ascites or pleural effusion, right ventricular 3rd heart sound, loud P2, anorexia and abdominal pain due to hepatic congestion
- **Right heart catheterization:** definitive diagnosis can be made using right heart catheterization showing **elevated pulmonary artery systolic pressure** (>25 mmHg).

SHOCK

Hemodynamic measurements in shock				
Parameter	**Normal**	**Hypovolemic shock**	**Cardiogenic shock**	**Septic shock**
Right atrial pressure (preload)	Mean of 4 mm Hg	↓	↑	Normal to slight ↓
Pulmonary capillary wedge pressure (preload)	Mean of 9 mm Hg	↓	↑	Normal to slight ↓
Cardiac index (pump function)	2.8-4.2 L/min/m^2	↓	↓↓	↑
Systemic vascular resistance (afterload)	Mean of 1150 dynes*sec/cm^5	↑	↑	↓
Mixed venous oxygen saturation	60%-80%	↓	↓	↑

HYPOVOLEMIC SHOCK

- Consider hypovolemia in any pt with MVA from hemorrhage unless otherwise proved
- Severe hemorrhage→↓ venous return→↓ end diastolic volume→ ↓CO→↑ sympathetic activity→↑ venous capacitance vessels→ improve venous return→ flat neck veins
- If positive pressure mechanical ventilation is given without correction of intravascular volume loss→↑ intrathoracic pressure→↑ right atrial pressure→↓ systemic venous return→ acute circulatory failure→ death. Additionally sedative meds given prior to intubation also relax venous capcitance vessels and may themselves cause circulatory failure by acutely decreasing venous return in hypovolemic pt
- May not repsond well to fluid resuscitation

Hemorrhage Classification	Class I	Class II	Class III	Class IV
Blood loss (cc)	1000	1000-1500	1500-2000	>2000
Blood loss %	<20	20-30	30-40	>40
Systolic blood pressure	Compensated	Orthostatic	Marked decrease	Profound decrease
Heart rate	<100	>100	>120	>140
Respiratory rate	14-20	20-30	30-40	>35
Urine output (cc/h)	>30	20-30	5-20	Anuria
CNS status	Normal / Anxious	Agitated	Confused	Confused / Obtunded
Capillary refill	Normal	Slight delay / Cool	Significant delay / Cool	Significant delay / Cold

SEPTIC SHOCK:

- Hyperdynamic phase: dec. in SVR, dec. BP, inc. HR and CO (warm shock)
- Hypodynamic phase: inc. SVR, dec. in CO→grave deterioration (cold shock)

EXERTIONAL HEAT STROKE

Exertional heat stroke	
Risk factors	• Strenuous activity during **hot & humid weather** • Dehydration • Poor acclimatization • Lack of physical fitness • Obesity • Medications: Anticholinergics, antihistamines, phenothiazines, tricyclics
Clinical manifestations	• Core temperature >40 C (104 F) immediately after **collapse AND** • Central nervous system dysfunction: Altered mental status, confusion, irritability, seizure • Additional organ or tissue damage: Renal/hepatic failure, disseminated intravascular coagulation, acute respiratory distress syndrome
Management	• Rapid cooling: Ice water immersion preferred; can consider: high-flow cool water dousing, ice/wet towel rotation, evaporative cooling • Fluid resuscitation • Electrolyte correction • Management of end-organ complications • No role for antipyretic therapy

- Sweating is the main mechanism of heat dissipation. If humidity >75% or excessive ambient heat→dec. sweating
- Antihistamines/anticholinergics→impair heat dissipation→heat stroke
- Often anhidrosis is described as classic finding, pts can have excessive sweating
- Dehydration common→tachycardia, hypotension, hemoconcentration (inc. Hb, leukocyte and platelet count) and inc. BUN.
- Leukocytosis →from severe stress

NON-EXERTIONAL HEAT STROKE

- Similar C/f and potential complications as above
- Occurs in absence of strenuous activity
- More freqeuntly affect elderly pt with significant underlying comorbidities that limit their ability to escape or cope with excessive heat
- **Rx:** evaporative cooling (eg spraying lukewarm water while fans blod air on pt) is more imp than ice immersion which is associated with inc mortality in this case

CARDIAC MYXOMA

Myxomas are the most common **benign** primary cardiac tumor

Cardiac myxoma	
Tumor characteristics	• 80% located in the left atrium

Clinical features	• **Constitutional** symptoms (eg, fever, weight loss, Raynaud phenomenon) → Because of IL-6
	• **Cardiovascular** complications
	  ○ Valvular abnormalities (eg, mitral disease)
	  ○ Heart failure due to anatomic obstruction
	  ○ Myocardial invasion causing arrhythmias, heart block, or pericardial effusion
	• **Embolization**
	• Lung invasion causing respiratory symptoms mimicking bronchogenic carcinoma

Diagnosis & management	• Echocardiogram • Prompt surgical resection

- Transesophageal echo is most sensitive though transthoracic is also adequate

HYPERTHYROIDISM

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite • Goiter
Physical examination	• Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

- Hyperthyroidism→↑beta adrenergic receptors→↑sympathetic activity
- Rx: beta blockers (like propranolol, atenolol) should be started in pts with hyperthyroidism as soon as it is diagnosed and continued till euthyroid with thinoamides, radioiodine, and/or surgery

SCLERODERMA RENAL CRISIS

- Malignant HTN (eg headache, blurry vision, nausea) and acute renal injury without previous kidney injury (↑creatine or BUN) in the setting of systemic sclerosis (scleroderma)→scleroderma renal crisis

- Affects 20% pts with diffuse cutaneous systemic sclerosis (SSc) within first 5 years of diagnosis
- **MOA:**
  1. ↑ vascular permeability
  2. Activation of coagulation cascade
  3. ↑ renin secretion
- Urinanalysis can be normal or show mild proteinuria
- Peripheral blood smear can show microangiopathic hemolytic anemia (similar to HUS/TTP) or DIC with fragmented red blood cells (eg schistocytes) and thrombocytopenia

➔ **Burr cells** (echinocytes): serrated edges—in liver disease and ESRD
➔ **Howell-Jolly bodies:** h/o splenectomy or functional asplenia
➔ **Spur cells:** irregularly spaced projections—in liver disease
➔ **Target cells:** in hemoglobinopathies (eg thalassemia) or CLD (esp. obstructive liver disease)

Contents

CARDIOLOGY-PEDIATRICS

BREATH HOLDING SPELLS

Breath-holding spells	
Cyanotic	Crying followed by breath-holding, cyanosis & loss of consciousness
Pallid	Minor trauma followed by breath-holding, pallor, diaphoresis, & loss of consciousness

- **BHS** is benign and parents should be reassured
- **Common in 6mo to 2 yrs** and usually stop by 5 yrs and child usually develops normally. May represent variant of vasovagal syncope. Some may develop vasovagal syncope later in life
- **Iron def. anemia** can also cause this and supplements are given if anemia found
- **In pallid form**, there may be confusion and sleepiness for a few min.
- **If recurrent and prolonged or FH of cardiac dis., syncope or sudden death**→ECG. Echo if murmur, poor growth, or diaphoresis/dyspnea with feeds of activity

TURNER SYNDROME

- Coarctation of aorta is common→continuous murmur is heard all over chest due to development of collaterals between hypertensive and hypoperfused vessels. Rib notching is due to dilation of collateral chest wall vessels.

CONGENITAL HEART DEFECTS

Normal fetal circulation:

- Blood is shunted away from lungs by PDA and systemic circulation mainly relies on right ventricle
- Right ventricle is larger than left in normal newborn
- ECG: right axis deviation R waves in precordial leads (V1-V3) on ECG

PDA-dependent congenital heart disease
• Coarctation of the aorta • D-transposition of the great arteries • Hypoplastic left heart syndrome • Total anomalous pulmonary venous connection • Tricuspid atresia

- If hypoxia fails to improve with inhaled oxygenation→congenital heart disease
- Oxygen saturation of 70-90% and central cyanosis→cyanotic heart disease

- Normally DA constricts and becomes non-functional around day 3 of life. Closure in PDA dependent CHD can lead to severe hypoxia, shock and lactic acidosis
- Keep it open with PGE1 until surgery can be performed
- Excessive inspired oxygen and indomethacin should be avoided as they constrict DA

Cyanotic heart disease in newborns

Diagnosis	Examination	X-ray findings
Transposition of the great vessels	• Single S2 • +/- VSD murmur	"Egg-on-a-string" heart (narrow mediastinum)
Tetralogy of Fallot	• Harsh pulmonic stenosis murmur • VSD murmur	"Boot-shaped" heart (right ventricular hypertrophy)
Tricuspid atresia	• Single S2 • VSD murmur	Minimal pulmonary blood flow
Truncus arteriosus	• Single S2 • Systolic ejection murmur (increased flow through truncal valve)	Increased pulmonary blood flow, edema
Total anomalous pulmonary venous return with obstruction	• Severe cyanosis • Respiratory distress	Pulmonary edema, "snowman" sign (enlarged supracardiac veins & SVC)

VSD = ventricular septal defect

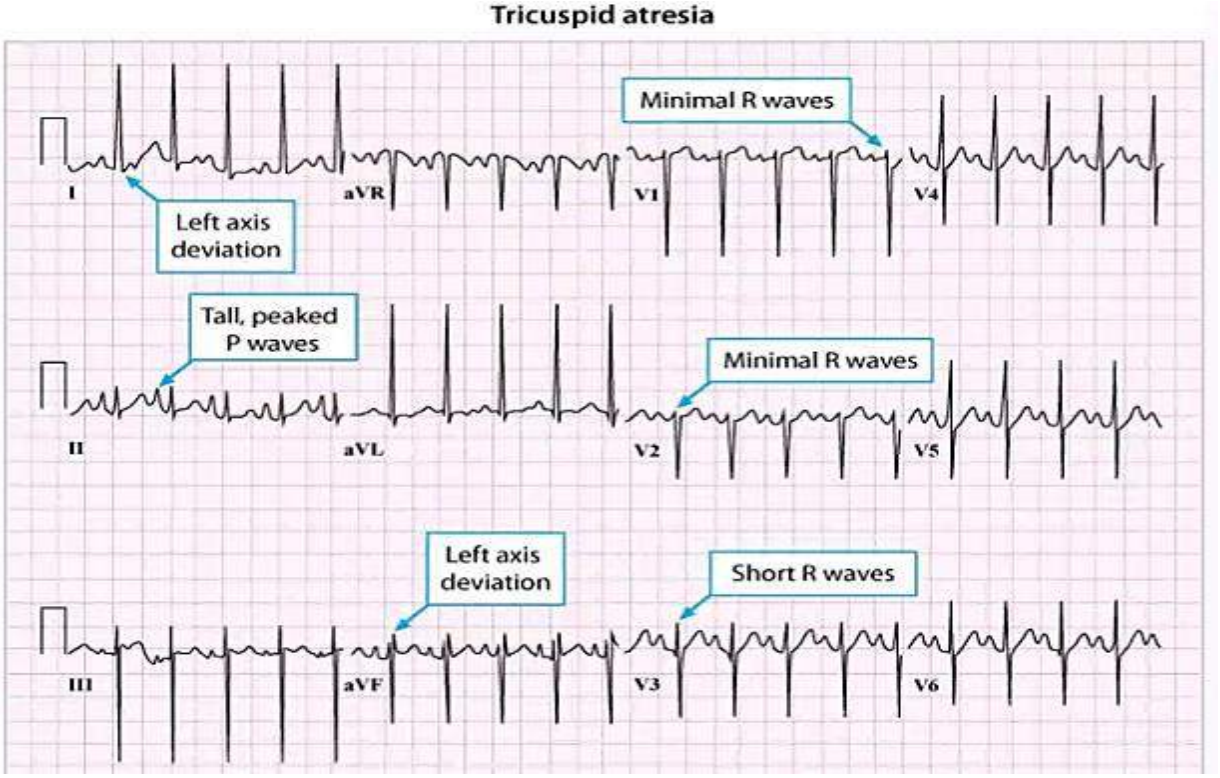
Transposition of great vessels:

- Most common neonatal cyanotic heart dis. Mostly present within 24 hours of birth
- Single S2 because pulmonary component is missing as it lies behind aorta
- PDA or VSD (both cause murmur) or patent foramen ovale (no murmur) is needed for mixing of oxygenated or deoxygenated blood after birth. Inadequate mixing→ rapid severe cyanosis and pulmonary edema, die if shunt is not developed (emergency atrial septostomy)
- If TGV is suspected, prostaglandins should be started to maintain mixing and echo should be obtained.

Tricuspid atresia:

- Cyanosis
- Lack of communication btw right heart chambers lead to hypoplastic right ventricle and diminished right ventricle forces on ECG
- Lack of right ventricle filling and pulmonary outflow tract→**underdevelopment of pulmonary valve and/or artery**→ dec. pulmonary markings on CXR
- ASD and VSD are needed for survival

- ECG: Left axis deviation and small or absent R waves in precordial leads. Tall peaked P waves because of ASD causing inc. blood flow to right atrium and subsequent enlargement
- Cause: unknown but can occur with any congenital heart defect and in FH of CHD
- Rx: surgical repair→ improve 10 year survival to 80%. Lack of repair→death in 1st year of life



Complete atrioventricular canal defect:

- Most common congenital heart defect in Downs syndrome
- Underdeveloped AV valves, ASD, VSD
- Diaphoresis/dyspnea with feeds usually present at 6 wks when pulmonary vascular resistance falls
- Auscultation findings:
  1. Loud S2 due pulmonary HTN
  2. Systolic ejection murmur from increased flow across pulmonary valve from left to right shunt across ASD
  3. Holosystolic murmur of VSD may be soft or absent if defect is large
- CXR: inc. pulmonary marking and cardiomegaly from excessive pulm blood flow and biventricular volume overload

VSD:

- Range from small, asymptomatic to large causing L→R shunt, failure to thrive, easy fatigability, and heart failure.
- Pansystolic murmur at left lower sternal border and diastolic rumble at apex due to increase flow of blood across mitral valve→Echo to evaluate size and location of defect
- Rx: depends on size of defect and severity of symptoms—generally combination of meds (eg diuretics) and transcatheter or surgical closure, ideally well before development of Eisenmenger syndrome
- Small VSDs close in 75% children spontaneously by age 2 years with no long term sequele

Ebstein anomaly:

- Malformed tricuspid valve into right ventricle→droopy tricuspid valve→severe tricuspid regurgitation→right atrial enlargement→tall P waves and right axis deviation
- Auscultation: "triple or quadruple gallop" (widely split S1 and S2 plus a loud S3 and/or S4) and holosystolic or early systolic murmur at left lower sternal border
- CXR: extreme cardiomegaly from heart failure

Tetralogy of Fallot:

Tetralogy of Fallot	
Clinical presentation	• Severe obstruction (eg, pulmonary atresia): Profound cyanosis & hypoxemia in the neonatal period • Moderate obstruction: Hypercyanotic "Tet" spells in infancy or childhood • Minimal obstruction: Heart failure in childhood or adulthood
Physical examination	• Harsh, systolic ejection murmur at left upper sternal border • Single S2
Chest x-ray	• "Boot-shaped" heart

Management	• Hypercyanotic "Tet"-spell:
	  • Knee-chest positioning
	  • Inhaled oxygen
	• Surgery before age 6 months

- Pt with mild obstruction can develop hypercyanotic or tet spell because of dramatic infundibular spasm during exertion or agitation. This situation is dangerous so they should be placed in knee-chest position immediately to inc. SVR, inc. pulm blood flow and improve symptoms and cyanosis.
- Oxygen should be given to stimulate pulm. Vasodilation and systemic vasoconstriction
- Morphine to relax pt. and IV fluids to improve right ventricular filling and pulmonary flow.
- Dec. vascular markings on CXR due to pulm outflow tract obstruction
- Boot shaped heart develops later but they have right axis deviation as in normal newborn
- Elective surgical repair is performed before 6mo of age to decrease morbidity and mortality from outgrowing the RVOT

Total anomalous pulmonary venous return:

- All pulmonary veins drain in to SVC→ right atrium and ventricular enlargement→right axis deviation as normal→ inc. markings on CXR due to inc. pulm blood flow

Truncus arteriosus:

- Strongly associated with DiGeorge syndrome
- Normal ECG
- CXR: cardiomegaly and inc. pulmonary vascular markings from heart failure and pulm overcirculation

Patent ductus arteriosus:

- Associated with congenital rubella syndrome and Char syndrome (affects face, heart and limbs)
- Continuous murmur cox of continuous flow of blood from aorta to pulm. Artery because pressure in aorta is always more than pressure in pulmonary artery
- C/F depend on size and length of PDA.
- Small PDA—usually asymptomatic. May show mildly accentuated peripheral pulses

PEDIATRIC VIRAL MYOCARDITIS

Qid 4854

Pediatric viral myocarditis	
Etiology	• Coxsackie B virus • Adenovirus
Clinical presentation	• Viral prodrome • Heart failure: Dyspnea, syncope, tachycardia, nausea, vomiting, hepatomegaly

Diagnostic studies	• Chest x-ray:
	  • Cardiomegaly
	  • Pulmonary edema
	• ECG: Sinus tachycardia
	• Echocardiogram:
	  • Decreased ejection fraction
	  • Diffuse hypokinesis
	• Endomyocardial biopsy (gold standard): Inflammatory infiltrate of the myocardium with myocyte necrosis

Prognosis	• Mortality:
	  • Newborns: ~75%
	  • Older infants/children: ~ 25%
	• Outcome of survivors:
	  • Full recovery within 2-3 months: ~66%
	  • Dilated cardiomyopathy/chronic heart failure: ~33%

- **M**yocarditis is potentially lethal
- **Cause:** viral, autoimmune and toxins
- **Pathogenesis:** direct viral injury and autoimmune inflammation that leads to myocyte necrosis→impairment of systolic and diastolic function
- **More severe in newborns**: can cause death because immature myocardium is less adaptable to acute insult
- **Symptoms overlap** with other pediatric illnesses—misdiagnosed as asthma or pneumonia

- **Holosystolic murmur:** can be heard 2* to dilated cardiomyopathy leading to MR
- **CXR: healthy infant <1 year:** transverse cardiothoracic ratio </=60%. **Healthy >1 year:** </=50%
- **ECG:** may show nonspecific T wave changes. **Echo is best**
- **Viral studies** should be sent to identify offending pathogen
- **Rx: s**upportive such as diuretics and inotropes. Affected children should be monitored in ICU due to risk of shock and fatal arrhythmias
- **Acute rheumatic fever:** occurs after 2-4 wks of group A streptococcal infection. Uncommon in children <3 years cox of fewer epithelial cell attachment sites in throat

KAWASAKI DISEASE

Kawasaki disease	
Diagnostic criteria	Fever ≥5 days plus ≥4 of the following findings: • Bilateral nonexudative conjunctivitis • Mucositis (injected or fissured lips, injected pharynx, or strawberry tongue) • Cervical lymphadenopathy with at least one lymph node being >1.5 cm in diameter • Erythematous polymorphous rash • Extremity changes (edema & erythema)
Treatment	Aspirin plus intravenous immunoglobulin
Complications	• Coronary artery aneurysms • Myocardial infarction & ischemia

- Diagnosis is clinical
- Irritability is also a common feature
- Typically in children <5yrs but can occur in late childhood as well
- Treatment should be started within 10 days of fever onset to prevent cardiac complications
- Baseline echo in all suspected pts and repeat 6-8wks later to monitor for changes
- D/d: in strep throat, there is pharyngeal exudate as well, rash is sandpaper like and spares palms and soles

DiGEORGE SYNDROME

DiGeorge syndrome	
Pathogenesis	• Chromosome 22q11.2 deletion • Defective development of pharyngeal pouches
Clinical features	• **C**onotruncal cardiac defects • **A**bnormal facies • **T**hymic aplasia/hypoplasia • **C**left palate • **H**ypocalcemia

- Truncus arteriosus is most commonly associated with DiGeorge syndrome. Other anomalies include ToF, interrupted aortic arch and septal defects
- If DGS is suspected, immediate serum calcium and echo should be ordered. Hypocalcemia→ tetany, seizures and arrhythmia which can exacerbate underlying heart disease

STRIDOR

Differential diagnosis of stridor in infants & children	
Diagnosis	**Distinguishing features**
Croup (laryngotracheo-bronchitis)	• Most common from age 6 months to 6 years • Associated with **"barky" cough**, fever, rhinorrhea & congestion
Laryngomalacia	• Stridor most severe at age 4-8 months • Persistent stridor that **worsens in supine** position & improves in prone position
Foreign body aspiration	• Stridor caused by laryngotracheal foreign bodies has **acute onset** • Associated with moderate-to-severe respiratory distress
Vascular ring	• Presents before age 1 year • Persistent stridor that **improves with neck extension** • Associated with **cardiac** abnormalities (50%)

CROUP:

- Often caused by parainfluenza virus

- Most common cause of inspiratory stridor
- Responds to treatment with racemic epinephrine or corticosteroids

LARYNGOMALACIA:

- Caused by increased laxity of supraglottic structures that result in collapse during inspiratory phase

VASCULAR RING:

- Result from abnormal development of aortic arch causing tracheal, bronchial, or esophageal compression→stridor, wheezing, cough, dysphagia, or difficulty feeding
- They are either complete (completely surrounding trachea and/ or esophagus) or incomplete
- Common examples: right sided aortic arch, double aortic arch, pulmonary sling, or anomalous left carotid or innominate artery
- Do not improve with nebulized racemic epinephrine, corticosteroids or bronchodilators
- Dx: require high index of suspicion, confirmed with barium contrast esophagogram, bronchoscopy, CT or MR angiography
- Rx: surgery is the only definitive treatment in severe disease

Contents

CARDIOLOGY-SURGERY

VENOUS VALVE INSUFFICIENCY

- Most common cause of lower extremity edema- approx. 2% population affected
- Edema aggravated after exertion/throughout the day and relieved with walking, rest/leg raising. Associated with cramping and heaviness
- Failure of venous valves causes blood to pool in dependent parts like legs→inc. in capillary hydrostatic pressure→inc. filtration of fluid out of capillary into interstitial space→dec. in intravascular volume→stimulates kidney to retain salt and water→ progression of edema
- Failure of venous valves→inc. pressure in post capillary venule→capillaries leak→loss of fluid, plasma proteins and RBCs into tissue→ RBC extravasation leads to hemosiderin deposition in tissue and classic coloration of stasis dermatitis—mostly involve medial leg below knee and above medial malleolus
- Inflammation of capillaries and venules+fibrin deposition and platelet aggregation cause microvascular disease and ultimately ulceration
- Xerosis—most common early finding; lipodermatosclerosis and ulceration—late disease
- **Initial treatment:** leg elevation, exercise and compression stockings→ no response: venous duplex ultrasound to identify reflux ~~or insufficiency~~→persistent and documented reflux: endovenous ablation

➔ Arterial occlusion causes pain, pallor, paresthesia, pulselessness and coolness to touch

RAPID DECELERATION BLUNT CHEST TRAUMA

Aortic injury

- Patient suffering from rapid deceleration blunt chest trauma or fall from a height >10 feet is at high risk of aortic injury
- Usually aortic transection, circulatory collapse and death are immediate sequelae
- Some may have incomplete or contained injury
- **Sx:** nothing specific, but anxiety, HTN and tachydcardia are ommon. Hypotension, external evidence of trauma and altered mental status usually present.
- **Management:** once stabilized with airway, breathing and circulation secured, perform upright CXR. CXR will show widened mediastinum, large let-sided hemothorax, deviation of mediastinum to right and disruption of normal aortic contour, depression of left mainstem bronchus. **Confirm dx** with CT scan and angiography
- **Rx:** antihypertensive where appropriate and surgical repair

Pulmonary contusion

- Most common finding after blunt chest trauma.
- CXR: opacities caused by hemorrhage in involved lung segments

Esophageal rupture

- Rare
- Cause pneumomediastinum and pleural effusion but not circulatory collapse

Myocardial rupture

- Cause sudden death but rarely cardiac tamponade in case of contained injury

Myocardial contusion

- Classically causes tachycardia, new bundle branch block or arrhythmia. Sternal injury is usually associated

Diaphragmatic rupture

- Abdominal pain, pain referred to shoulder, SOB and vomiting
- Radiography: abdominal viscera above diaphragm and loss of diaphragmatic contour

Bronchial rupture

- Rare
- Pneumothorax that does not resolve with chest tube placement, pneumomediastinum and subcutaneous emphysema

COMPARTMENT SYNDROME

Clinical features of compartment syndrome	
Common	• Pain out of proportion to injury • **Pain ↑ on passive stretch** • Rapidly increasing & tense swelling • **Paresthesia (early)**
Uncommon	• ↓ sensation • Motor weakness (within hours) • Paralysis (late) • ↓ distal pulses (uncommon)

- Reperfusion of limb following arterio-occlusive ischemia for longer than 4-6 hours can lead to intracellular and interstitial edema and can also lead to intracellular swelling.
- Compartment syndrome may occur when edema causes the pressure within a muscular fascial compartment to rise **above 30mmHg** or delta pressure (diastolic pressure-compartment pressure) **<20-30mmHg** leading to further muscle and nerve ischemia.
- Compartment syndrome is more common after traumatic injuries of extremities (esp. long bone fractures) but can occur post-ischemia
- Rx: if compartment pressures are improving, pt can be closely observed. If no rapid improvement then **fasciotomy** is performed to avoid long-term complications.

➔ **Bone infarction** can also produce erythema and warmth but not swelling

➔ **Recurrent embolism** can produce similar features as compartment syndrome but there are absent pulses, pallor and lack of swelling

➔ **DVT** can cause calf tenderness and exacerbation pain on passive stretching but it is often asymptomatic and generally associated with only vague aching pain

AV FISTULA Qid: 4459 CVS

Congenital	Acquired
Patent ductus arteriosus	Trauma
Angiomas	Iatrogenic (e.g., femoral catheterization)
Pulmonary AVF	Atherosclerosis (e.g., aortocaval fistula)
CNS AVF	Cancer

- AV fistula→ dec. in systemic vascular resistance, inc. cardiac preload, and inc. cardiac output and stroke volume to maintain oxygenation of peripheral tissues→ wide pulse pressure, strong peripheral arterial pulsation (e.g. brisk carotid upstroke), systolic flow murmur, tachycardia, flushed extremities→left ventricular hypertrophy and point of maximal impulse shift to left→high output cardiac failure
- Other causes of high output cardiac failure: thyrotoxicosis, Paget disease, anemia and thiamine def.
- **Dx:** doppler usg
- **Rx:** surgical for large AVF

ACUTE POST-OP MEDIASTINITIS

- This is usually a possible complication of cardiac surgery due to intraoperative wound contamination
- Complicate 5% sternotomies
- Present usually within 14 days post-op
- **C/F:** fever, tachycardia, chest pain, leukocytosis, and sternal wound drainage or purulent discharge
- **CXR:** widened mediastinum (mostly in non-postop mediastinitis but can occur post-op too)
- **Dx:** clinical and confirmed during surgery when pus is noted in mediastinum
- **Rx:** drainage, surgical debridement with immediate closure and prolonged antibiotic therapy. Antibiotics alone do not appropriately treat mediastinitis
- **Mortality:** 10-50% even with appropriate treatment

➔ **A.** fib commonly occurs within a few days after CABG and is usually self-limited, with resolution in <24hours. Rate control with beta blockers or amiodarone is best. Anticoagulation and/or cardioversion reserved if it persists >24hours after CABG

PERICARDIOTOMY SYNDROME

- **C/F:** fever, leukocytosis, tachycardia and chest pain
- **Autoimmune**
- Occur few wks following a procedure with a pericardium incision.
- Rx: NSAIDS or steroids for inflammation and pericardial puncture if tamponade occurs

POSTPERICARDIOTOMY SYNDROME

- Pleuropericardial disease. Occurs days to months after cardiac surgery or injury
- Inflammation from surgical intervention can lead to reactive pericarditis, pericardial effusion, or even cardiac tamponade. Pleural effusion can also occur leading to blunting of costophrenic angles
- Most children develop small and self-limited pericardial effusion post-operatively
- Infants with larger effusions: abdominal pain, vomiting, and decreased appetite

- Older children: usually pericardial friction rub and pleuritic chest pain
- Can progress to cardiac tamponade with Becks traid.
- Tachycardia to maintain cardiac output (CO)
- Tachypnea and dyspnea when CO becomes compromised
- Rx: pericardiocentesis or pericardiotomy

RETROPERITONEAL HEMATOMA

- H/o recent cardiac catheterization, anticoagulation, sudden onset of hypotension, tachycardia, flat neck veins and back pain suggest retroperitoneal hematoma due to bleeding from arterial access point
- **Local vascular complications at catheter insertion site**: bleeding hematoma (localized or retroperitoneal extension), arterial dissection (rare), acute thrombosis, pseudoaneurysm or AV fistula
- Most hemorrhage or hematoma occur **within 12 hours** of catheterization
- **C/F of hematoma:** localized discomfort and/or swelling of soft tissue. If puncture site is above inguinal ligament, hematoma can extend into retroperitoneal space even with minimal visible localized hematoma→sudden hemodynamic instability, ipsilateral **flank or back pain.**
- **Diagnosis:** confirmed with non-contrast CT scan of abdomen and pelvis or abdominal USG
- **Treatment:** supportive, with intensive monitoring, bed rest, and IV fluids or blood transfusion. Surgical repair of hematoma or retroperitoneal hemorrhage is rarely required.
- **Prevention:** local hematoma is not uncommon, so pt should be advised to avoid strenuous activity or lifting heavy objects for one week post catheterization. Radial artery approach leads to fewer local vascular complications, hence preferred

CARDIOLOGY-GYN/OBS

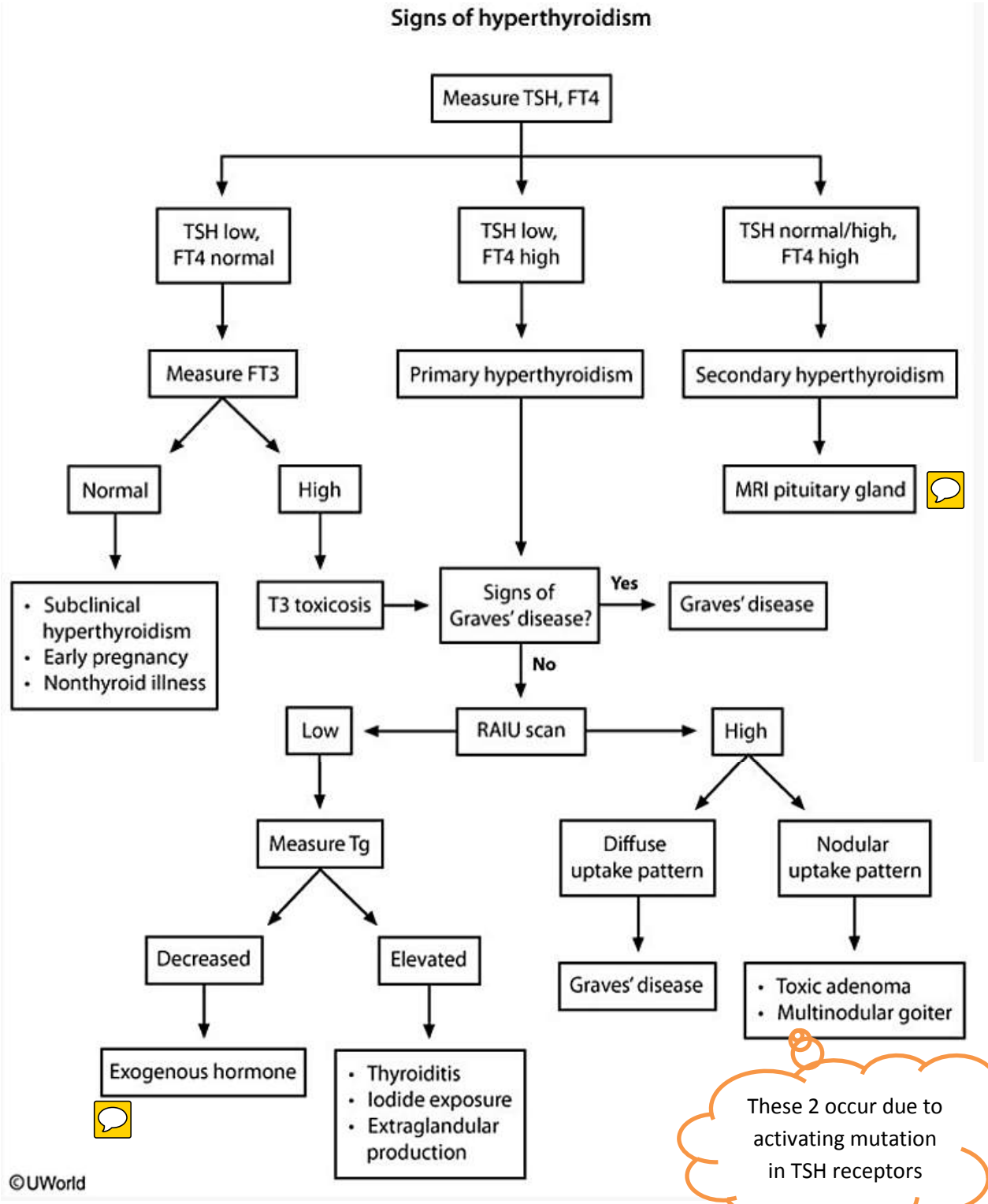
OCPs AND HYPERTENSION

- OCPs can cause HTN esp in pts with previous H/o HTN in pregnancy and family H/o HTN
- Discontinuing can correct HTN in 2 to 12 month. In 5% cases it can lead to overt HTN
- Inform the pt regarding risks of continuing and benefits of leaving OCPs + alternative methods of contraception
- If discontinuation does not correct it, go for diet and exercise modification (helpful esp in obese pts)→ if still does not correct, low dose thiazide diuretics are needed
- **Mechanism:** estrogen mediated increase in hepatic angiotensinogen synthesis or other effects on renin-angiotensin system

Contents

THYROID GLAND

HYPERTHYROIDSIM

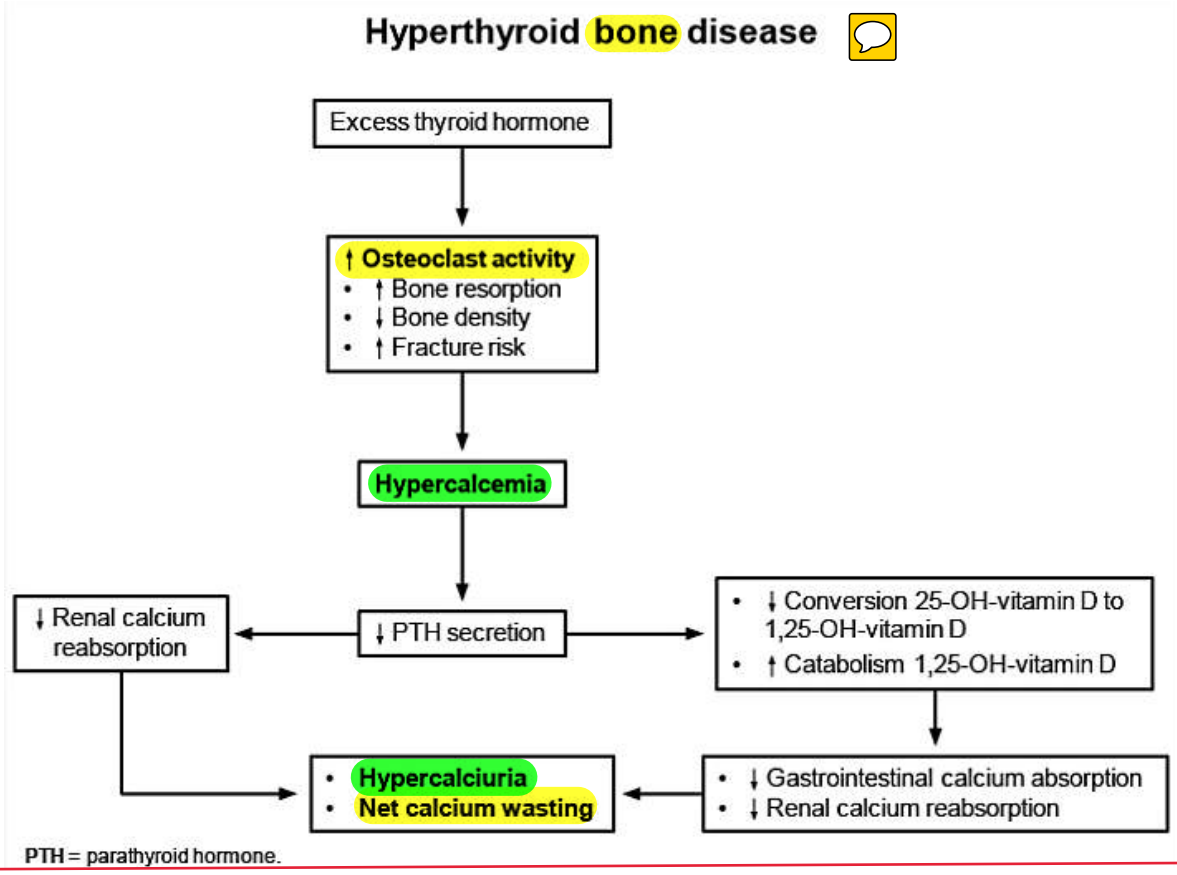


These 2 occur due to activating mutation in TSH receptors

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite • Goiter
Physical examination	• Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

Cardiovascular effects of thyrotoxicosis	
Rhythm	• Sinus tachycardia • Premature atrial & ventricular complexes • **Atrial fibrillation**/flutter
Hemodynamic effects	• **Systolic hypertension** & ↑pulse pressure • ↑Contractility & cardiac output • ↓Systemic vascular resistance • ↑**Myocardial oxygen demand**
Heart failure	• High-output failure • Exacerbation of pre-existing low-output failure
Angina symptoms	• Coronary vasospasm • Pre-existing coronary atherosclerosis

↑ sensitivity to catecholamines. MVP, MR or TR are also associated



- Upto 60-80% pts with untreated hyperthyroidism develop myopathy
- **Acute thyrotoxic myopathy:** present with more severe distal or proximal muscle weakness, but usually without bulbar or respiratory muscle involvement
- **Chronic thyrotoxic mypopathy:** usually proximal muscle weakness, weeks to months after onset of hyperthyroidism
- Thyrotoxicosis can cause hypercalcemia due to increased bone resorption
- **Objective findings:** possible muscle atrophy, high-frequency and low-amplitude tremor with movement (unlike Parkinson), normal to ↑ DTRs with short relaxation time. Treatment of hyperthyroidism improve myopathy
- **Dx:**
  - TSH→low→free T4→ ↑→ hyperthyroidism→24-hour thyroid radioiodine uptake and scan→ differentiate Grave's from other causes
  - EKG→ rule out arrhythmia
- **Rx:**

I. **Propranolol**— best initial treatment→symptomatic relief until cause is identified and definitively treated→relieve tremor, tachycardia, sweating, anxiety→ starting dose: 10 mg orally→↑ed gradually until appropriate response achieved, usually 20mg 4 times a day is needed

II. **Radioactive iodine→**definitive treatment, clinical improvement is achieved in approx. 6-18 wks. CI: pregnancy and very severe ophthalmopathy. Young pts without cardiovascular dis. tolerate it well. but pts with cardiovascular dis. do not tolerate temporary ↑ in thyroid hormone and are pre-treated with ATDs

III. **Subtotal thyroidectomy →definitive treatment**

IV. **Propylthiouracil→**> 2/3rd recur after 6 months after stopping meds→ usually given only when radioiodine is CI like pregnancy. Most common side effect of anti-thyroid drugs is allergic reaction.

anti thyroid drug = agranulocytosis

Agranulocytosis: usually develop within 90 days of treatment; ~~fever and sore throat → stop drug immediately, check WBC count start IV antibiotic esp covering Pseudomonas~~. If total WBC <1000/mm3 → permanently discontinue drug; if > 1500/mm3 → drug is not the cause of fever and sore throat

Treatment of Graves' disease

Treatment	Adverse effects
Antithyroid drugs (thionamides)	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen, cholestasis • Propylthiouracil: **Hepatic failure**, ANCA-associated vasculitis
Radioiodine ablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation side effects
Surgery	• Permanent hypothyroidism • Risk of recurrent laryngeal nerve damage • Risk of hypoparathyroidism

Most serious but rare so routine WBC count not needed; due to immune destruction of granulocytes

Preferred in US

Can be prevented by high dose corticosteroid before and after treatment

- Chances of developing permanent hypothyroidism in radioiodine ablation are most common in pts with Grave's dis. as whole thyroid gland is hyperfunctional. Although this complication can develop in any pt.
- Pt. with toxic adenoma and multinodular goiter usually remain euthyroid after procedure

THYROID STORM

Clinical features of thyroid storm	
Precipitating factors	• Thyroid or non-thyroid surgery • Acute illness (eg, trauma, infection), childbirth • Acute iodine load (eg, iodine contrast)
Clinical presentation	• Fever as high as 40-41.1 C (104-106 F) • Tachycardia, hypertension, congestive heart failure, cardiac arrhythmias (eg, atrial fibrillation) • Agitation, delirium, seizure, coma • Goiter, lid lag, tremor, warm & moist skin • Nausea, vomiting, diarrhea, jaundice
Treatment	• Beta blocker (eg, propranolol) to ↓ adrenergic manifestations • PTU followed by iodine solution (SSKI) to ↓ hormone synthesis & release • Glucocorticoids (eg, hydrocortisone) to ↓ peripheral T4 to T3 conversion & improve vasomotor stability • Identify trigger & treat, supportive care

PTU = propylthiouracil; **SSKI** = potassium iodide.

In undiagnosed or inadequately treated hyperthyroidism

Dx: on clinical grounds and confirmed with TFTs

Iodine is given 1 hour after PTU to prevent excess incorporation of iodine in thyroid hormone

- Proposed mechanisms include a rapid increase in blood thyroid hormone levels, increased cellular response to thyroid hormones, and an exaggerated response to catecholamines.

THYROIDITIS

Thyroiditis		
	Clinical features	**Diagnostic testing**
Hashimoto thyroiditis Chronic lymphocytic thyroiditis	• Predominant **hypothyroid** features • Diffuse goiter	• Positive thyroid peroxidase antibody (**TPO antibody**) • Variable radioiodine uptake
Silent thyroiditis (painless thyroiditis)	• **Mild, brief hyperthyroid phase** • Spontaneous recovery • Small, nontender goiter • Variant of *Hashimoto thyroiditis*	• Positive TPO antibody • Low radioiodine uptake
Subacute thyroiditis (de Quervain's thyroiditis)	• Likely from postviral inflammatory process • Prominent fever & hyperthyroid symptoms • **Painful/tender goiter**	• **Elevated erythrocyte sedimentation rate** & c-reactive protein • Low radioiodine uptake

HYPOTHYROIDISM

Hypothyroidism:

- Primary (thyroid gland--↓T3, T4 and ↑TSH >10 IU/L), secondary (pituitary--↓T3, T4 and ↓ or inappropriately normal TSH) and tertiary (hypothalamus—same labs as 2^{o}).
- Rarely hypothyroidism features occur because of **generalized resistance to thyroid hormone**
- **Anti-TPO and antithyroglobulin antibodies** are present in Hashimoto thyroiditis. In rare cases. Anti-TSH antibodies are present leading to small thyroid gland. Anti-TPO antibodies are ↑ early and ↓ with course of disease and treatment
- **C/F:** hyperlipidemia, hyponatremia, asymptomatic ↑in creatine kinase (<10x normal) and ↑ transaminases (AST and ALT), normochromic normocytic anemia due to decreased muscle mass, pernicious anemia in chronic autoimmune thyroiditis→macrocytosis without megaloblastic anemia, iron def. anemia due to mennorhagia

- **Hyperlipidemia**
  - **Hypothyroidism→** ↓ LDL surface receptors (type 2a hyperlipidemia) and/or ↓ LDL receptor activity→↑cholesterol with ↑ LDL
  - →↓lipoprotein lipase activity→↑triglyceride (isolated ↑ is rare)
  - **Lipid** abnormalities correct slowly despite adequate hypothyroidism treatment
  - **Statins** given with caution due to ↑ risk of myopathy in these pts
- **Hyponatremia:**
  - ↓ clearance of free water→hyponatremia (hypothyroidism and adrenal insufficiency should be ruled out before diagnosis SIADH)
- ↑ NE, aldosterone, systemic vascular resistance→↑BP

Major drug interactions of levothyroxine	
↓ levothyroxine absorption	• Bile acid binding agents (e.g., cholestyramine) • Iron, calcium, aluminum hydroxide • Proton pump inhibitors, sucralfate
↑ TBG concentration	• Estrogen (oral), tamoxifen, raloxifene • Heroin, methadone
↓ TBG concentration	• Androgens, glucocorticoids • Anabolic steroids • Slow-release nicotinic acid
↑ thyroid hormone metabolism	• Rifampin • Phenytoin • Carbamazepine

Qid: 4154

→by ↑ing activity of deiodination (major method), glucoronidation and sulfation enzymes in liver

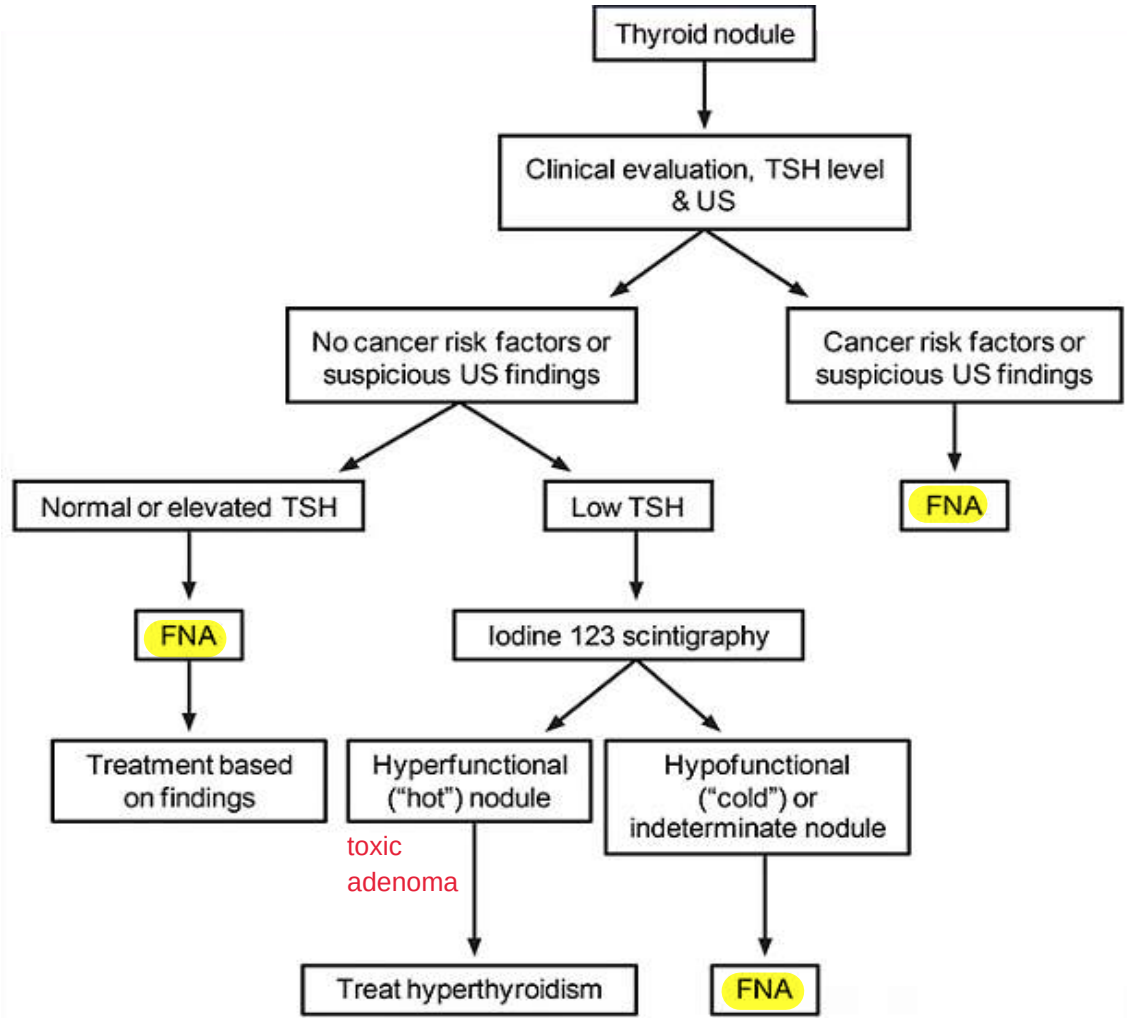
- **TBG**—synthesized and sialylated in liver. **Oral estrogen or pregnancy (↑estrogen)→** ↓ clearance of TBG→↑TBG→↓free T4→↑dose of levothyroxine. **Transdermal estrogen** bypass liver→ TBG not affected

GENERALIZED RESISTANCE TO THYROID HORMONE:

- Occurs because of peripheral tissue resistance to thyroid hormone. Autosomal dominant
- **Severe disease:** Pt usually present at early age with growth and mental retardation
- **Mild disease:** pt usually present later with signs of hypothyroidism with elevated T3 and T4 levels and normal or mildly ↑ TSH

Subclinical hypothyroidism:
- NO symptoms / normal thyroxine level with a mild elevation in TSH.
- mainly due to hashimoto thyroiditis (anti-TPO)
- high titers of anti-TPO antibodies are associated with an increased risk of progression from subclinical to overt hypothyroidism.
- High titers of antr-TPO are also associated with increased risk of **miscarriage** in both euthyroid and hypothyroid women
- Treatment with levothyroxine is recommended in patients with subclinical hypothyroidism who have elevated anti-TPO antibodies even if they do not have symptoms.

THYROID NODULE



- **Thyroid nodule evaluation** is based on these factors: **Cancer risk factors (**e.g. family history, cervical LAD, radiation exposure in childhood), compression symptoms (e.g. hoarseness, difficult swallowing) and current thyroid status (e.g. euthyroid, hypo/hyperthyroidism)
- **Suspicious US findings:** hypoechoic, internal vascularity, microcalcifications etc

THYROID CANCERS

Types of thyroid malignancies	
Epithelial (thyroid follicular cells) (90%-95%)	• **Papillary** (>70%) • Follicular • Anaplastic
Parafollicular C-cells (3%-4%)	• Medullary thyroid cancer
Other cells (<5%)	• Lymphoma • Sarcoma • Metastatic (renal, breast, melanoma, colon)

Risk factors: family history and childhood exposure to radiation

PARATHYROID GLANDS

HYPERPARTHYROIDISM

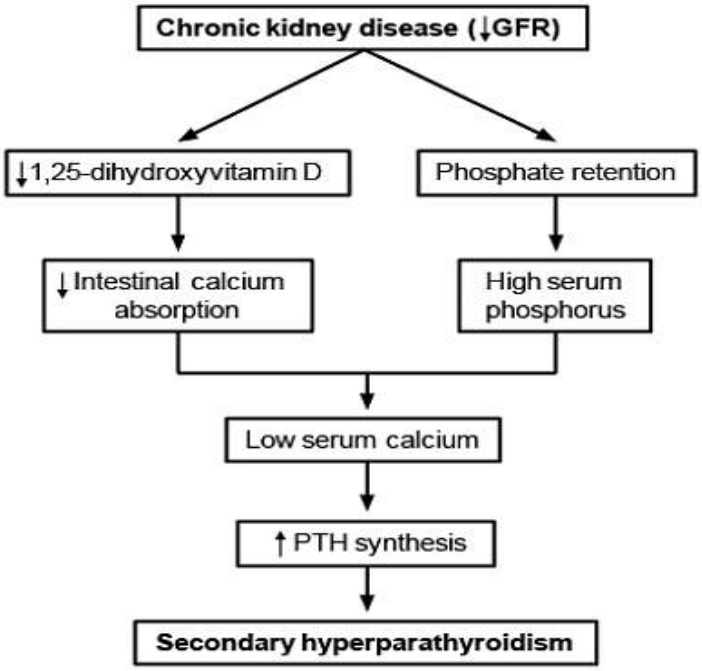
Primary hyperparathyroidism:

Overview of primary hyperparathyroidism	
Etiology	• Parathyroid adenoma (90%), hyperplasia (6%), carcinoma (1%-2%) • Associated with multiple endocrine neoplasia I and 2A syndromes
Symptoms	• 80% of patients are asymptomatic (identified via routine testing) • Few present with nonspecific symptoms (eg, fatigue, weakness, mild depression) • Abdominal pain, renal stones, bone pain/fractures & psychiatric manifestations occur infrequently
Diagnosis	• Hypercalcemia with elevated or inappropriately normal PTH • 24-hour urinary calcium >250 mg • Urine calcium/creatinine >0.02 differentiates PH from familial hypocalciuric hypercalcemia • Bone mineral density testing to evaluate for osteopenia/osteoporosis (known complication) • Three-dimensional sestamibi scan plus ultrasound locates hyperactive parathyroid tissue prior to surgery
Treatment	• Parathyroidectomy for symptomatic patients or selected asymptomatic patients

- In **familial hypocalciuric hypercalcemia** –24 hour urinary calcium is usually <100mg
- Surgery prevent PH complications and is recommended for following pts:
  1. Serum calcium >/= 1mg/dl above upper limit of normal range
  2. Young age <50
  3. Bone marrow density T-score <-2.5 at any site
  4. Reduced renal function (estimated GFR <60mL/min)
- Bisphosphonate can be used in those who refuse surgery and have prior history of osteopenia/osteoporosis
- Medical surveillance is for older pts who have near normal calcium level and no h/o osteopenia/osteoporosis
- Pts with malignancy related hypercalcemia have very severe hypercalcemia, hypophosphatemia and +PTH related peptide

Familial hypocalciuric hypercalcemia
- defect in calcium sensor of parathyroid gland
- there is a loss of negative feedback on PTH by hypercalcemia
- PTH levels are normal to high despite high serum calcium levels (↑PTH /↑Ca)
- urine excretion of calcium is low key feature distinguishing primary hyperparathyroidism from FHH

Secondary hyperparathyroidism:



GFR = glomerular filtration rate; PTH = parathyroid hormone.

- Magnitude of rise in PTH directly correlate with severity of renal failure

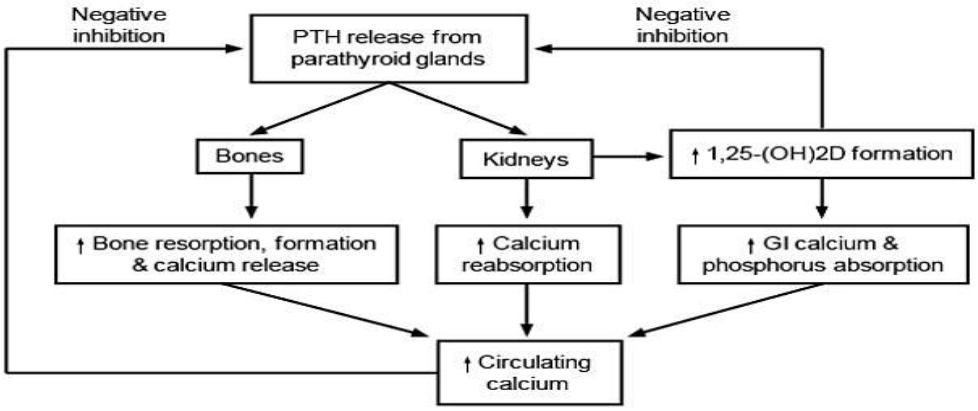
HYPOPARATHYROIDISM

Primary hypoparathyroidism:

- Hypocalcemia+ hyperphosphatemia+ normal renal function tests
- **Causes:**
  1. Post-surgical (most common)—thyroidectomy or sub-total parathyroidectomy (i.e. removal of 3 ½ parathyroid glands for parathyroid hyperplasia)→usually severe symptoms even with mild hypocalcemia
  2. Autoimmune—most common non-surgical cause
  3. Congenital absence or mal-development of parathyroid glands (eg DiGeorge)
  4. Defective calcium sensing receptors on parathyroid glands
  5. Non-autoimmune destruction of parathyroid gland sue to infiltrative dis. Such as hemochromatosis, Wilson and neck irradiation
- **C/F:**
  1. may be asymptomatic initially→found incidentally or may complain only of non-specific symptoms like fatigue, anxiety, depression
  2. Perioral tingling and numbness
  3. Muscle cramps
  4. Tetany
  5. Carpopedal spasm
  6. Seizures in severe cases
  7. **Can prolong QT interval**

CALCIUM METABOLISM

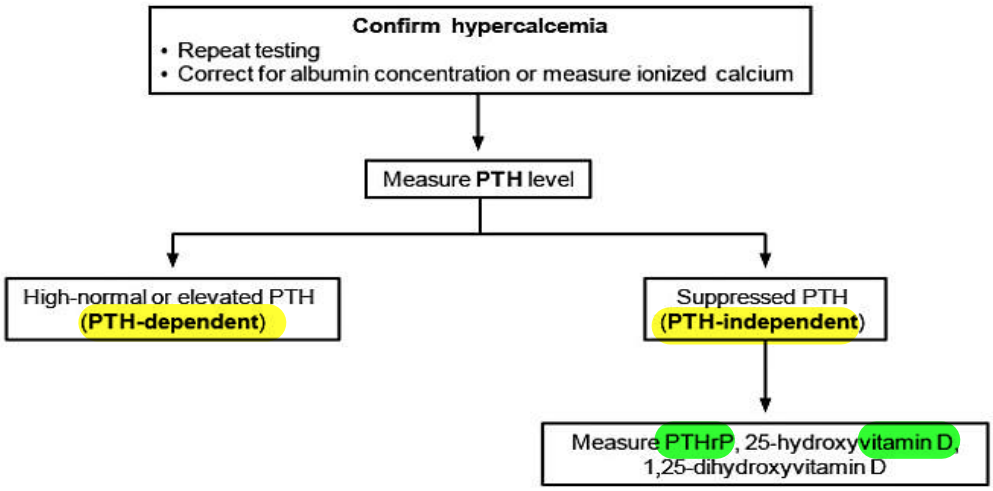
PTH, vitamin D & calcium axis



GI = gastrointestinal; **PTH** = parathyroid hormone.

Hypercalcemia

Diagnosis of hypercalcemia



Causes
- **Primary** (or tertiary) **hyperparathyroidism**
- Familial hypercalcemic hypocalciuria
- Lithium

Causes
- **Malignancy** most common cause
- Vitamin D toxicity
- Granulomatous diseases
- Drug-induced (eg, thiazides)
- Milk-alkali syndrome
- Thyrotoxicosis
- Vitamin A toxicity
- Immobilization

PTH = parathyroid hormone; **PTHrP** = parathyroid hormone-related protein.

Vitamin D induced hyperglycemia

Causes of vitamin D-induced hypercalcemia	
Exogenous	Non-prescription: • Supplemental megadoses or fortified foods Prescription: • Vitamin D2 or D3 • Calcidiol (25-OH-vitamin D) • Calcitriol (1,25-OH-vitamin D) • Calcipotriene (topical vitamin D derivative)
Endogenous*	• Granulomatous diseases (eg, sarcoidosis) • Lymphoma

*Conversion of 25-OH-vitamin D to 1,25-OH-vitamin D

Malignancy-associated hypercalcemia

Malignancy-associated hypercalcemia		
Cause	**Tumor**	**Mechanism**
PTHrP production (**80%** of malignancy-induced hypercalcemia)	• Squamous cell cancers (eg, lung, head, neck, esophagus) • Renal & bladder cancer • Ovarian & endometrial cancer • Breast cancer	Activation of PTH receptor, excessive bone resorption
1,25(OH)2 vitamin D production	• Lymphomas (all types)	Excessive gut absorption of calcium
Bone metastasis	• Breast cancer • Multiple myeloma • Lymphomas	Release of local factors (eg, cytokines) to stimulate bone resorption
Ectopic PTH production (very rare)	• Variable	Bone resorption

PTH = parathyroid hormone; **PTHrP** = parathyroid hormone-related protein.

Humoral Hypercalcemia of Malignancy (HHM)

- ↑PTHrP→↑bone resorption and ↑ absorption from distal convulated tubule→↑calcium. Does not induce conversion of 25-OH vitamin D to 1,25-diOH vitamin D to the same extent as PTH and hence its levels will be low or low normal
- Severe hypercalcemia (>14 g/dl) as compared to mild to moderate hypercalcemia (<14g/dl) in primary hyperparathyroidism and mild hypercalcemia (<12 g/dl) in thiazide use
- Rapid onset hypercalcemia→Dx on clinical grounds, confirmed with ↑ PTHrP and suppressed PTH level

- Usually seen in advanced malignancy→poor prognosis

→ Phosphorus level is usually normal in lytic bone mets. And is also a rare condition as compared to HHM

Hypercalcemia of immobilization

- Unclear mechanism but likely due to increased osteoclastic bone resorption
- ↑risk is pts with ↑ pre-existing bone turnover like younger individuals and older people with Paget's disease
- **Onset of hypercalcemia:** depends on bone turnover and calcium excretion by kidneys—median time 4 wks after onset of immobilization.
  - **Pts with CRF**: develop hypercalcemia as early as 3 days of immobilization
- Prolonged immobilization→ significant bone loss→prevent by giving bisphosphonates→Rx: hydration and bisphosphonates

---

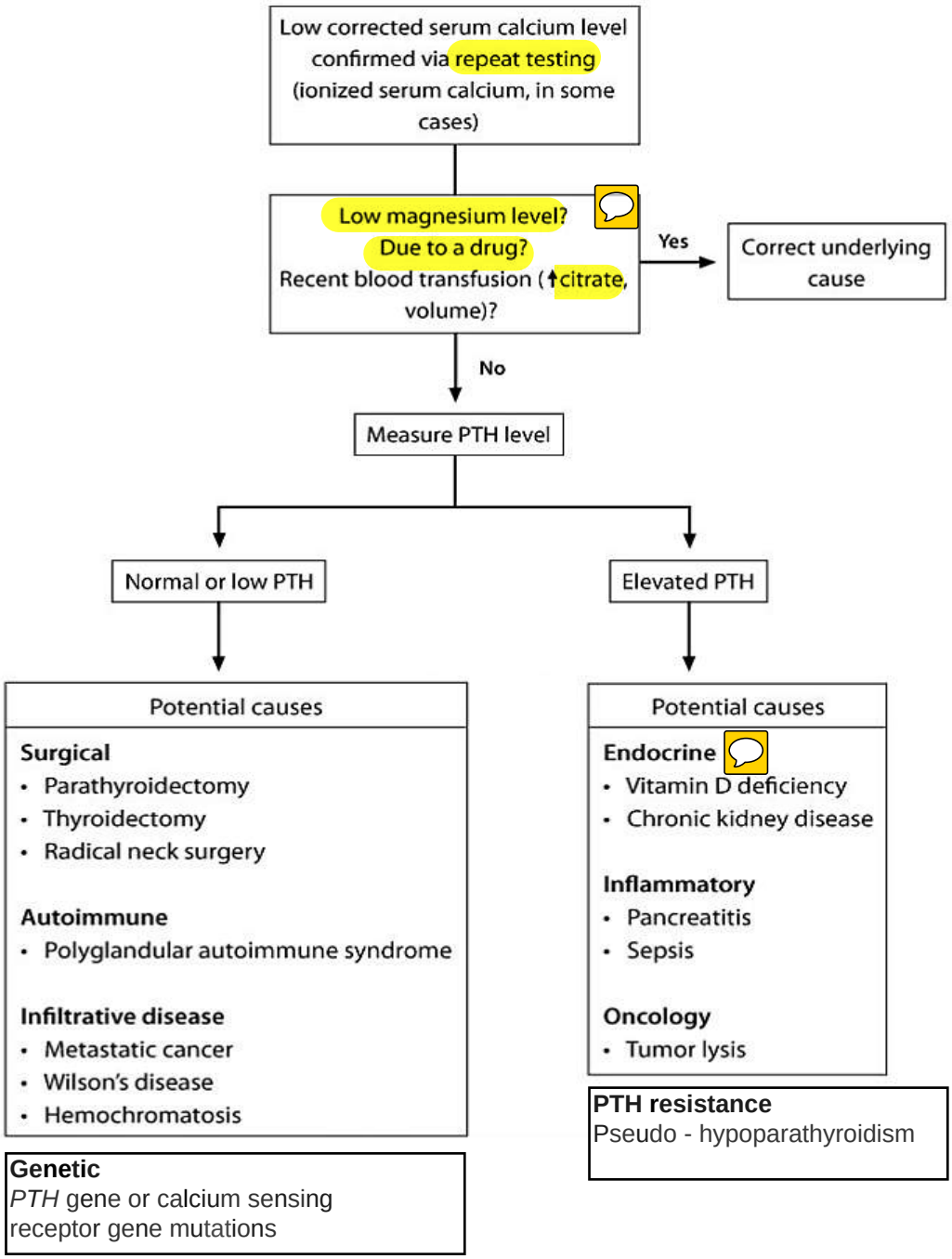
Hypocalcemia

- Cytochrome P450 inducers can cause conversion of vitamin D into inactive metabolites
- Renal failure, rhabdomyolysis and phosphate administration→Precipitation of calcium with phosphate→hypocalcemia
- Certain drugs like phenytoin, bisphosphonates, calcium chelators
- **Rhabdomyolysis→** initially cause hypocalcemia due to precipitation of calcium with phosphorus released from damaged muscles. Later develop hypercalcemia during diuretic/ recovery phase of illness
- 40% calcium is bound to proteins mainly albumin
- Hypoalbuminemia→ may decrease total calcium level and not ionized calcium level

The serum calcium concentration decreases by **0.8 mg/dL for every 1 g/dL decrease in serum albumin**, expressed in the following formula:

Corrected calcium = (measured total calcium) + 0.8 (4.0 g/dL - serum albumin in g/dL)

Diagnostic approach to hypocalcemia



Acute hypocalcemia	
Causes	• **Neck surgery** (parathyroidectomy) • Pancreatitis • Sepsis • Tumor lysis syndrome • Acute alkalosis • **Chelation**: Blood (citrate) transfusion, EDTA, foscarnet
Clinical features	• Muscle cramps • Chvostek & Trousseau signs • Paresthesias • Hyperreflexia/tetany • Seizures
Treatment	• IV calcium gluconate/chloride

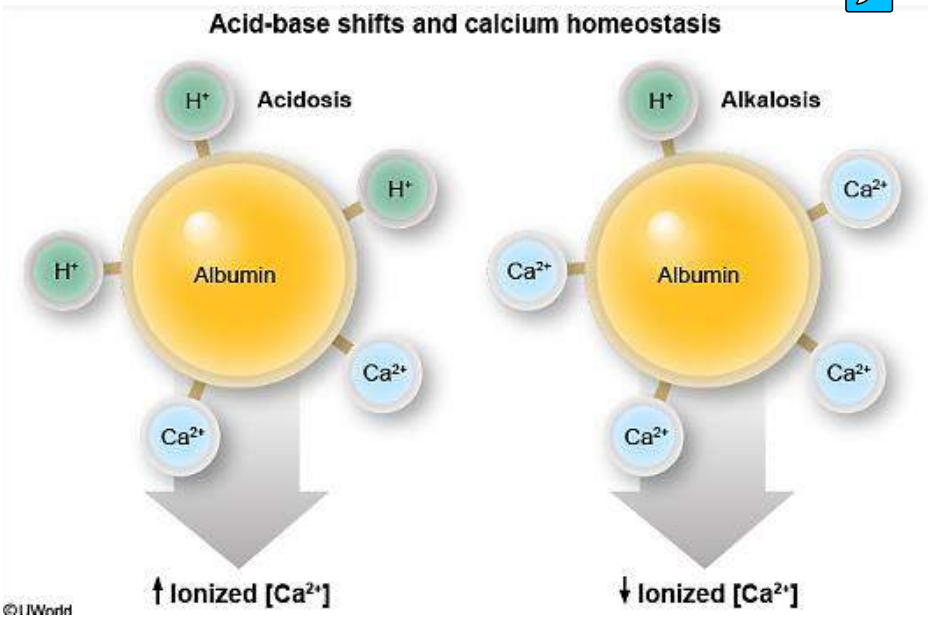
Hypocalcemia occurs in acute pancreatitis and not chronic pancreatitis

Plus laryngospasm, encephalopathy and heart failure

EDTA = ethylenediaminetetraacetic acid.

- Hypocalcemia is uncommon after blood transfusion in pts with normal liver. Pts with ↓ liver function are prone to hypocalcemia because of ↓ ability of liver to remove citrate rapidly
- Hypomagnesemia→can present similarly as hypocalcemia
- **Hypomagnesemia**→PTH resistance + ↓ PTH secretion→↓PTH→hypocalcemia and normal or ↓ phosphate (↓ GI absorption and ↑urinary loss of phosphare in alcoholics). Common in alcoholics due to ↑ urinary loss, malnutrition, acute pancreatitis and diarrhea. Does not respond to calcium. Magnesium repletion→ quick PTH recovery→ calcium takes time to reach normal level
- ***Severe* hypermagnesemia**→hyporeflexia, apnea, paralysis and cardiac arrest
- **Very severe hypermagnesemia**→inhibit PTH→hypocalcemia. It typically occurs after infusion of magnesium like in pre-eclampsia and eclampsia

Effect of acidosis and alkalosis on ionized calcium level



OSTEOMALACIA

Clinical features of osteomalacia	
Causes	• Malabsorption • Intestinal bypass surgery • Celiac sprue • Chronic liver disease • Chronic kidney disease
Symptoms/ signs	• May be asymptomatic • Bone pain and muscle weakness • Muscle cramps • Difficulty walking, waddling gait
Diagnosis	• ↑ Alkaline phosphatase, ↑ PTH • ↓ serum calcium and phosphorus, ↓ urinary calcium • ↓ 25 OH-D levels • X-rays may show thinning of cortex with reduced bone density , eventual codfish vertebral bodies (concave shape) • Bilateral and symmetric **pseudofractures** (Looser zones) are characteristic radiologic finding

- Osteomalacia—due to **defective mineralization of osteoid bone matrix**
- can occur in children and adults (rickets—in children—defective mineralization of growth plate)
- **Causes:** most commonly vitamin D deficiency. Also caused by RTA type 2 and inadequate calcium intake
- **Vitamin D deficiency**→↓Ca++ and PO4→↑PTH→↑calcium reabsorption from bones (↑ alkaline phosphatase) and kidneys and ↑ phosphorus loss from kidneys→more severe phosphate def. than calcium deficiency esp. in early stages
- **C/f:** fracture esp in weight bearing joints of lower extremities.

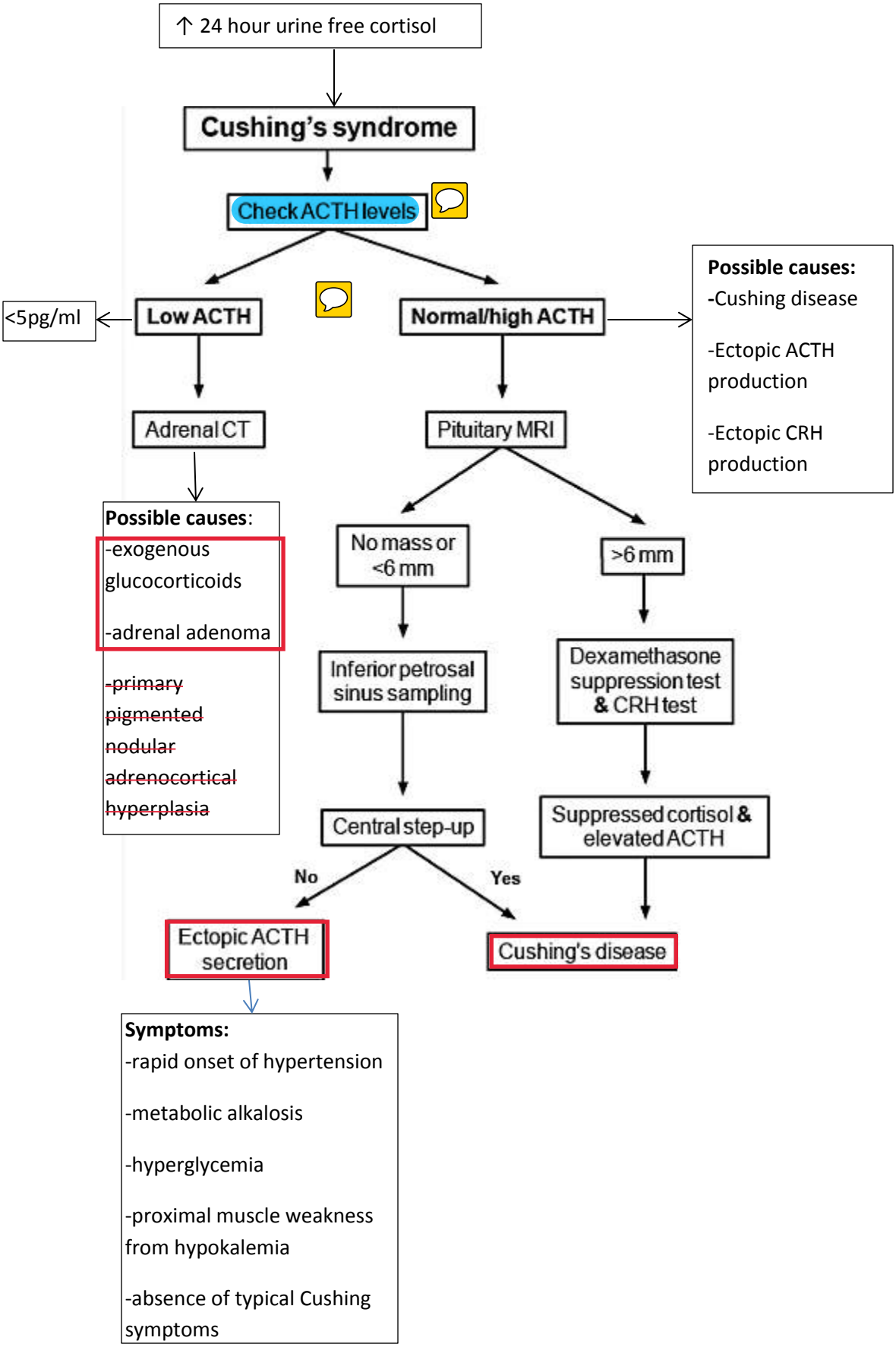
PAGET'S DISEASE

- Normal serum calcium, phosphorus, and parathyroid hormone
- Marker of bone resorption (c-telopeptide, n-telopeptide) and bone formation (alkaline phosphatase, osteocalcin)—significantly ↑.

path: accelerated focal bone remodeling

ADRENAL GLAND

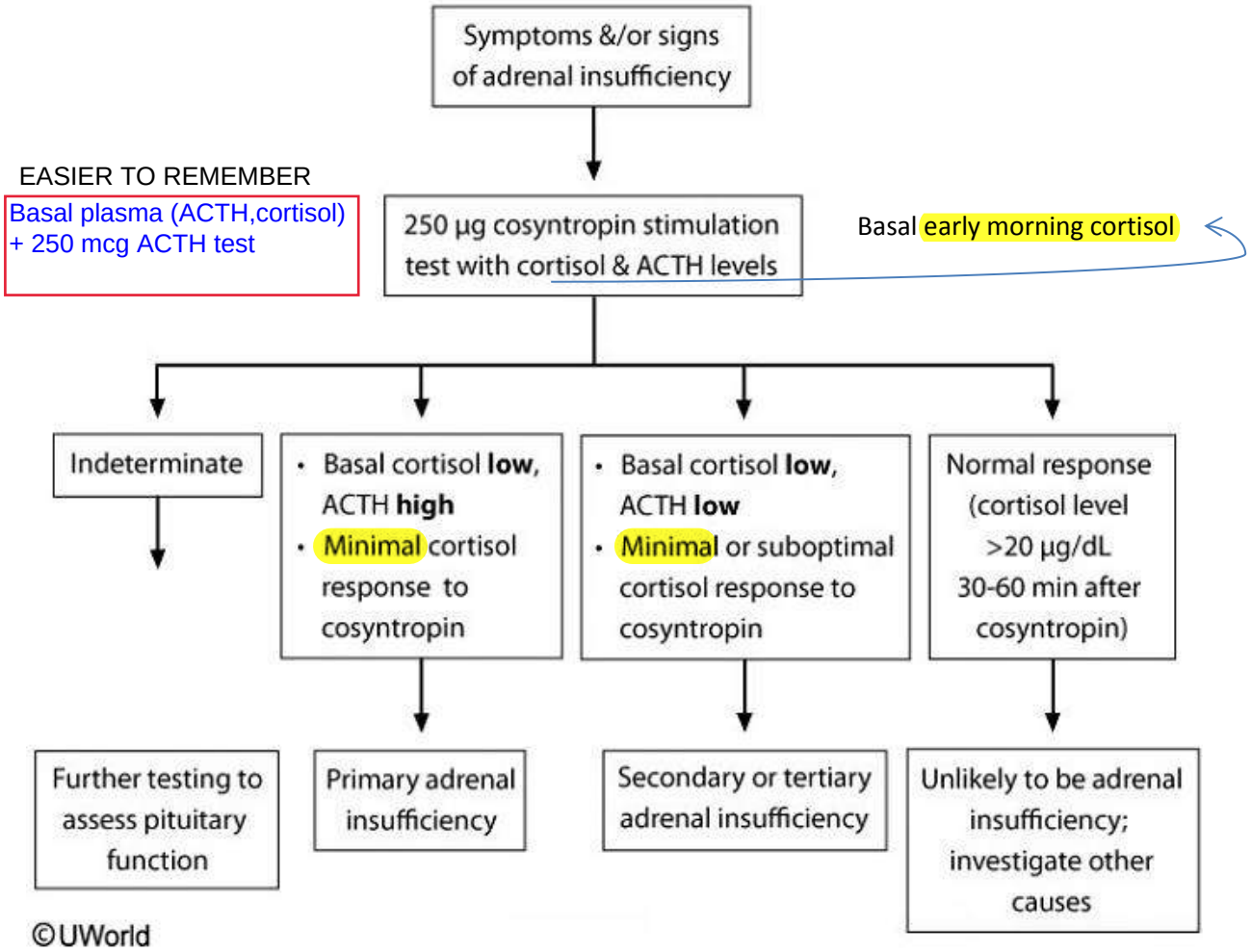
CUSHING SYNDROME



Features of Cushing syndrome	
Clinical manifestations	• Progressive central obesity (eg, fat accumulation in the cheeks and dorsocervical & supraclavicular fat pads) • Skin atrophy and wide purplish striae • Proximal muscle weakness • Hypertension • Glucose intolerance • Skin hyperpigmentation (due to ACTH excess)
Diagnosis	• 24-hour urinary cortisol excretion • Late evening salivary cortisol • Low-dose dexamethasone suppression test

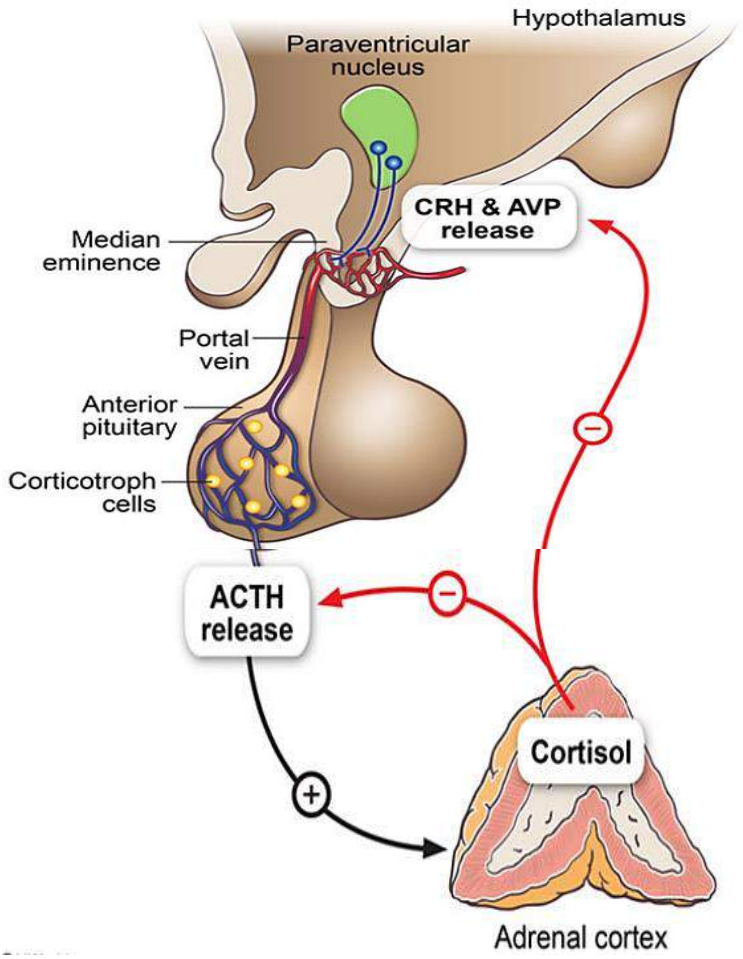
Ectopic ACTH production is most common with lung cancer (small cell lung cancer—rapid onset of Sx) and carcinoid (eg bronchial, pancreas, thymus—slow onset of Sx)

ADRENAL INSUFFICIENCY



Primary versus central adrenal insufficiency		
	Primary	Secondary
Most common cause	Autoimmune	Chronic glucocorticoid therapy
Cortisol	↓	↓
ACTH	↑	↓
Aldosterone	↓	Normal
Clinical features	• Severe symptoms • Hyperpigmentation • Hyperkalemia • Hyponatremia • Hypotension	• Less severe symptoms • No hyperpigmentation • No hyperkalemia • Possible hyponatremia Hyponatremia is because of ↑ ADH secretion

Hypothalamic-pituitary-adrenal axis



- **primary AI** have loss of glucocorticoid, mineralocorticoid, and adrenal androgen secretion.
  - hyperpigmentation due to increased pituitary secretion of ACTH and melanocyte-stimulating hormone.
- **secondary AI** have only glucocorticoid and drenal androgen deficiency with preservation of mineralocorticoid production (regulated primarily by the renin-angiotensin system, not the pituitary)
→ Therefore, hyperkalemia, significant hypotension, and hyperchloremic acidosis are not seen.
- The key differentiating features of PAI from central adrenal insufficiency are **hyperpigmentation** and **hyperkalemia** seen in PAI.

C/F of Primary Adrenal Insufficiency (Addison's disease)

- **Normal anion gap metabolic acidosis**. ↓ cortisol, aldosterone and sex steroids

Clinical features of primary adrenal insufficiency	
Etiology	• Autoimmune • Infections (eg, tuberculosis, HIV, disseminated fungal) • Hemorrhagic infarction (eg, meningococcemia, anticoagulants) • Metastatic cancer (eg, lung)
Clinical presentation	**Acute** crisis • Most commonly with shock • Abdominal tenderness with deep palpation (unclear etiology) • Unexplained fever • Nausea, vomiting, weight loss & anorexia • Hyponatremia, hyperkalemia, hypercalcemia & eosinophilia **Chronic** • Fatigue, weakness & anorexia • Gastrointestinal (eg, nausea, vomiting, abdominal pain) • Weight loss • Hyperpigmentation or vitiligo • Hypotension, hyponatremia, hyperkalemia & hypercalcemia • Anemia & eosinophilia
Diagnosis	• Measure ACTH and serum cortisol with high-dose (250 µg) ACTH stimulation test • **Primary adrenal insufficiency:** Low cortisol, high ACTH • **Secondary/tertiary adrenal insufficiency:** Low cortisol, low ACTH

Diseases like coccidioidomycosis, histoplasmosis, and cryptococcosis. Sarcoidosis

TB is very imp cause of chronic adrenal insufficiency in endemic areas

Altered mental status.

Chronic may lead to acute adrenal crisis

Salt-craving

Secondary Adrenal insufficiency: **CHRONIC STEROID USE**

- HPA not suppressed if glucocorticoids taken for <3 weeks or in dose <5mg→ do not need stress dose
- Intermediate dose of glucocorticoids (5-20mg or equivalent)→evaluation with early morning cortisol level before surgery for need of stress dose
- HPA is suppressed if prednisone is taken daily for >/= 3weeks in a dose >/=20mg (or equivalent). Those with Cushingoid features are also at ↑ risk of HPA suppression→need higher doses of short term glucocorticoid in acute condition ("stress dose")
- Normal HPA function not fully recover until 6-12 months of discontinuation of meds
- Etomidate can inhibit steroid synthesis inhibition and acute adrenal crisis→avoid in pts suspected of HPA suppression
- **C/f:** hyponatremia, hyperkalemia, hypoglycemia and hypotension needing large amount of IV fluids

Acute adrenal insufficiency (adrenal crisis) Qid: 4077	
Risk factors	Adrenal hemorrhage/infarction Acute illness, injury, or surgery in patients with: • Chronic adrenal insufficiency • Chronic glucocorticoid use • Congenital adrenal hyperplasia
Clinical features	• **Hypotension/shock** • Nausea/vomiting, abdominal pain • Weakness • Fever • Acute kidney injury
Diagnostic testing	• Cortisol • Electrolytes, BUN, creatinine, glucose • ACTH • Renin • ACTH stimulation test when stable
Treatment	• **Hydrocortisone or dexamethasone** • High-flow intravenous fluids • Monitor serum electrolytes

Screening:

- All the above 3 tests i.e **basal early morning cortisol, ACTH and cosyntropin** (synthetic ACTH analog) are performed simultaneously to expedite diagnosis as result for ACTH can take several days
- Low cortisol (<5µg/dl)+ high ACTH (>50pg/dl)→ **primary adrenal insufficiency (Addison disease)**
- Low cortisol (<5µg/dl)+ low ACTH (<50pg/dl)→ **central adrenal insufficiency (pituitary or hypothalamus)**
- Early morning cortisol 5-15 µg/dl→indeterminate
- Early morning cortisol >15 µg/dl→very low risk of adrenal insufficiency

→24 hour urine cortisol is not recommended for this

Rx:

- Hydrocortisone is started as soon as diagnosis is established
- May not wait for test results and start hydrocortisone in acute condition

Insulin tolerance test (also called insulin hypoglycemia test)—difficult test and not commonly performed

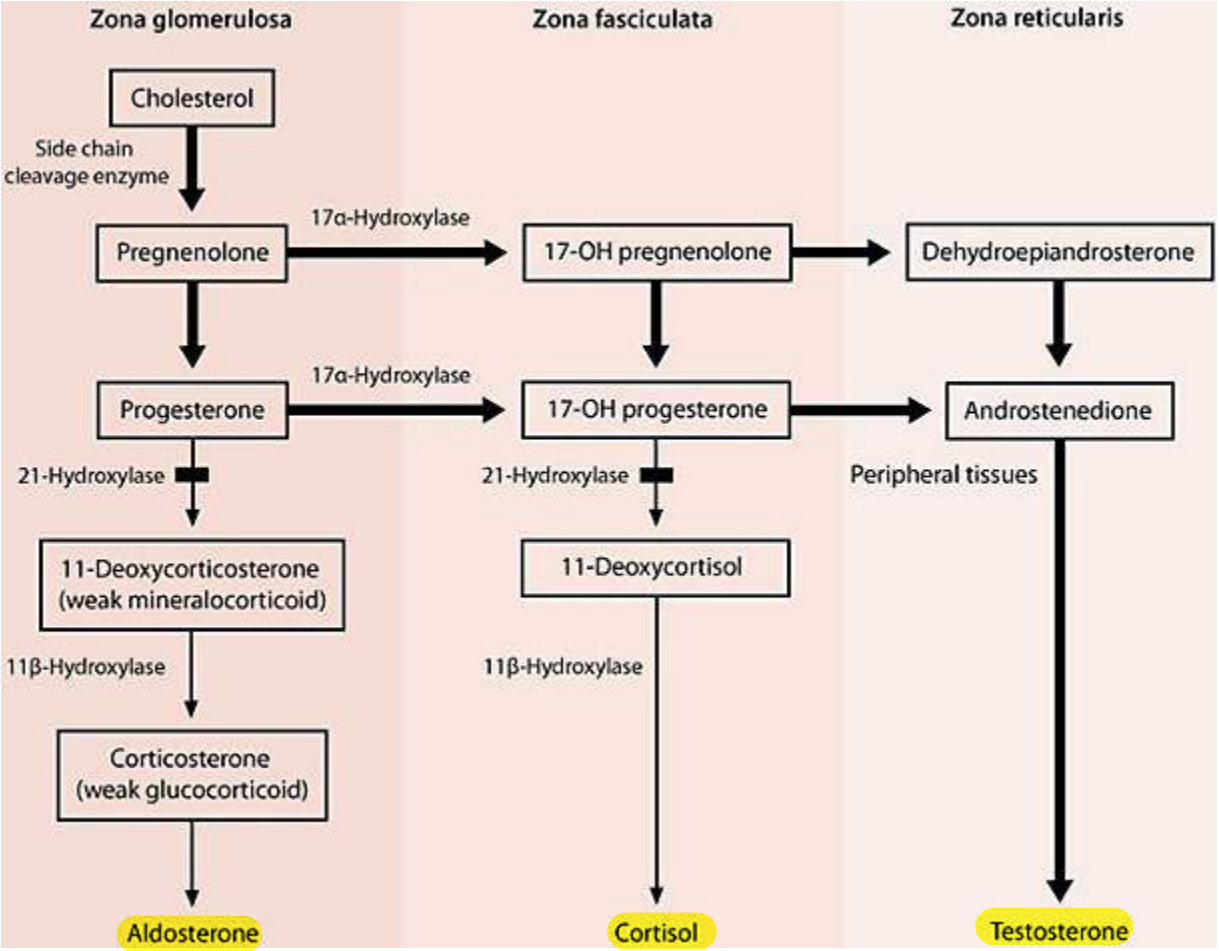
- Insulin→hypoglycemia→activates hypothalamic pituitary adrenal axis (in normal individuals)→ response is blunted in pts with primary and central AI

CONGENITAL ADRENAL HYPERPLASIA

- Depends on the deficiency of enzyme

21-hydroxylase deficiency:

- Most commonly due to **21-hydroxylase deficiency**—90% cases



Enzyme deficiency	Hormonal abnormalities	Symptoms
21-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 17-hydroxyprogesterone	• Ambiguous genitalia in girls • Salt wasting (vomiting, hypotension, $\downarrow Na^+$, $\uparrow K^+$)
11β-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 11-deoxycorticosteone (weak mineralocorticoid) & 11- deoxycortisol	• Ambiguous genitalia in girls • Fluid & salt retention, hypertension
17α-hydroxylase	• ↓ Cortisol & testosterone • ↑ Mineralocorticoids • ↑ Corticosterone (weak glucocorticoid)	• All patients phenotypically female • Fluid & salt retention, hypertension

- Marked **↑ 17-hydroxyprogesterone** is diverted towards adrenal androgen synthesis and leads to **hyperandrogenism→** impair hypothalamic sensitivity to progesterone→ rapid ↑ GnRH synthesis→ ↑LH and FSH→↑gonadal steroid production **(↑17-hydroxyprogesterone, DHEA, testosterone, LH,**

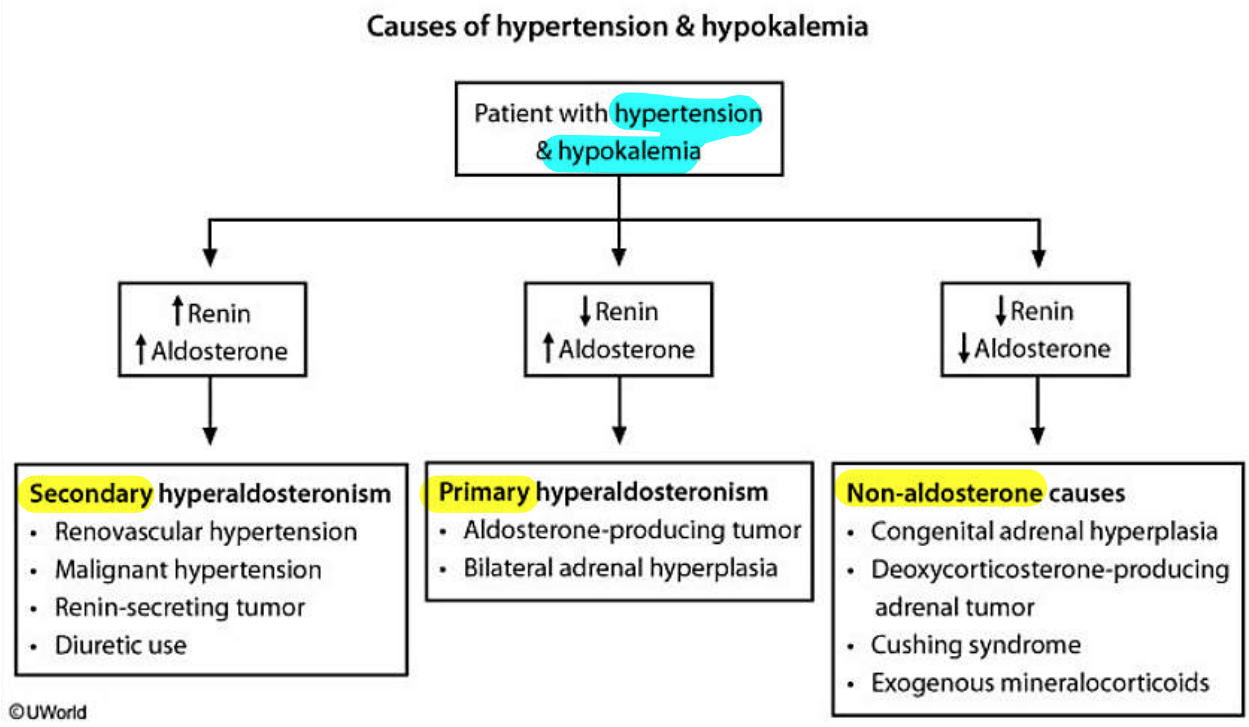
FSH)—**ACTH stimulation test**→ exaggerated 17 hydroxyprogesterone response. Cosyntropin stimulation test is gold standard for partial deficiencies

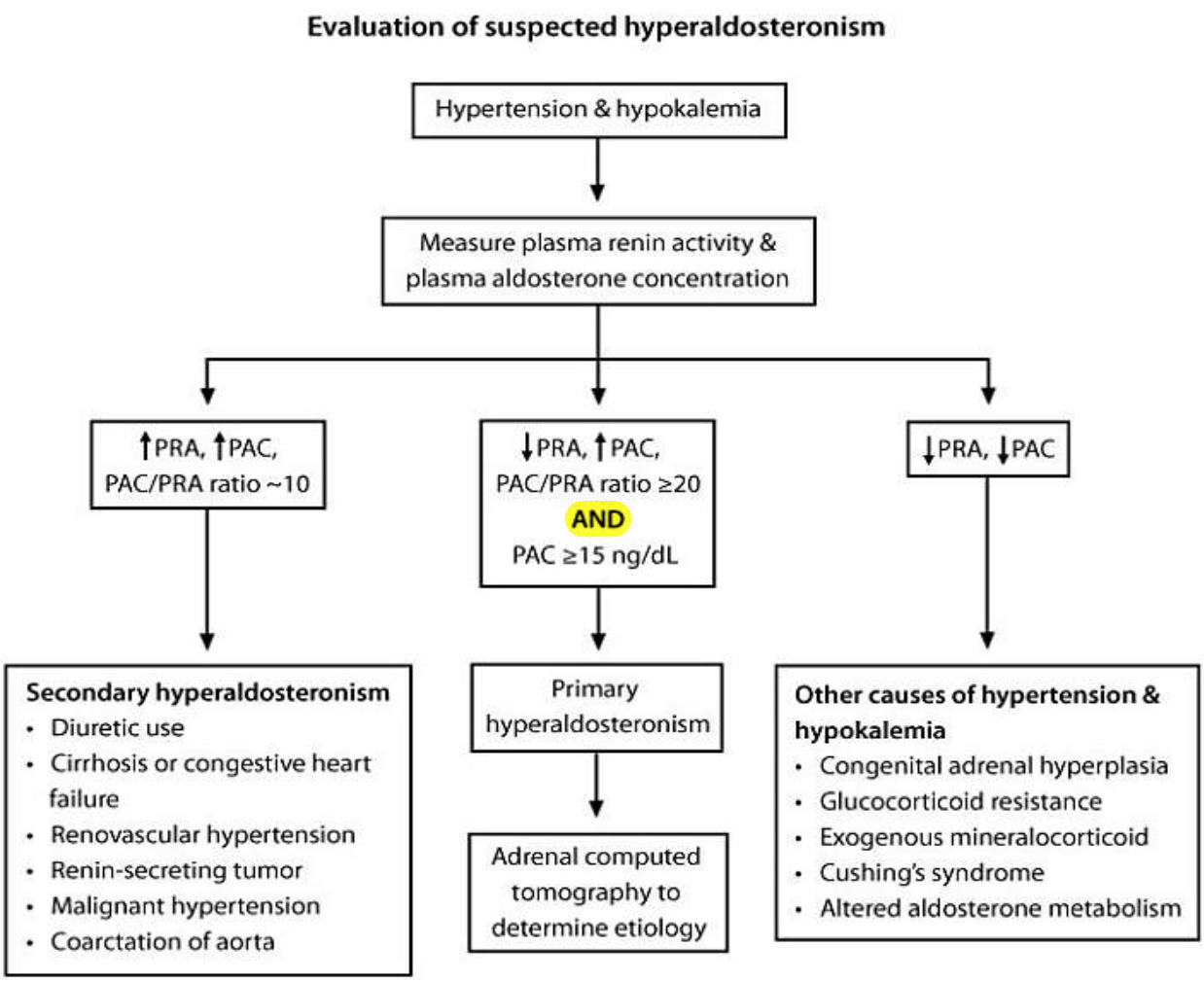
- ↓ in cortisol→↑ACTH→adrenal hyperplasia
- ↓ aldosterone→ salt wasting
- **C/F:** depend on degree of enzyme deficiency
  1. **Severe (classic) 21 hydroxylase def**—present in infancy with **virilization and salt losing crisis**
  2. **Late-onset (non-classic) 21 hydroxylase def** (CYP21A2 deficiency)—mild, <u>females</u> present in teens or twenties with **cystic acne non-responsive to meds, irregular menses,** and **hirsuitism,** virilization not seen; <u>boys</u> present with precocious puberty—hyponatremia variable in both sexes

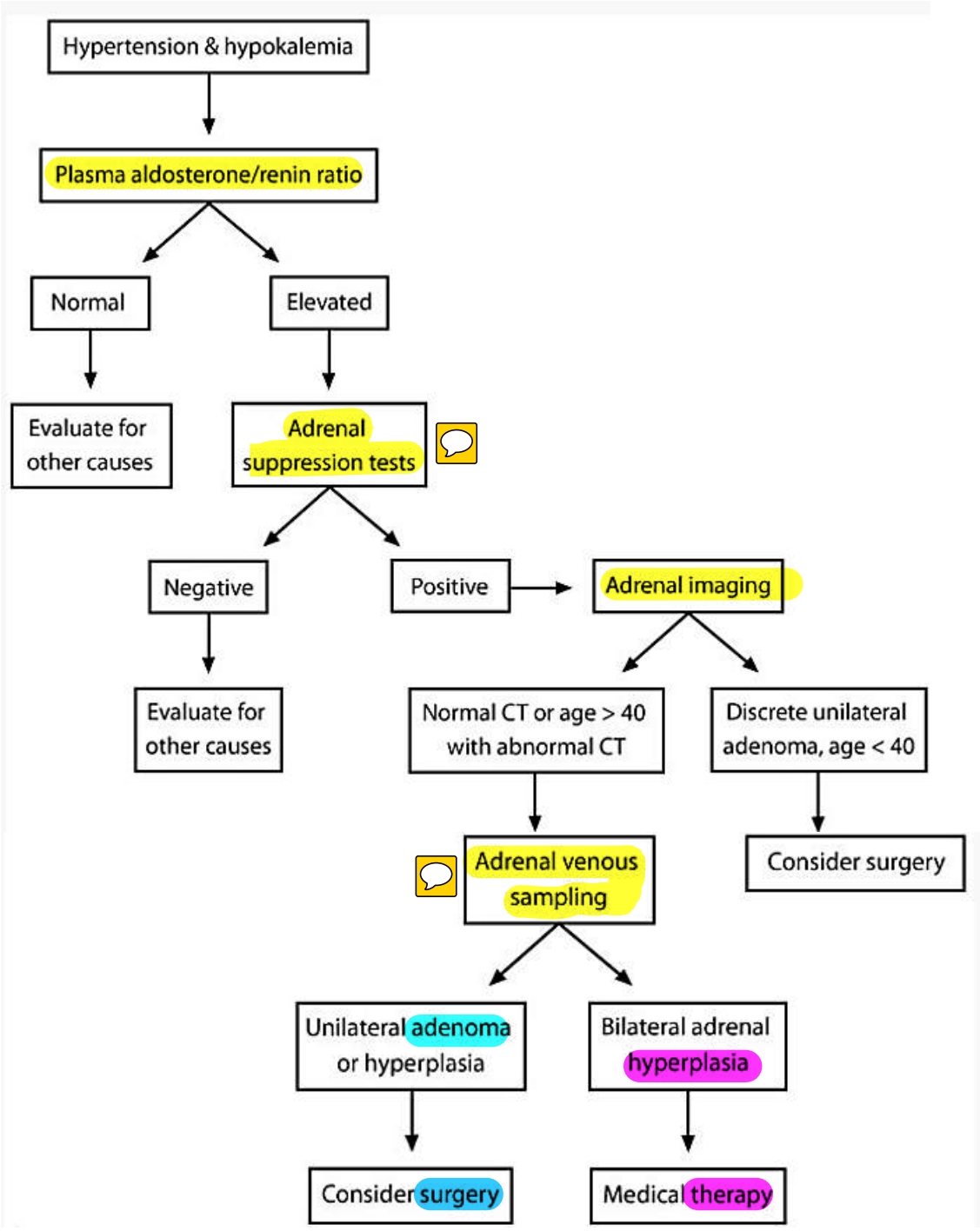
ADRENOCORTICAL CANCERS:

- Rare, aggressive
- Present in adulthood usually
- **Types**: androblastoma, arrhenoblastoma, stromal and hilus cell tumor
- **C/F:** rapidly progressive hirsuitism and sometimes virilization
- **Labs:** serum DHEA-S (adrenal androgen)—markedly ↑ >700µg/Dl

HYPERALDOSTERONISM




Evaluation of suspected hyperaldosteronism
Hypertension & hypokalemia
Measure plasma renin activity & plasma aldosterone concentration
↑PRA, ↑PAC, PAC/PRA ratio ~10
↓PRA, ↑PAC, PAC/PRA ratio ≥20 AND PAC ≥15 ng/dL
↓PRA, ↓PAC
Secondary hyperaldosteronism
• Diuretic use
• Cirrhosis or congestive heart failure
• Renovascular hypertension
• Renin-secreting tumor
• Malignant hypertension
• Coarctation of aorta
Primary hyperaldosteronism
Adrenal computed tomography to determine etiology
Other causes of hypertension & hypokalemia
• Congenital adrenal hyperplasia
• Glucocorticoid resistance
• Exogenous mineralocorticoid
• Cushing's syndrome
• Altered aldosterone metabolism


Hypertension & hypokalemia
Plasma aldosterone/renin ratio
Normal
Elevated
Evaluate for other causes
Adrenal suppression tests
Negative
Positive
Adrenal imaging
Evaluate for other causes
Normal CT or age > 40 with abnormal CT
Discrete unilateral adenoma, age < 40
Adrenal venous sampling
Consider surgery
Unilateral adenoma or hyperplasia
Bilateral adrenal hyperplasia
Consider surgery
Medical therapy

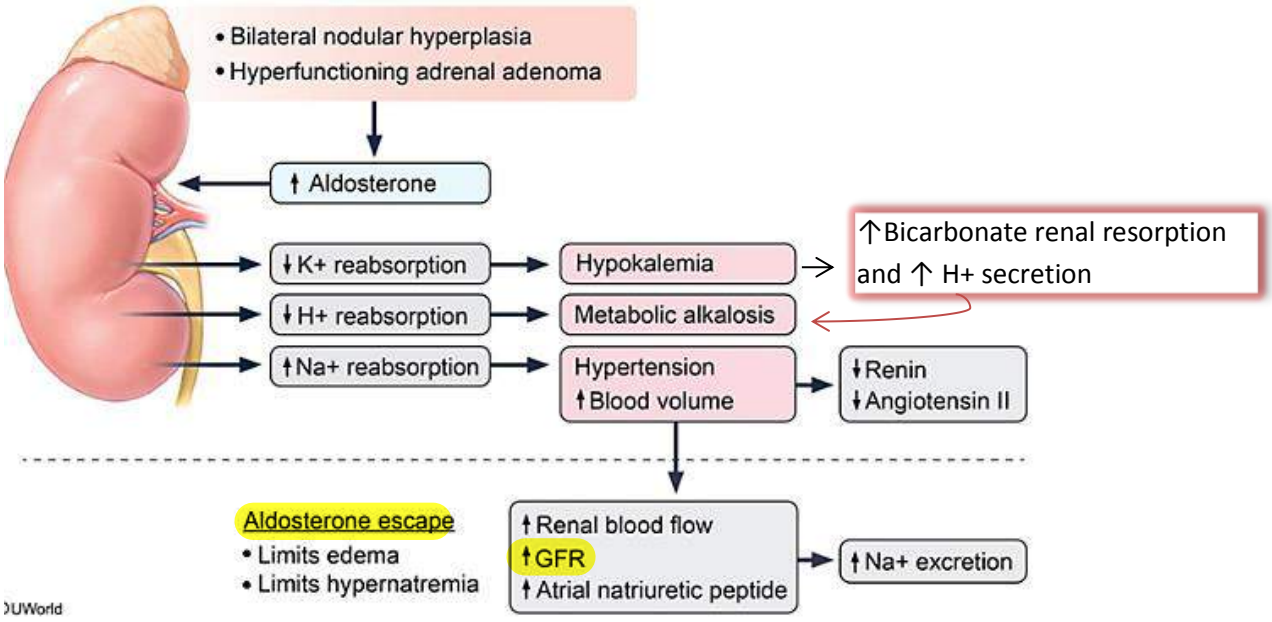
In **primary hyperaldosteronism**,

Clinical features of primary hyperaldosteronism	
Clinical presentation	• Hypertension, metabolic alkalosis, hypokalemia, mild hypernatremia • No significant peripheral edema due to aldosterone escape
Diagnosis	• Elevated plasma aldosterone, low plasma renin • Plasma aldosterone to plasma renin activity ratio >20 suggests diagnosis • Adrenal suppression testing after oral saline load confirms diagnosis • Abdominal imaging (eg, CT) & adrenal venous sampling to distinguish between unilateral adrenal adenoma & bilateral adrenal hyperplasia
Treatment	**Unilateral adrenal adenoma** • Surgery (preferred) • Aldosterone antagonists (eg, spironolactone, eplerenone) for poor surgical candidates or patients refusing surgery **Bilateral adrenal hyperplasia**: Aldosterone antagonists

In case of resistant HTN, thiazides or ACEi can be added

- Edema and hypernatremia is prevented by mechanism of aldosterone escape→most common cause of 2° HTN. Serum K+ may be normal initially**, but use of diuretics cause significant symptomatic hypokalemia.**
- Best screening test is early morning PAC/PRA ratio. Drugs that alter PAC/PRA ratio like spironolactone, eplerenone, amiloride, triamterene should be discontinued 4 weeks prior to testing.

Pathogenesis of primary hyperaldosteronism
(and aldosterone escape)



PHEOCHROMOCYTOMA

"Triad of pheochromocytoma are headaches, palpitations and sweating."

- Pheochromocytomas and paraganglionomas are catecholamine secreting tumors, from chromaffin cells of adrenal medulla and extra-adrenal paraganglia, respectively
- Intermittent or sustained HTN, pallor due to vasoconstriction
- Paroxysm of severe HTN can be precipitated by ↑ in intra-abdominal pressure (eg tumor palpation, positional change), surgical procedures and a number of medications, particularly **anesthetic agents**

PITUITARY GLAND

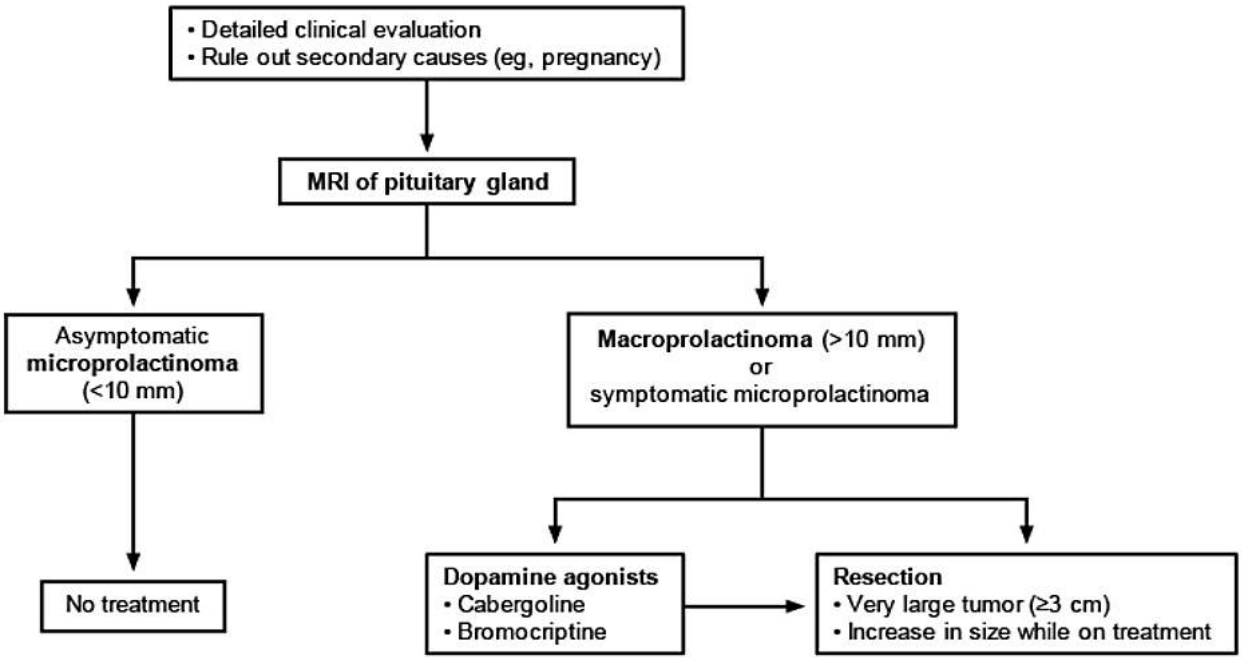
HYPOPITUITARISM

Clinical features of hypopituitarism	
Etiology	**Pituitary causes** • Primary (eg, adenoma) or metastatic mass • Infiltration (eg, hemochromatosis, lymphocytic hypophysitis) • Hemorrhage (pituitary apoplexy) or infarction (Sheehan syndrome) **Hypothalamic causes** • Mass lesions • Radiation therapy • Infiltration (sarcoidosis) • Trauma to skull base • Infections (tuberculosis meningitis)
Clinical presentation	**ACTH deficiency (secondary adrenal insufficiency)** • Postural hypotension, tachycardia, fatigue, weight loss, hypoglycemia, eosinophilia **Hypothyroidism (central)** • Fatigue, cold intolerance, constipation, dry skin, bradycardia, slowed deep-tendon reflexes **Gonadotropins** • Women: Amenorrhea, infertility • Men: Infertility, loss of libido

PROLACTINOMA

Prolactinoma overview	
Clinical features	• **Premenopausal women**: Oligo/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Rule out renal insufficiency (creatinine) & hypothyroidism (thyroid-stimulating hormone, thyroxine) • Magnetic resonance imaging of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

Management of hyperprolactinemia in premenopausal women



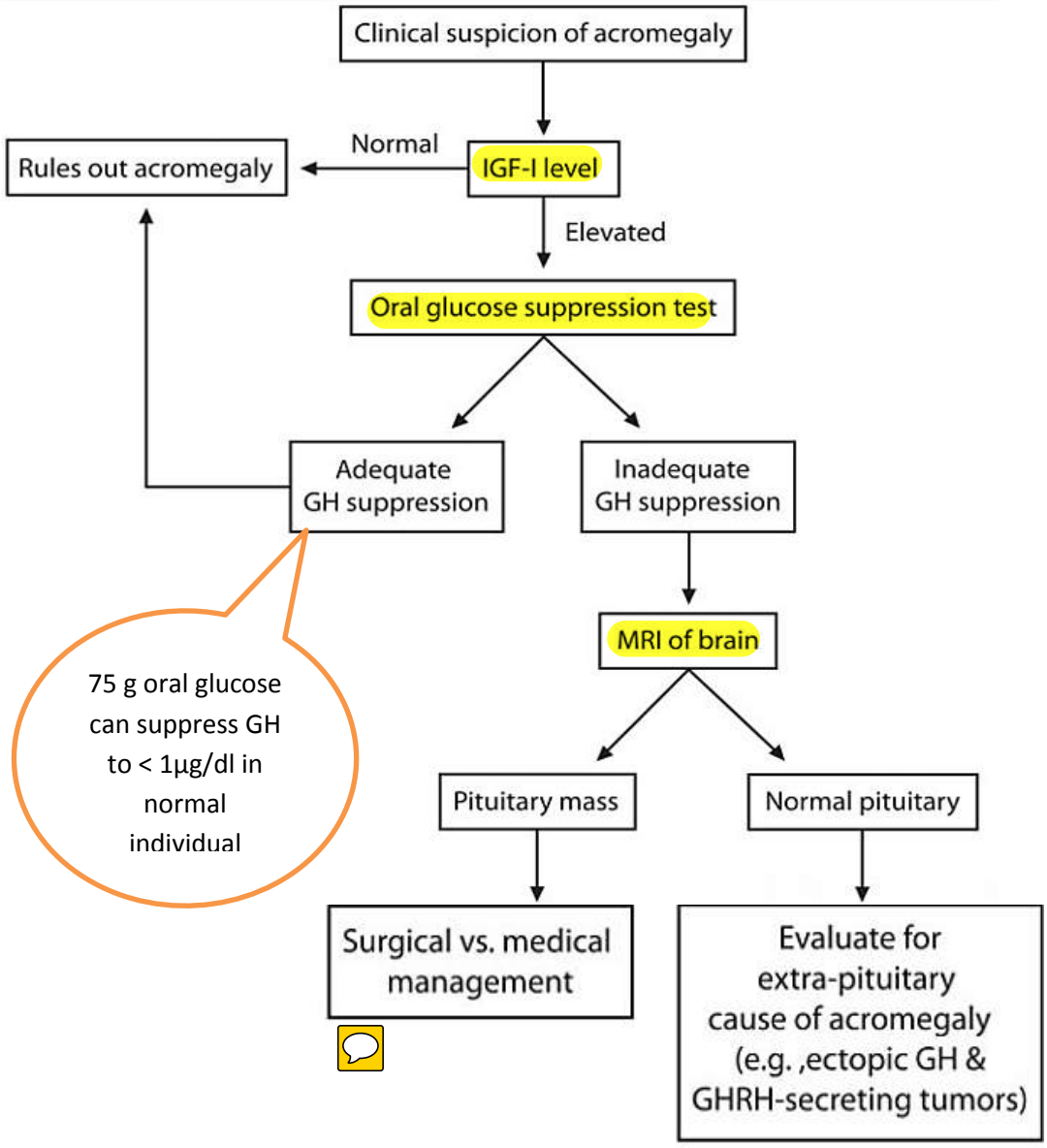
- Pt: women→ glactorrhea, amenorrhea
  men→ erectile dysfunction , ↓ libido

- significant elevations in the prolactin level (eg, serum prolactin level >200 ng/ml OR repeat level >100 ng/ml) suggest a prolactin-secreting tumor (prolactinoma).
- Elevated prolactin levels suppress gonadotropin-releasing hormone, LH, and estradiol.

- Prolactinomas are usually detected early (<10-mm microadenomas) in premenopausal women due to associated endocrine symptoms (oligo/amenorrhea, infertility, galactorrhea).

- Men and postmenopausal women often have minimal early symptoms and are more likely to seek evaluation when a large tumor (>1 cm, macroadenoma) causes mass-effect symptoms (eg, headache, visual field defects).
Qid: 3492 / 3493

GROWTH HORMONE SECRETING PITUITARY ADENOMA:



The following are some non-cardiac causes of death in patients with acromegaly:

1. Strokes: the incidence of strokes is higher in patients with acromegaly
2. Colon cancer: this condition is thought to occur with increased frequency
3. Renal failure: this can result from hypertension and hyperglycemia
4. Adrenal failure: this can occur due to hypothalamo-pituitary problems due to a pituitary tumor, although surgical resection and radiotherapy of the pituitary tumor can also cause secondary adrenal failure

- GH stimulates hepatic insulin-like growth factor 1 (IGF-1) secretion, which is responsible for most of the clinical manifestations of acromegaly.
- MOST COMMON cause is pituitary adenoma.

Common clinical features of untreated acromegaly	
Local tumor effect	Pituitary enlargement, visual field defects, headache, cranial nerve defects
Musculoskeletal/Skin	Gigantism, mal-occluded jaw, arthralgias/arthritis, proximal myopathy, hyperhidrosis, skin tags, carpal tunnel syndrome
Cardiovascular	Cardiomyopathy, hypertension, heart failure, valvular disease (eg, mitral and aortic regurgitation)
Pulmonary/GI	Sleep apnea, narcolepsy, colon polyps/cancer, diverticulosis
Enlarged organs	Tongue, thyroid, salivary glands, liver, spleen, kidney, prostate
Endocrine	Galactorrhea, decreased libido, diabetes mellitus, hyperparathyroidism, hypertriglyceridemia

- Arise from somatotrophs
- Most common cause of death is cardiovascular causes which include: coronary artery disease, cardiomyopathy, left ventricular hypertrophy, arrhythmias and diastolic dysfunction. 30% pts have HTN as well. treatment of acromegaly markedly ↓ cardiovascular mortality

NON- FUNCTIONING PITUITARY ADENOMA

- Arise from gonadotrophs in pituitary gland
- Gonadotrophs normally secrete LH and FSH with α and β subunits. β-subunit is different in both.
- Adenoma secretes α-subunit mainly (non-functioning)
- Space-occupying lesion which cause hypofunctioning of remaining gland→ ↓LH→↓testosterone (central hypogonadism); →↓TSH→↓thyroxine (central hypothyroidism); mildly elevated prolactin because of disruption of normal dopamine inhibitory pathway (in prolactonoma, prolactin is >200ng/ml)
- Diagnosis is not established until tumor is large enough to cause mass-effect

SHEEHAN SYNDROME

Sheehan syndrome	
Pathogenesis	• Heavy peripartum blood loss complicated by hypotension &/or blood transfusion • Postpartum pituitary infarction
Clinical features	• Symptoms of hypopituitarism (↓ prolactin, ACTH, TSH, FSH, LH, &/or growth hormone): ○ Lactation failure ○ Amenorrhea ○ Loss of sexual hair ○ Anorexia/weight loss ○ Lethargy ○ Hyponatremia

Non-lactating women typically resume menses 10 wks postpartum

- hypotension

- Symptoms can occur in immediate post-partum period or several years later
- Management: evaluation of pituitary hormones and replacement as needed

DIFFERENTIAL DIAGNOSIS OF HYPERANDROGENISM IN FEMALES

Differential diagnosis of hyperandrogenism in females	
Diagnosis	**Clinical features**
PCOS	Oligo-ovulation, clinical or biochemical hyperandrogenemia, polycystic ovaries on imaging, no evidence of another diagnosis
Nonclassic CAH	Oligo-ovulation, hyperandrogenemia, ↑ 17-OH-progesterone levels
Ovarian/adrenal tumors	Older age, rapidly progressive symptoms, ↑ androgen levels (>3 times upper limit of normal)
Hyperprolactinemia	Amenorrhea, galactorrhea, ↑ prolactin levels
Cushing's syndrome	Cushingoid features, nonsuppressible dexamethasone suppression test, ↑ 24-hour urinary free cortisol
Acromegaly	Excessive growth, ↑ GH & IGF-1 levels

CAH = congenital adrenal hyperplasia; **GH** = growth hormone; **IGF-1** = insulin-like growth factor-1; **PCOS** = polycystic ovary syndrome.

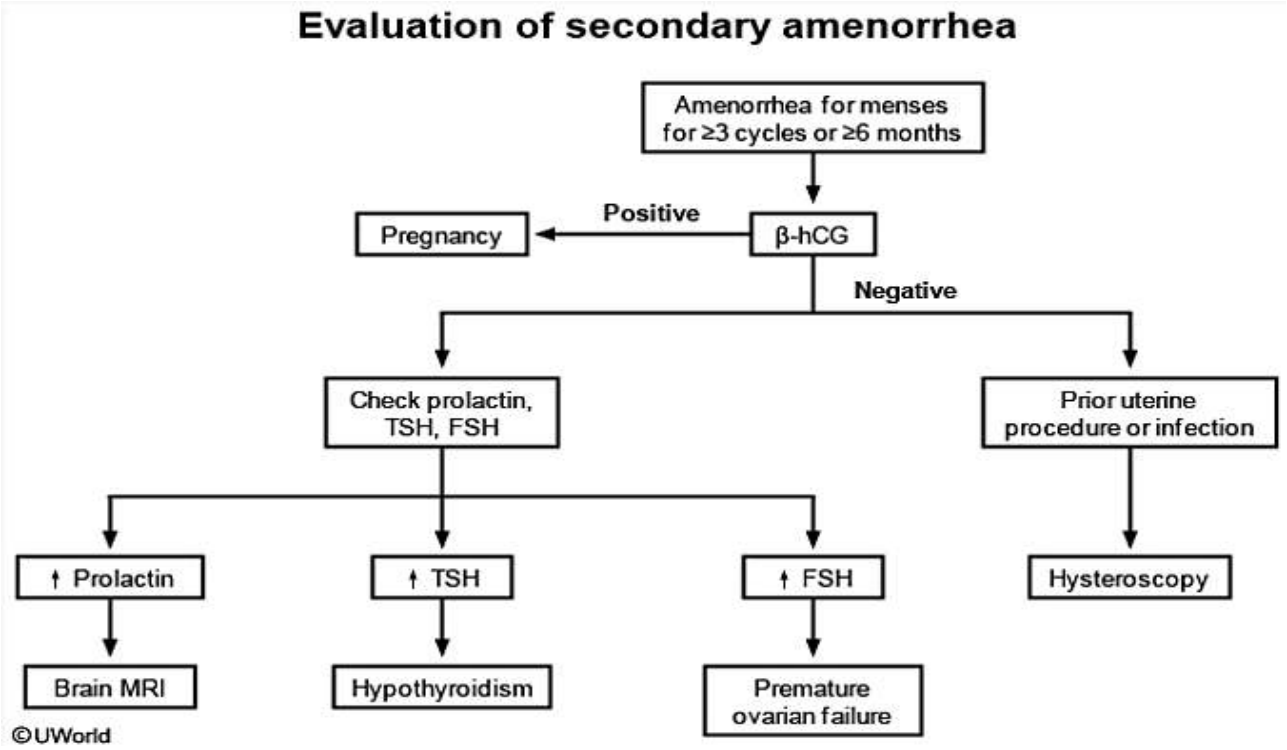
Idiopathic hirsuitism:

- Due to excessive conversion of testosterone to DHT in hair follicles. Usually +ve family history, no virilization. 17 OH-progesterone and androgens usually normal

Ovarian or Adrenal tumor:

- Rapidly progressing androgenic symptoms (hirsuitisim, virilization)→ovarian or adrenal tumor secreting excess androgen
- Measure testosterone and DHEAS as initial workup
- ↑ testosterone and normal DHEAS→ovarian tumor
- ↑ DHEAS and relatively normal testosterone→adrenal tumor
- DHEAS is specific for adrenal glands and is sulfated form of DHEA. DHEA is produced by both ovaries and testes

SECONDARY AMENORRHEA



COMMON CAUSES OF HYPOGONADOTROPIC HYPOGONADISM IN MALES

Common causes of hypogonadotropic hypogonadism in men
• Gonadotroph cell damage (eg, tumor, trauma, suprasellar surgery or radiation, infiltrative diseases, apoplexy) • Prolactinoma • Cushing syndrome (endogenous & iatrogenic) • Narcotic use • Severe systemic illness • Diabetes mellitus • Hemochromatosis • Anabolic steroid & testosterone use • Morbid obesity

- Alcohol intake can cause hypogonadism by suppressing LH release from pituitary or by directly inhibiting testosterone production from testes

GYNECOMASTIA

Common pathological causes of gynecomastia	
Increased estrogen production or peripheral conversion	• Testicular, adrenal, or human chorionic gonadotropin-secreting tumors • Cirrhosis or malnutrition • Thyrotoxicosis • Congenital excessive aromatase activity • Androgen use • Drugs (eg, spironolactone, cimetidine), herbal products (eg, tea tree oil, lavender oil)
Androgen deficiency	• Primary or secondary male hypogonadism (eg, Klinefelter syndrome, testicular damage) • Hyperprolactinemia • Renal failure

- Approx. 2/3rd pubertal boys develop gynecomastia. Usually resolve in few months to 2 years without interventions. If persistent→ look for other causes

METABOLIC SYNDROME

- **Features:** hypertension, impaired glucose tolerance and dyslipidemia
- pts are characteristically overweight with ↑waist-to-hip ratio

***Extremely high yield question for the USMLE!!!**

- **Insulin resistance is the main cause**
- **Diagnostic criteria:** 3 or more of below 5 should be present
  - Abdominal obesity (Men: waist circumference >40 inches; Women: waist circumference >35 inches)
  - Fasting glucose >100-110 mg/dl
  - Blood pressure >130/80 mmHg
  - Triglycerides >150 mg/dl
  - HDL cholesterol (Men <40 mg/dl and women <50 mg/dl)

Other features of insulin resistance (not involved in metabolic syndrome)

- Endothelial dysfunction
- Procoagulable state
- ↑ sympathetic activity
- ↑ markers of inflammation
- ↓ uric acid excretion
- ↑ sodium absorption
- Disordered breathing
- ↑ testosterone secretion by ovaries
- Impaired endothelial dependent vasodilation

DIABETES MELLITUS

DIABETES SCREENING

Current guidelines for screening for DM

- The **US Preventive Services Task Force (USPSTF)** recommends screening in patients with sustained blood pressure (treated or untreated) >135/80 mm Hg. However, there is insufficient evidence to establish the benefits of screening patients with blood pressure ≤135/80 mm Hg.
- The **American Diabetes Association** recommends screening in all patients age ≥45 years, as well as those at any age with additional risk factors for diabetes.

Diabetes risk factors in adults with BMI >25 kg/m^2
• Physical inactivity • First-degree relative with diabetes • High-risk race/ethnicity (eg, African American, Latino, Native American, Asian, Pacific Islander) • Women whose children's birth weight ≥9 lb • History of gestational diabetes mellitus • Hypertension or prior cardiovascular disease • Dyslipidemia (low HDL & high triglyceride level) • History of polycystic ovarian syndrome • History of glucose intolerance

SCREENING FOR GLUCOSE INTOLERANCE AND T2DM:

- 75 g 2-hour OGTT—preferred method
- If OGTT not feasible→ fasting blood glucose (FPG) (no calories for >/=8hours) and glycated hemoglobin A1c (HbA1c)→ not sensitive in detecting glucose intolerance
- Pt. with ↑ risk of diabetes have these values:
  - FPG of 100-125 mg/dL (5.6-6.9 mmol/L)
  - 2-hour OGTT level of 140-199 mg/dL (7.8-11.0 mmol/L)
  - HbA1c of 5.7%-6.4% (39-46 mmol/mol)
- T2DM diagnosis:
  - FPG >/= 126 mg/dL (7.0 mmol/L)
  - HbA1c >6.5% (48 mmol/mol)
  - 2-hour OGTT level of 200 mg/dL (11.1 mmol/L)
  - Random plasma glucose >/=200 mg/dl (11.1 mmol/L) plus symptoms

Tests used for screening

Screening tests for diabetes mellitus	
Test	**Interpretation**
A_{1c}	• Preferred test in nonfasting state • ≥6.5% = Diabetes mellitus • 5.7-6.4% = Increased risk for diabetes • <5.7% = Normal
Fasting blood glucose	• No caloric intake for >8 hours • **≥126 mg/dL** = Diabetes mellitus • 100-125 mg/dL = Increased risk for diabetes • <100 mg/dL = Normal
Random glucose levels	• **≥200 mg/dL** with symptoms of hyperglycemia = Diabetes mellitus • 140-199 mg/dL = Increased risk for diabetes • <140 mg/dL = Normal
Oral glucose tolerance test	• Most sensitive test • 75 g glucose load with glucose testing for 2 hours • **≥200 mg/dL** = Diabetes mellitus • 140-199 mg/dL= Increased risk for diabetes • <140 mg/dL = Normal
• Testing may be repeated in cases of discordant or equivocal results • If a patient is asymptomatic, a positive test should be reconfirmed with the same test on a different day	

DIABETES COMPLICATIONS

Clinical features of diabetic autonomic neuropathy	
Cardiovascular	• Tachycardia, impaired exercise tolerance • Postural hypotension with loss of diurnal blood pressure variation
Peripheral nerves	• Dry skin, pruritus, callus formation • Foot ulcers & poor wound healing • Charcot arthropathy (increased fracture risk with resultant secondary ulceration)
Gastrointestinal	• Gastroparesis with delayed gastric emptying • Esophageal dysmotility with possible dyspepsia • Intestinal involvement with possible diarrhea, constipation, or fecal incontinence
Genitourinary	• Erectile dysfunction & retrograde ejaculation in men, decreased libido & dyspareunia in women • Decreased ability to sense full bladder leading to incomplete emptying & decreased urination • Eventual recurrent urinary tract infections &/or overflow incontinence (eg, dribbling, poor urinary stream)

~~Parasympathetic innervation of bladder→ regulates detrusor contraction & internal sphincter relaxation→ voiding→neurogenic bladder dysfunction→ urinary retention and bladder distention—post void residual volume >50 mL—Sx can occur cyclically both day and night~~

Effect of intensive glycemic control in type 2 diabetes	
Macrovascular complications (eg, acute myocardial infarction, stroke)	No change (possible long-term ↓)
Microvascular complications (eg, nephropathy, retinopathy)	↓
Mortality	No change (A1c 6%-7%) ↑ (A1c <6%)

- Recommended tight glycemic control to prevent microvascular complications include A1c 6-7%
- For prevention of macrovascular risk, control of other factors like smoking, BP and lipids is important
- Tight glycemic control ↑ risk of hypoglycemia

Neuropathy:

- 50% patients get this
- Depends on duration of dis. and level of control

- Can be: **distal symmetrical sensorimotor polyneuropathy**, proximal motor neuropathy, mononeuropathy (can be cranial 3,4 or 6 or peripheral radial, median or peroneal) and/or autonomic neuropathy
- **Distal symmetrical sensorimotor** polyneuropathy is most common. "Stocking glove neuropathy". ↑ incidence in pts with risk factors of atherosclerosis (dyslipidemia, HTN, smoking, obesity)
- Sensory involvement depends on type of nerve involved:
- **Pure small fiber**→more pain, allodynia and paresthesias; sensory loss is not marked and ankle jerks preserved
- **Pure large fiber**→ less pain, more numbness; pressure, proprioception, vibration ↓, ankle jerk lost
- Neuropathic pain—characteristically present at rest and worst at night
- As diabetic neuropathy progress→ pain subsides but sensory loss persists
- **Rx:** difficult to treat. TCAs, gabapentin or NSAIDS. Mexilitine, phenytoin, carbamazepine, topiramate, topical capsaicin cream have also been used. TCAs worsen urinary symptoms due to cystopathy and orthostatic hypotension (due to cardiovascular diabetic neuropathy). Gabapentin is alternative for these pts. NSAIDS should be avoided in pts with renal dysfunction

Autonomic neuropathy:

- Can cause esophageal dysmotility (dysphagia), gastric symptoms (gastroparesis), intestinal function (diarrhea, constipation or incontinence, enteropathy), abnormal sweating, postural hypotension, cystopathy, erectile dysfunction
- **Gastroparesis C/F:** nausea, anorexia, vomiting, early satiety and post prandial fullness. Can cause hypoglycemia with insulin given before meal with impaired gastric emptying and impaired absorption
- **Rx of gastroparesis:** optimizing glucose control, ↑ fiber intake, small, frequent meals, meds to improve gastric emptying. **Metoclopramide** is prokinetic and antiemetic→symptomatic relief; may cause extrapyramidal SE (<1%). **Erythromycin** (more useful when given IV in acute condition) and **cisapride** (restricted use in US due to cardiac arrhythmia and death)
- Antihistamines like promethazine and diphenhydramine and 5HT3 inhibitors like ondansetron and granisetron have more antiemetic properties. Can be used in combo with prokinetic agents when vomiting is predominant symptom

Diabetic foot ulcers:

- **Risk factors**
- **Diabetic neuropathy**, previous foot ulcer, vascular dis. and foot deformity
- **3 causes:** peripheral neuropathy, microvascular insufficiency and immunosuppression
- Usually have undermined or punched out borders
- **Risk assessment** for development of foot ulcer:
- **Monofilament test** is used to document peripheral sensory neuropathy: 10-g Monofilament-placed on plantar surface at right angle with increasing pressure until filament buckles. Pts with neuropathy have a higher pressure threshold and loss of monofilament sensation, which are associated with ↑ risk of foot ulcer. Other sensory deficits include: ↓ vibratory sense (measured with tuning fork), ↓ pinprick pain and ↓ temperature sense

Foot ulcers can be classified as follows:

Grade 0: High-risk foot without an ulcer.
Grade 1: Superficial ulcer with full skin thickness involvement, but no involvement of underlying tissue.
Grade 2: Deep ulcer penetrating to ligament or muscle, but no bone involvement or abscess formation.
Grade 3: Deep ulcer with cellulitis, abscess formation or osteomyelitis.
Grade 4: Localized gangrene
Grade 5: Extensive gangrene involving the whole foot.

Grade 1 and 2: Proper wound care, debridement and removal of all infected and necrotic tissue

Grade 3: Short period hospitalization, surgical debridement, culture of material obtained from deep in ulcer, bone biopsy and IV antibiotics covering gram – ve and anaerobic organisms

4-5: Urgent hospitalization & surgical consult

Management depends on grade of foot ulcer and involvement of multiple disciplines

six interventions have been shown to be useful in the management of diabetic foot ulcers:

1. Off-loading
2. Debridement
3. Wound dressings
4. Antibiotics
5. Revascularization
6. Amputation

Erectile dysfunction:

1. **Etiology:** meds and condition like autonomic neuropathy, penile circulation abnormalities, and hypogonadotropic hypogonadism
2. **Hypogonadism can be**
1. **Primary—** ↓ testosterone and/or sperm count, ↑LH and FSH
2. **Secondary (central) –** ↓ testosterone and/or sperm count, low or normal LH and FSH→ measure prolactin level→**if ↑prolactin, testosterone <150ng/dL, visual field defects or features of other pituitary dysfunction**→ MRI of pituitary→ abnormal→dopaminergic agonist
→ **if normal prolactin and MRI**→ testosterone therapy required
3. **Obese** type 2 diabetics→↑ risk of developing hypogonadotropic hypogonadism
4. Measure early morning total testosterone levels (due to circadian rhythm of testosterone) in all diabetics to exclude testosterone deficiency

DIABETIC KETOACIDOSIS

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Patient characteristics	• Type 1 diabetics usually • Younger age	• Type 2 diabetics usually • Older age
Clinical symptoms	• Less pronounced altered mentation • More rapid onset of hyperglycemic symptoms • Hyperventilation & abdominal pain common	• More pronounced altered mentation • Gradual onset of hyperglycemic symptoms • Hyperventilation & abdominal pain less common
Laboratory studies	• Glucose 250-500 mg/dL • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg	• Glucose >600 mg/dL • Bicarbonate >18 mEq/L • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg

Diabetic ketoacidosis	
Patient characteristics	• Young age • Brittle type 1 diabetes • May be initial manifestation of diabetes
Clinical symptoms	• Acute to subacute onset ○ **Initial**: Polydipsia/polyuria, blurred vision, weight loss ○ **Later**: Altered mentation, hyperventilation, abdominal pain
Diagnosis	• **Glucose 250-500 mg/dL** • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones
Treatment	• High-flow IV fluids • IV insulin • Follow & replace potassium

1. Bedside capillary blood glucose can be obtained in seconds and treatment should be initiated while awaiting confirmatory testing
2. Abdominal pain and tenderness correlate with severity of disease
3. Infection can precipitate DKA: infection→↑catecholamines and cortisol release→ ↑glucagon→hyperglycemia, ketonemia and osmotic diuresis→↓blood volume→activation of renin angiotensin aldosterone→**net renal K+ loss**→serum level of K+ ↑ because of lack of insulin and academia

Hyperosmolar hyperglycemic state	
Patient characteristics	• Type 2 diabetes • Older age
Clinical symptoms	• Gradual hyperglycemic symptoms (eg, polyuria, polydipsia) • Altered mentation
Laboratory studies	• Glucose >1000 mg/dL • Normal pH & bicarbonate • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg
Initial management	• Aggressive hydration with **normal saline** • **Intravenous insulin** • Careful monitoring & supplementation of **potassium**

Osmotic diuresis→loss of 8-10 liters fluid→hydration most imp.

Plasma osmolality= (2xplasma Na+mEq/l)+(plasma glucose mg/dl)÷18

Regular or short acting insulin

- **Triggers:** infections, MI, stroke, trauma, burns and drugs like thiazide diuretics.
- **Thiazide diuretic→**↓intravascular volume→↓GFR + ↑counter-regulatory hormone→ ↓GFR→ ↓glucose excretion; ↑counter-regulatory hormones→↑glucose production and ↓glucose utilization→↑osmotic diuresis
- **Hyponatremia in HHS:** due to osmotic shift from intracellular to extracellular space, ↑ urinary loss cox of osmotic diuresis, ↑ ADH secretion leads to free water retention. However, in chronic hyperglycemia, ADH response and release will be decreased
- Normal saline is given for 1st few hours of treatment irrespective of sodium level, with a subsequent change to 0.45% NS if corrected sodium (measured sodium in mEq/l+[2mEq/l sodium for each 100 mg/dl that glucose is above 100 mg/dl]) is normal or high on subsequent lab

Management of DKA & HHS	
IV fluids	• High-flow 0.9% normal saline is initially recommended • Add dextrose 5% when serum glucose is ≤200 mg/dL
Insulin	• Initial continuous **IV insulin** infusion • Switch to **SQ** (basal bolus) insulin for the following: Able to eat, glucose <200 mg/dL, anion gap <12 mEq/L, serum HCO_3 ≥15 mEq/L • Overlap SQ & IV insulin by 1-2 hours
Potassium	• Add IV potassium if serum K^+ ≤5.2 mEq/L • Hold insulin for serum K^+ <3.3 mEq/L • Nearly all patients K^+ depleted, even with hyperkalemia
Bicarbonate	• Consider for patients with pH <6.9
Phosphate	• Consider for serum phosphate <1.0 mg/dL, cardiac dysfunction, or respiratory depression • Monitor serum calcium frequently

DKA = diabetic ketoacidosis; **HHS** = hyperglycemic hyperosmolar nonketotic state; **IV** = intravenous; **SQ** = subcutaneous.

Or plasma bicarb <5mEq/L or severe hyperkalemia. Complications of bicarb: cerebral edema esp. in children; shift O2 dissociation curve to left→↓ tissue oxygenation; hypokalemia and alkalosis. Hence given in only above conditions

- **Measure:**
  - Blood glucose—every hour
  - Electrolytes – every 2-4 hours
  - Anion gap—every 2-4 hours
- **Best markers for resolution of ketonemia:**
  - Serum anion gap—measures unmeasured anion conc. In blood and returns to normal with elimination of ketoacid anions
  - Direct assay beta-hydroxybutyrate (BH), which is predominant ketone in DKA
  - Rise of serum bicarb and arterial pH further confirm improvement
  - **IV** insulin therapy lower glucose by 50-75mg/dL per hour but ketosis and acidosis resolve slowly

TREATMENT OF DIABETES

Medication	↓ A1c	Points to remember
Metformin (biguanide)	1.0%-2.0%	• Initial therapeutic agent for most type 2 diabetics • Weight neutral, low risk of hypoglycemia • Lactic acidosis is a life-threatening complication
Sulfonylureas	1.0%-2.0%	• Generally added in patients with metformin failure • Weight gain & hypoglycemia are main side effects
Pioglitazone (TZDs)	1.0%-1.5%	• Used if unable to tolerate metformin or sulfonylureas • Side effects: weight gain, edema, CHF, bone fracture, bladder cancer • Low risk of hypoglycemia when used alone or with metformin • Can be used in renal insufficiency
DPP-IV inhibitors (eg, sitagliptin)	0.5%-0.8%	• Low risk of hypoglycemia • Weight neutral • Can be used in renal insufficiency
GLP-1 receptor agonist (eg, exenatide)	0.5%-1.0%	• Possible second agent for metformin failure, especially if weight loss is desired • Low hypoglycemia risk when used alone or with metformin

CHF = congestive heart failure; DPP = dipeptidyl peptidase-4; GLP-1 = glucagonlike peptide-1; IV = intravenous; TZDs = thiazolidinediones.

- Guidelines recommend adding insulin to metformin if HbA1c is > 8.5%
- **Insulin** significantly↑ weight and risk of hypoglycemia
- **DPP4 inhibitors** increase endogenous incretins and improve glycemic control

- the recommended target hemoglobin A1c for most patients should be 6%-7%.

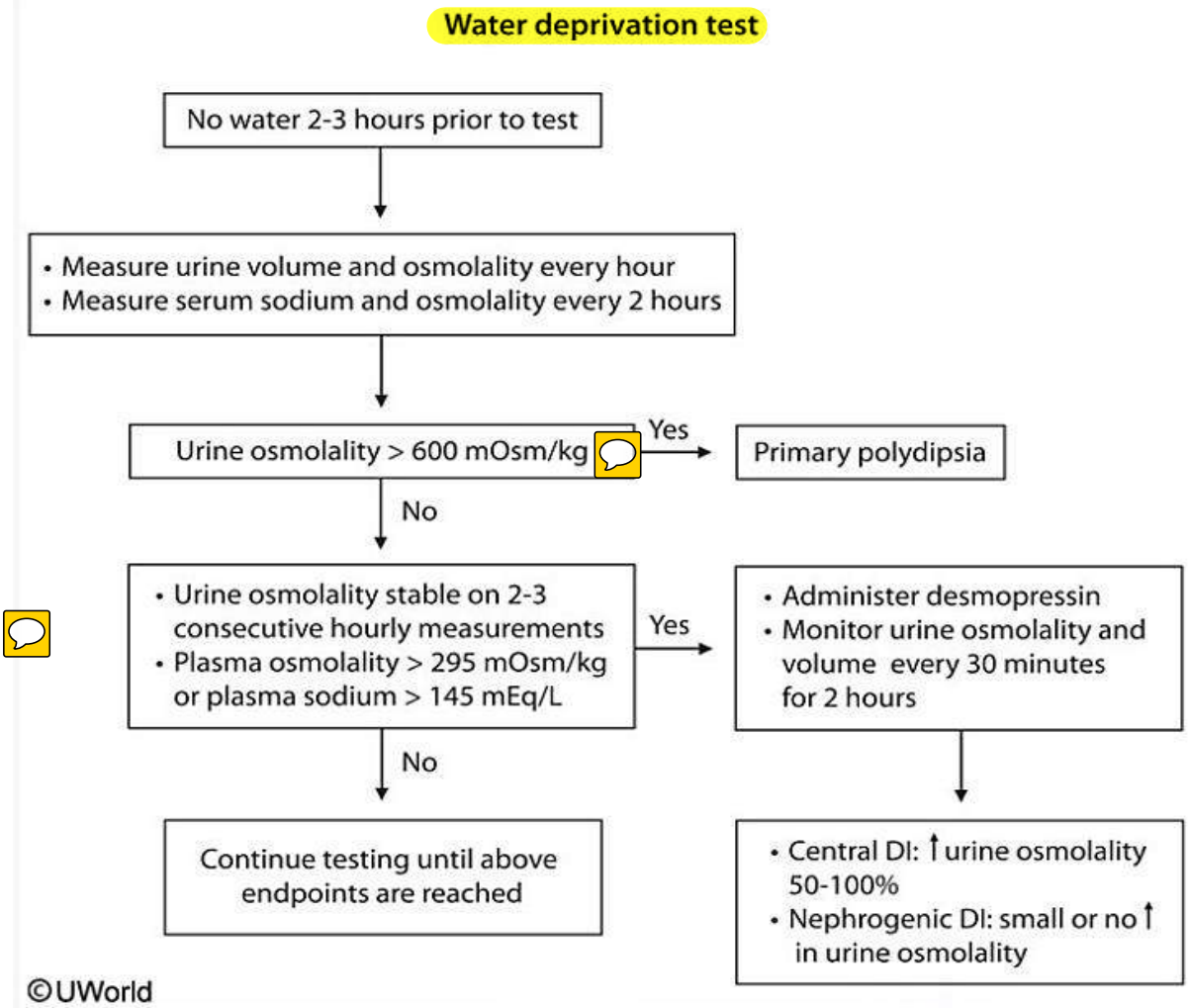
DIABETES INSIPIDUS

ADH-related causes of polyuria & polydipsia			
	Primary polydipsia	Central DI	Nephrogenic DI
Defect	↑ Water intake	↓ ADH release from pituitary	ADH resistance in kidney
Etiology	• Antipsychotics • Anxious, middle-age women	• Idiopathic • Trauma • Pituitary surgery • Ischemic encephalopathy	• Chronic lithium use • Hypercalcemia • Hereditary (*AVPR2* mutations)
Clinical features	Low serum Na	High serum Na	Normal serum Na

ADH = antidiuretic hormone; DI = diabetes insipidus.

In central, thirst mechanism is also affected. In nephrogenic, thirst mechanism is intact→↑ water intake normalize Na+ conc. to some extent

WATER DEPRIVATION TEST:



DIABETES INSIPIDUS

- Euvolemic hypernatremia (in contrast, psychogenic polydipsia causes euvolemic hyponatremia). Typically present with severe polyuria and mild hypernatremia
- Based on urine osmolality, diabetes insipidus is divided into:
  - Complete DI: the urine osmolality is less than 300 mOsm/kg (often less than 100 mOsm/kg)
  - Partial DI: urine osmolality ranges from 300-600 mOsm/kg.
- Other causes of nephrogenic DI: severe hypokalemia, tubulointerstitial renal disease, and medications. The most commonly implicated mediations are lithium, demeclocycline, foscarnet, cidofovir, and amphotericin.
- Rx Central DI: initial therapy with desmopressin, intranasal (preferred) or oral. Hydrochlorothiazide may be added for additional effect
- Rx Nephrogenic DI: discontinue medication if medication induced, with salt restriction and selected .diuretics (e.g. amiloride) if cannot discontinue the drug
  HCTZ→ water deprivation→ ↑ sodium and water absorption in proximal tubule

TESTOSTERONE DEFICIENCY

Features suggestive of testosterone deficiency

- Incomplete sexual development
- Decreased libido and potency
- Decreased early-morning erections
- Gynecomastia
- Decreased secondary sexual characters (eg, decreased shaving frequency)
- Small testicles (normal adult testes: length, 4-7 cm; volume, 20-25 mL)
- Hot flashes (severe hypogonadism)
- Low sperm count
- Osteoporosis

Pre-pubertal <3ml measured by Prader orchidometer

TESTICULAR TUMORS

LEYDIG CELL TUMOR

- Most common stromal sex cord tumor; occur in all age groups including young children
- Leydig cells are primary source of testosterone and also capable of estrogen production due to ↑ aromatase activity
- Tumor cells→↑estrogen production→↓FSH+LH→endocrine manifestations occur in 20-30% pts—most commonly gynecomastia and in pre-pubertal cases cause precocious puberty

CHORIOCARCINOMA

- Germ cell tumor; produce β-hCG

TERATOMA

- If ↑AFP or β-hCG→ indicate coexistence of other germ cell tumor

SEMINOMA

- Serum markers usually normal
- ↑ beta hCG in seminomas that contain syncyciotrophoblast giant cells

YOLK SAC TUMOR (ENDODERMAL SINUS TUMOR)

- Germ cell tumor→↑AFP

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome	
Diagnostic criteria	≥2 of 3 of the following: **Rotterdam Criteria** • Androgen excess: Biochemical or clinical (hirsutism, acne, androgenic alopecia) • Oligo- or anovulation • Polycystic ovaries on ultrasound: ≥12 follicles 2-9 mm in diameter and/or ovarian volume >10 mL **AND** Exclusion of other hyperandrogenic conditions (eg, hypothyroidism, hyperprolactinemia, nonclassic CAH, Cushing syndrome, androgen-secreting tumors)
Treatment options	• Weight loss • Combined hormonal contraceptives for hyperandrogenism & menstrual dysfunction • Clomiphene citrate for ovulation induction • Metformin for coexisting type 2 diabetes mellitus
Comorbidities	• Overweight/obesity • Glucose intolerance/diabetes mellitus • Dyslipidemia • Obstructive sleep apnea • Endometrial hyperplasia/cancer

CAH = congenital adrenal hyperplasia.

- Metformin also prevents diabetes in very obese pts (BMI >35 kg/m2) with impaired fasting glucose and impaired glucose tolerance
- Spironolactone—antiandrogenic→ impair development of male external genitalia in fetus and hence given to those who have absolute CI to OCPs:

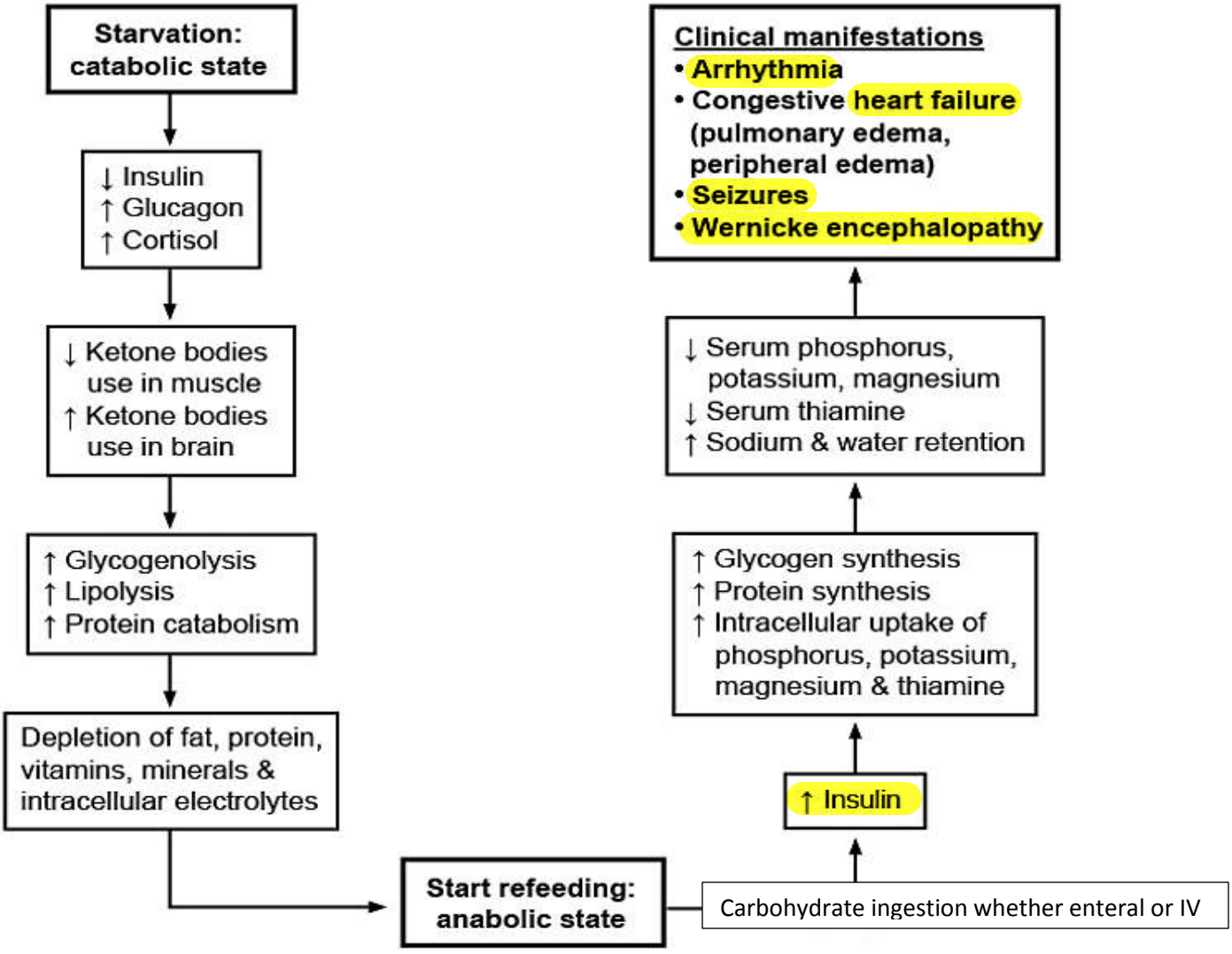
Absolute contraindications to combined hormonal contraceptives

- Migraine with aura
- ≥15 cigarettes/day & age ≥35
- Stage 2 hypertension (≥160/100 mm Hg)
- History of venous thromboembolic disease
- History of stroke or ischemic heart disease
- Breast cancer
- Cirrhosis & liver cancer
- Major surgery with prolonged immobilization
- <3 weeks postpartum

-

REFEEDING SYNDROME

Pathogenesis of refeeding syndrome



- Phosphorus—main electrolyte that is depleted as needed for energy (ATP)
- Aggressive initiation of nutrition without adequate repletion of electrolytes→cardiopulmonary failure

- Patients with anorexia have euthyroid hypothyroxinemia→normal TSH and normal to ↓serum thyroxine and triiodothyronine
- Carbohydrate intake cause a rapid ↓ in renal excretion of sodium and when fluid is given for rehydration, it leads to volume overload

CARCINOID SYNDROME

Features of carcinoid syndrome	
Clinical manifestations	• Skin: flushing, telangiectasias, cyanosis • Gastrointestinal: diarrhea, cramping • Cardiac: valvular lesions (right > left side) • Pulmonary: bronchospasm • Miscellaneous: Niacin deficiency (dermatitis, diarrhea & dementia)
Diagnosis	• Elevated 24-hour urinary excretion of 5-HIAA • CT/MRI of abdomen & pelvis to localize tumor • OctreoScan to detect metastases • Echocardiogram (if symptoms of carcinoid heart disease are present)
Treatment	• Octreotide for symptomatic patients **&** prior to surgery/anesthesia • Surgery for liver metastases

Secretory diarrhea

- Most commonly occur in distal small intestine, proximal colon and lungs
- Most commonly metastasizes to liver
- Secretes: histamine, serotonin and VIP

ZOLLINGER- ELLISON SYNDROME

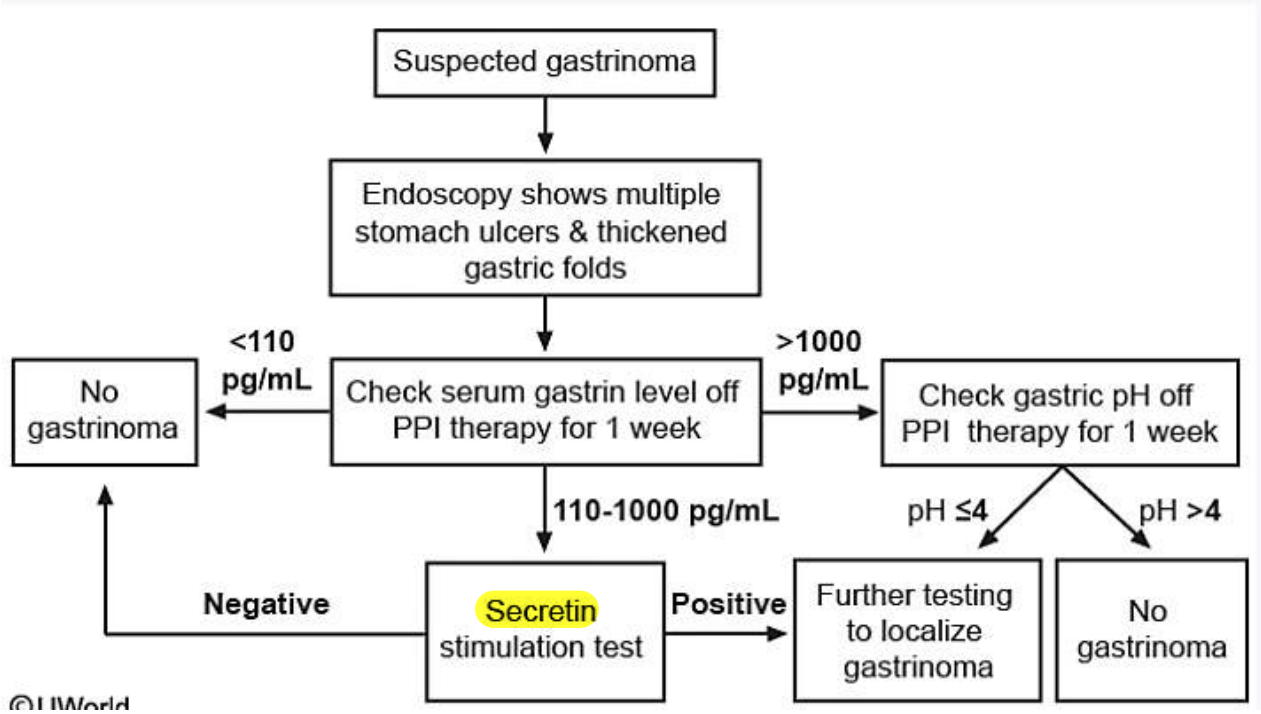
Zollinger-Ellison syndrome	
Epidemiology	• Age 20-50 • 80% Sporadic/20% MEN1
Clinical features	• Multiple & refractory peptic ulcers • Ulcers distal to duodenum • Chronic diarrhea
Diagnosis	• Markedly elevated serum gastrin (>1000 pg/mL) in the presence of normal gastric acid (pH <4)
Workup	• Endoscopy • CT/MRI & somatostatin receptor scintigraphy for tumor localization

Dyspepsia, reflux sx, abdominal pain, weight loss, diarrhea, frank GI blood loss

To reveal ulcers and occasionally may reveal primary duodenal gastrinoma

MEN1 = multiple endocrine neoplasia type 1.

- ↑ gastrin→ parietal cell hyperplasia→ ↑ gastric acid production→ inactivation of pancreatic enzymes and injury to mucosal brush border→diarrhea and steatorrhea
- once gastrinoma is confirmed→ screen for MEN 1 with assays of parathyroid, ionized calcium and prolactin



- **Fasting** gastrin levels should be measured
- Check gastric pH if gastrin is >1000 as gastrin may also be elevated due to failure of gastric acid secretion (achlorhydria)

- Secretin→ stimulate gastrin release by gastrinoma cells and inhibit normal G cell secretion of gastrin
- The calcium infusion study is usually reserved for patients who have gastric acid hypersecretion and are strongly suspected of having gastrinoma despite a negative secretin test. Calcium infusion can lead to an increase in serum gastrin levels in patients with gastrinoma

GLUCAGONOMA

Clinical features of glucagonoma	
Clinical presentation	**Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum, extremities • Lesions enlarge & coalesce over next 7-14 days with central clearing & blistering, crusting & scaling at borders **Diabetes mellitus** • Mild hyperglycemia easily controlled with oral agents & diet • Usually does not require insulin **Gastrointestinal symptoms** • Diarrhea, anorexia, abdominal pain, or occasional constipation **Other findings** • Weight loss • Neuropsychiatric (eg, ataxia, dementia, proximal muscle weakness) • Association with venous thrombosis
Diagnosis	• Hyperglycemia with elevated glucagon >500 pg/mL • Normocytic, normochromic anemia due to likely anemia of chronic disease or glucagon directly affecting erythropoiesis • Abdominal imaging (computed tomography or magnetic resonance imaging) to localize tumor &/or metastases

INSULINOMA

- Beta cell tumor→↑ insulin production +↑ c-peptide and proinsulin (>5pmol/l)
- Normally hypoglycemia <60mg/dl→near complete suppression of insulin which does not occur in insulinoma

VIPoma

Clinical features of VIPoma	
Clinical presentation	• **Watery diarrhea** (can be tea colored and odorless) • Hypo- or achlorhydria due to ↓ gastric acid secretion • Associated flushing, lethargy, nausea, vomiting, muscle weakness/cramps
Laboratory findings	• **Hypokalemia** (↑intestinal potassium secretion) • Hypercalcemia (increased bone resorption) • Hyperglycemia due to increased glycogenolysis • Stool studies show secretory diarrhea with ↑ sodium & osmolal gap <50 mOsm/kg
Diagnosis	• Watery diarrhea with VIP level >75 pg/mL • **Abdominal CT** or MRI to localize tumor in pancreas (usually in pancreatic tail)

- Common in age group: 30-50 yo
- Stool volume can be greater than 3L/day
- 60-80% have metastasized to liver by the time of diagnosis
- **Treatment:** IV volume repletion, octreotide to ↓ diarrhea and possible hepatic resection with mets to liver

NON-BETA CELL TUMOR

- Usually large mesechymal tumor
- Produce IGF II→ insulinomimetic effect when bind to insulin receptor→ hypoglycemia→↓ insulin, c-peptide and proinsulin
- Labs: measure IGF II

MULTIPLE ENDOCRINE NEOPLASIA

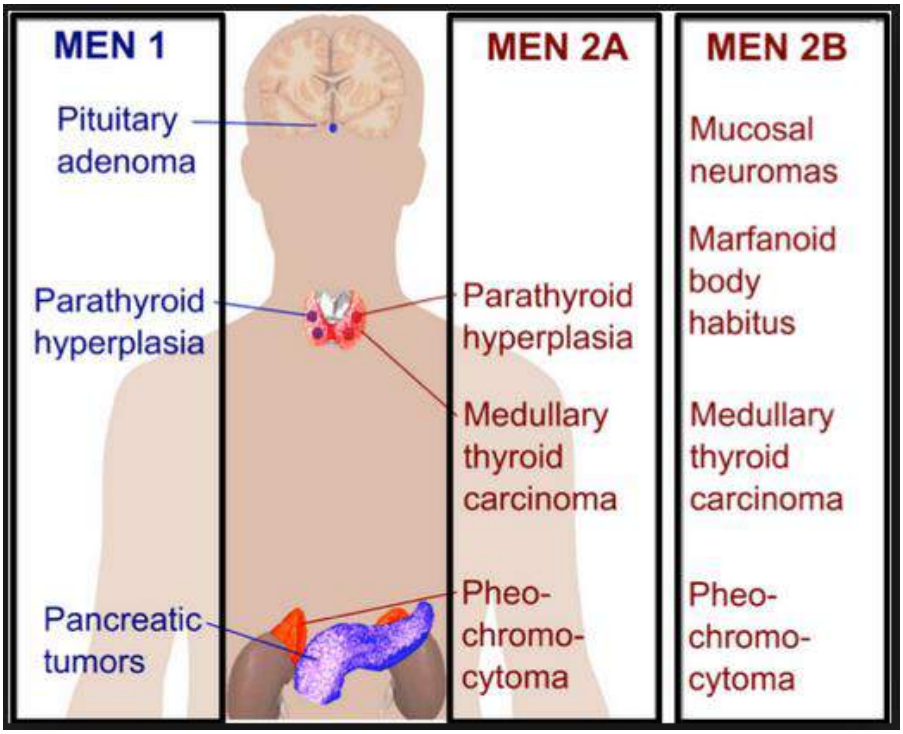
- MEN1 is caused by single mutation in MEN1 tumor suppressor gene on chromosome 11
- MEN 2A and 2B are caused by RET proto-oncogene on chromosome 10. RET gene is also responsible for familial medullary thyroid cancer (FMTC)

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (hypercalcemia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Parathyroid hyperplasia
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

Classification of multiple endocrine neoplasia (MEN)	
Type I	• Primary hyperparathyroidism (>90%) • Enteropancreatic tumors (60%-70%) • Pituitary tumors (10%-20%)
Type 2A	• MTC (>90%) • Pheochromocytoma (40%-50%) • Parathyroid hyperplasia (10%-20%)

Type 2B	• MTC
	• Pheochromocytoma
	• Other
	  ◦ Mucosal & intestinal neuromas
	  ◦ Marfanoid habitus

Gastrinoma is most common pancreatic tumor in MEN1—present at 20-50 years with heart burn, abdominal pain and diarrhea—frank GI bleeding can also occur



- MEN 2B is more aggressive than MEN 2A.
- Other features of MEN 2B include: skeletal deformities like kyphoscholiosis, lordosis etc.
- DNA testing (RET protooncogene germline mutation) using PCR is more useful in diagnosing/screening for MEN 2 syndromes than biochemical tests like calcitonin level→+ test→elective total thyroidectomy
- Biochemical tests like 24-hour urine metanephrines and free catecholamines or plasma free metanephrines are needed to make diagnosis of pheochromocytoma

- MEN2A and MEN2B are associated with pheochromocytoma, which may initially be asymptomatic but can cause severe hypertensive crisis during surgical resection of the thyroid masses.
- For this reason, patients with MTC should be tested for RET mutations and (if positive) pheochromocytoma with a **plasma fractionated metanephrine assay**.
- pheochromocytoma should be resected prior to thyroidectomy.

Qid: 3494

MEN 1

Multiple endocrine neoplasia type 1	
Organ/System	**Clinical features**
Pituitary adenomas (10%-20%)	Pituitary tumors that are prolactin secreting, growth hormone secreting, ACTH secreting, or non-hormone secreting
Primary **hyperparathyroidism** (>90%)	• Multiple parathyroid adenomas or parathyroid hyperplasia • Hypercalcemia (asymptomatic or associated with polyuria, kidney stones or decreased bone density)
Pancreas/GI tract (60%-70%)	• **Gastrinoma** - recurrent peptic ulcers • Insulinoma - hypoglycemia • VIPoma - secretory diarrhea, hypokalemia, hypochlorhydria • Glucagonoma - weight loss, necrolytic migratory erythema, hyperglycemia

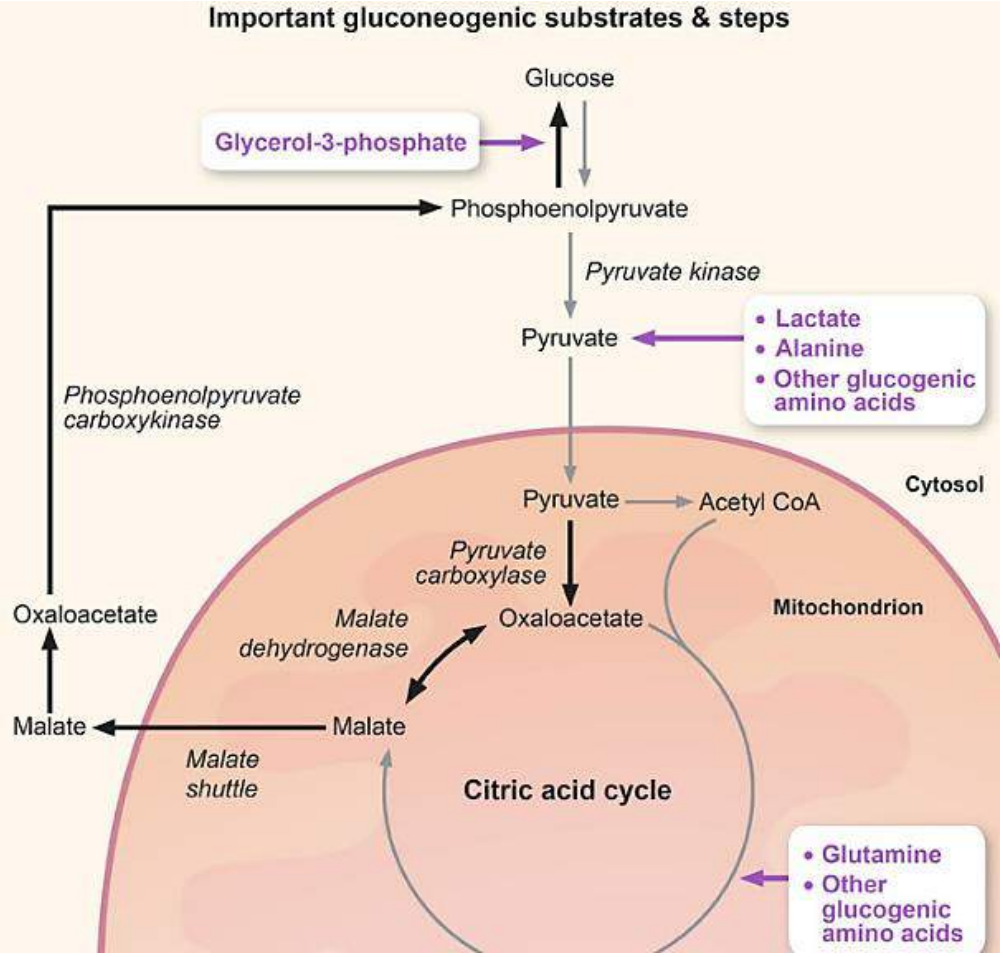
GI = gastrointestinal.

Typically occur at <40yrs, 20 yrs earlier than sporadic cases e' high recurrence after subtotal parathyroidectomy

COMMON CAUSES OF MYOPATHY

Common causes of myopathy	
Connective tissue diseases	• Polymyositis/dermatomyositis • Inclusion body myositis • Vasculitis • Overlap syndrome (mixed connective tissue disease)
Endocrine/ metabolic	• Hypothyroidism, thyrotoxicosis • Cushing's syndrome • Electrolytes ($\downarrow K^+$, calcium, phosphorus)
Drugs/toxins	• Corticosteroids, statins • Zidovudine, colchicine • Alcohol, cocaine, heroin
Miscellaneous	• Infections, trauma, hyperthermia

IMPORTANT GLUCONEOGENIC SUBSTRATES AND STEPS



POINTERS

- Progesterone analogs (eg medroxyprosterone acetate, megesterol acetate)→ used to improve appetite and weight gain in pts with cancer related anorexia/cachexia syndrome

Contents

ENDOCRINOLOGY-PAEDS

THYROID GLAND

CONGENITAL HYPOTHYROIDISM

- Familial or sporadic
- **Causes:**
  1. Thyroid dysgenesis (i.e. aplasia, hypoplasia or ectopic gland)—85% cases
  2. Inborn errors of thyroxin synthesis—10% cases
  3. Transplacental maternal thyrotropin-receptor blocking antibodies—5%
- **C/F:**

Congenital hypothyroidism	
Etiology	Thyroid dysgenesis (most common)
Clinical manifestations	• Majority of infants asymptomatic • Symptoms include lethargy, hoarse cry, poor feeding, constipation, jaundice, dry skin, large fontanelles
Diagnosis	• ↑TSH & ↓free T4 levels • Most infants identified by newborn screening
Treatment	Levothyroxine

(initial dose of 10mcg/kg, then titrated accordingly)

1. Normal at birth due to transfer of maternal hormones
2. Gradually develop apathy
3. Abdominal bloating
4. Pathologic jaundice
5. Difficult breathing
6. Noisy respiration
7. Hypothermia
8. Refractory macrocytic anemia (rest features I remember)

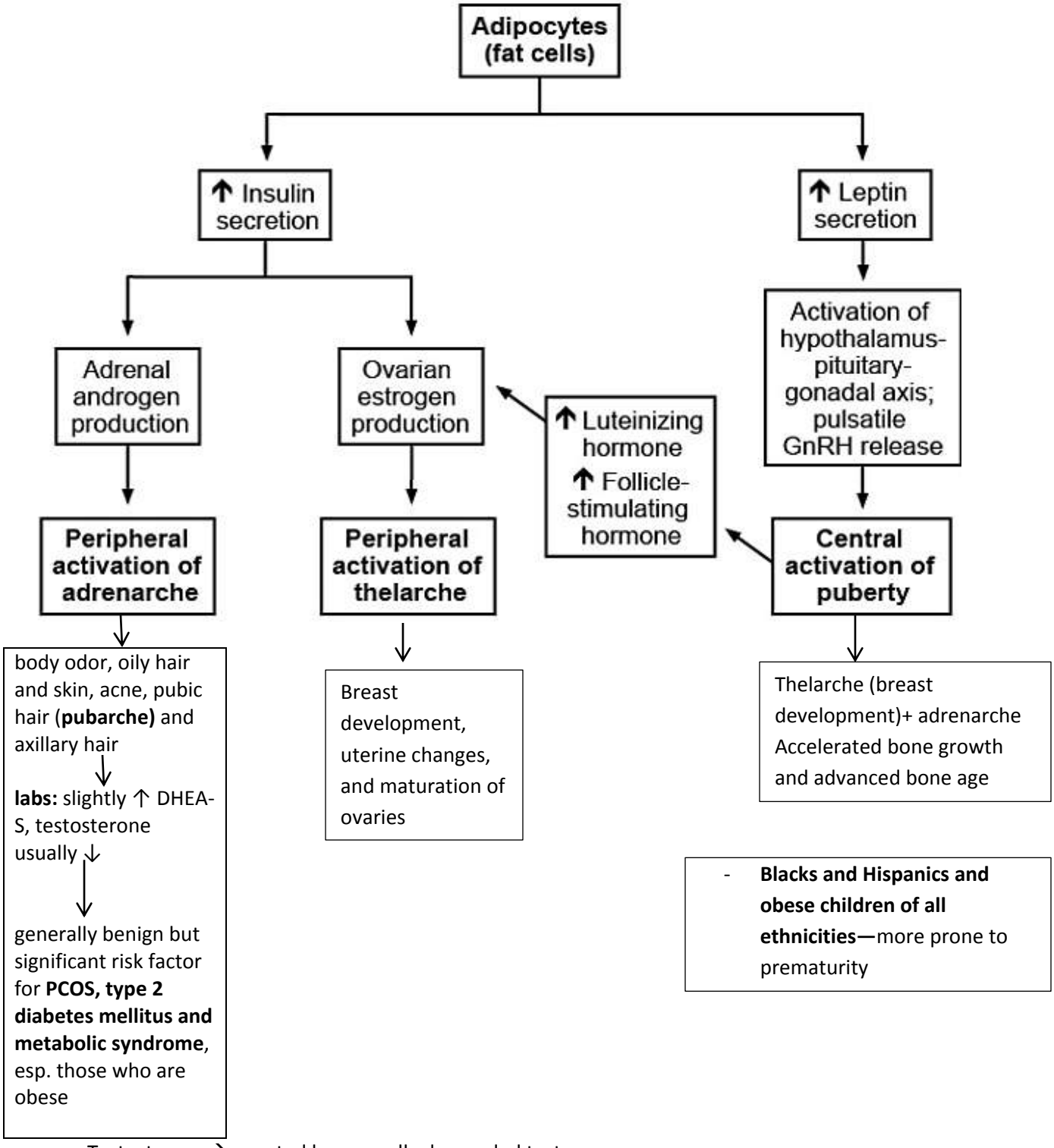
NEONATAL THYROTOXICOSIS

Neonatal thyrotoxicosis	
Pathophysiology	• Transplacental passage of maternal anti-TSH receptor antibodies • Antibodies bind to infant's TSH receptors & cause excessive thyroid hormone release
Clinical features	• Warm, moist skin • Tachycardia • Poor feeding, irritability, poor weight gain • Low birth weight or preterm birth
Diagnosis	• Maternal anti-TSH receptor antibodies ≥500% normal
Treatment	• Self-resolves within 3 months (disappearance of maternal antibody) • Methimazole PLUS β blocker

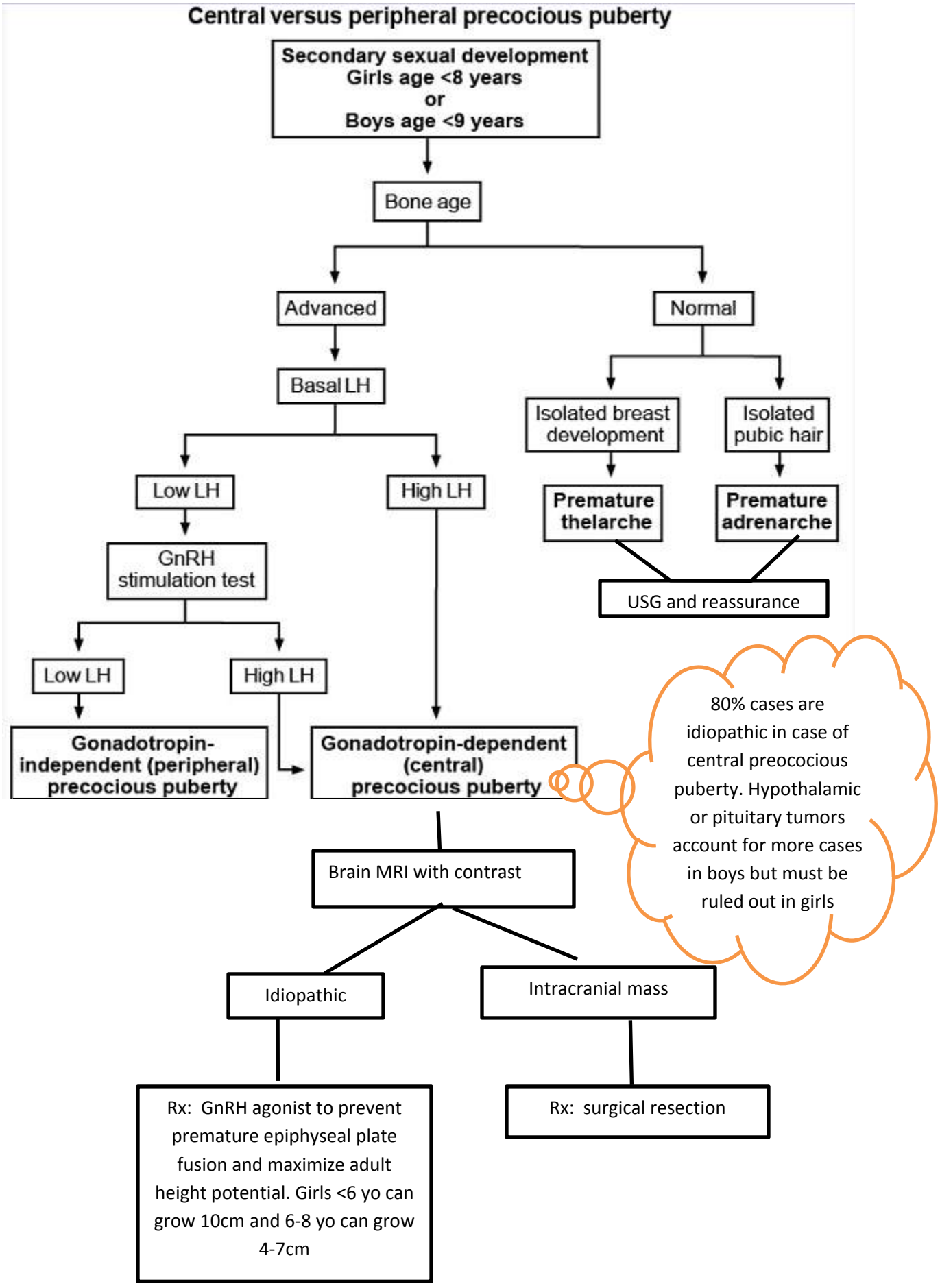
In 3rd trimester

- Elevated anti-TSH receptor antibody levels can occur despite maternal treatment of Grave's disease and euthyroidism or hypothyroidism during pregnancy
- Risk ↑ if maternal anti-TSH antibodies is > 5 times the upper limit of normal
- Severe cases of thyrotoxicosis can result in symptomatic fetuses: fetal tachycardia, hydrops, growth restriction

OBESITY AND PRECOCIOUS SEXUAL DEVELOPMENT

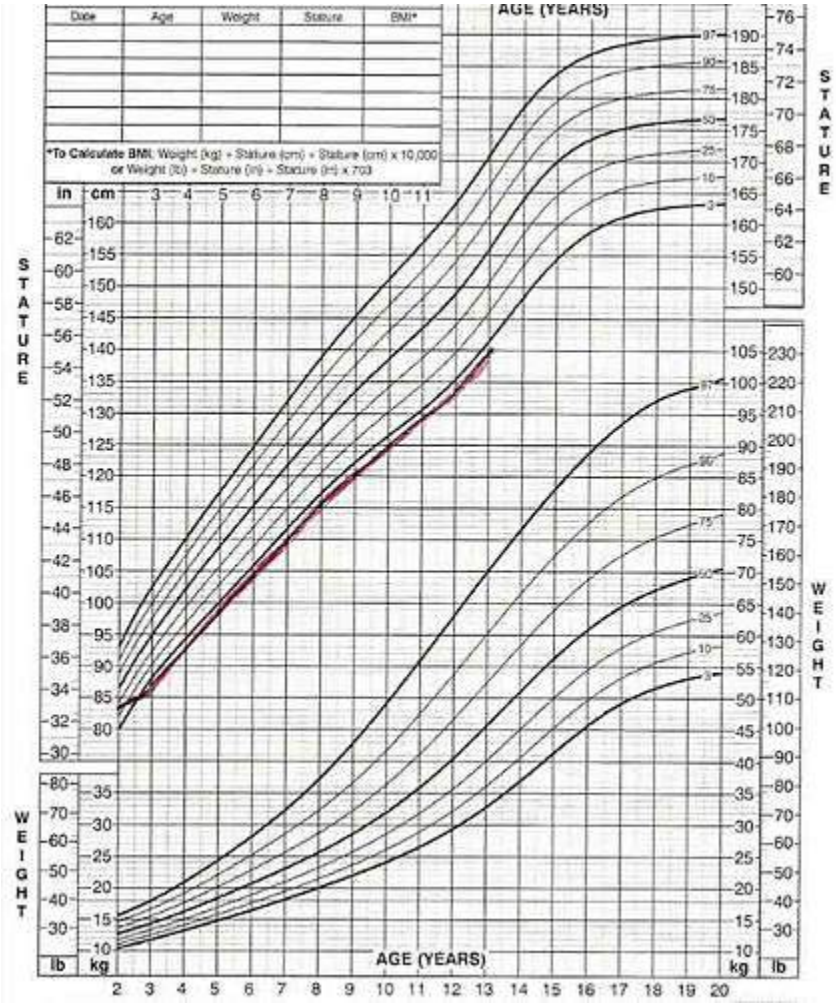


- Testosterone→secreted by normally descended testes
- Undescended testes→adrenarche often delayed as abdominal and inguinal testes are dysfunctional
- All pts with central precocious puberty should receive CT or MRI of brain. Treated with GnRH analog


Central versus peripheral precocious puberty
Secondary sexual development
Girls age <8 years
or
Boys age <9 years
Bone age
Advanced
Normal
Basal LH
Isolated breast development
Isolated pubic hair
Low LH
High LH
Premature thelarche
Premature adrenarche
GnRH stimulation test
USG and reassurance
Low LH
High LH
Gonadotropin-independent (peripheral) precocious puberty
Gonadotropin-dependent (central) precocious puberty
80% cases are idiopathic in case of central preococious puberty. Hypothalamic or pituitary tumors account for more cases in boys but must be ruled out in girls
Brain MRI with contrast
Idiopathic
Intracranial mass
Rx: GnRH agonist to prevent premature epiphyseal plate fusion and maximize adult height potential. Girls <6 yo can grow 10cm and 6-8 yo can grow 4-7cm
Rx: surgical resection

CONSTITUTIONAL GROWTH DELAY

- Most common cause of short stature and pubertal delay in adolescents
- Normal birth height and weight.
- Between 6mo to 3 yrs, height growth velocity slows, and child drops percentiles on growth velocity curves
- At 3 yrs, gains normal growth velocity and follows growth velocity at 5th to 10th percentiles
- Puberty and adolescent growth spurts are delayed but eventually reached
- Bone age radiograph shows a bone age that is delayed compared to chronological age



Contents

ENDOCRINOLOGY-GYN/OBS

THYROID GLAND

Maternal thyroid axis during pregnancy		
Hormone	**Change**	**Mechanism**
Total T_4	↑ ↑ (1.5x pre-pregnancy state)	• β-hCG stimulates thyroid hormone production • ↑ TBG binds extra T_4, which results in a significant ↑ in total T_4 & a slight ↑ in free T_4
Free T_4	↑	
TSH	↓	• ↑ β-hCG & ↑ T_4 in 1st trimester suppress TSH secretion

TBG = thyroxine-binding globulin.

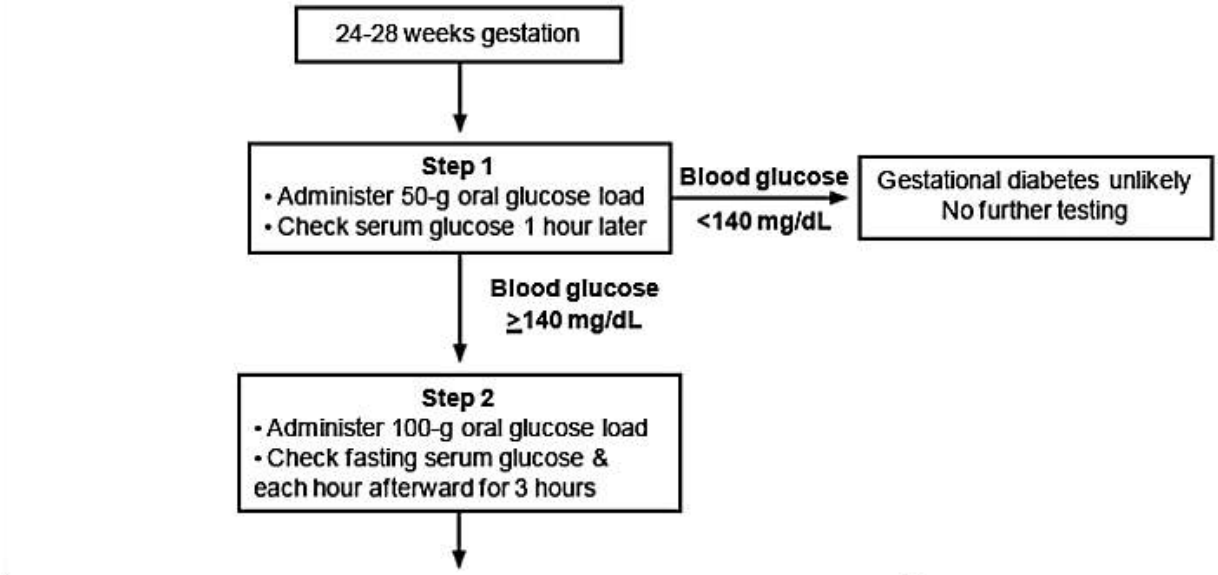
- In pts with hypothyroidism, levothyroxine dose should be increased in pregnancy by 30% at the time pregnancy is detected and should be adjusted subsequently (typically in 4-wk increments) based on TSH using pregnancy specific norms
- T4 should also be monitored using pregnancy specific norms
- **Adverse effects of hypothyroidism on mother and fetus:** eg gestational HTN, preeclampsia, premature delivery and postpartum hemorrhage

GENETIC TESTING

- Women with high risk of aneuploidy (previous fetal aneuploidy, abnormal USG and aneuploidy screening, age >/= 35, history of balanced Robertsonian translocation)→offer further genetic testing
- Cell-free fetal DNA is a highly sensitive and specific maternal blood test that can detect trisomy 13, 18 and 21

GESTATIONAL DIABETES MELLITUS

Two-step approach for screening & diagnosing gestational diabetes mellitus



Diagnosis of gestational diabetes mellitus (≥2 abnormal values)		
Blood glucose level	**Carpenter & Coustan**	**NDDR**
Fasting	≥95 mg/dL (5.3 mmol/L)	≥105 mg/dL (5.3 mmol/L)
1-hour	≥180 mg/dL (10 mmol/L)	≥190 mg/dL (10.6 mmol/L)
2-hour	≥155 mg/dL (8.6 mmol/L)	≥165 mg/dL (9.2 mmol/L)
3-hour	≥140 mg/dL (7.8 mmol/L)	≥145 mg/dL (8 mmol/L)

NDDR = National Diabetes Group Criteria.

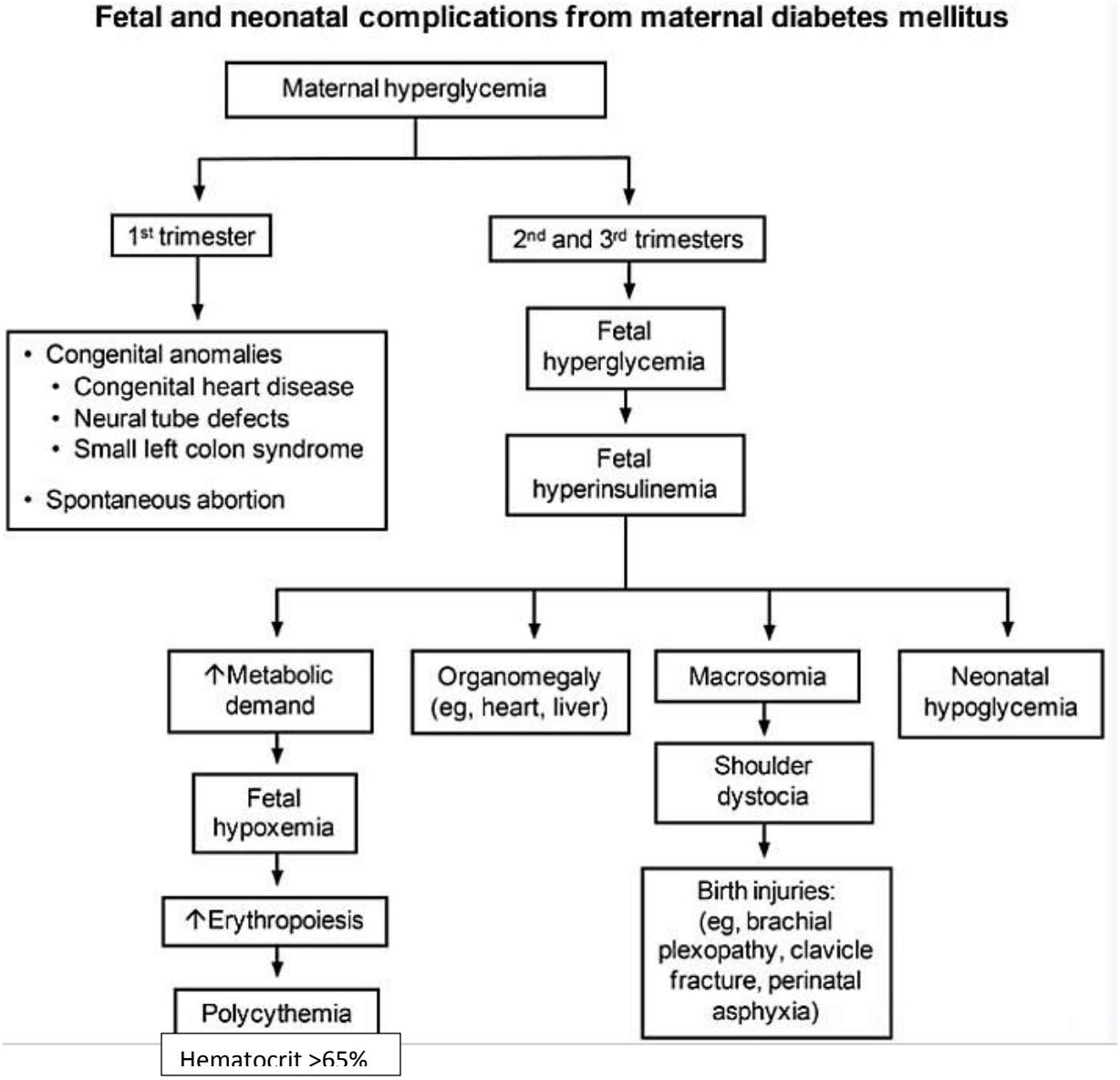
Gestational diabetes mellitus	
Target blood glucose levels	• Fasting ≤95 mg/dL (5.3 mmol/L) • 1-hour postprandial ≤140 mg/dL (7.8 mmol/L) • 2-hour postprandial ≤120 mg/dL (6.7 mmol/L)
Treatment	• 1st-line: Dietary modifications • 2nd-line: Insulin, oral agents (eg, metformin, glyburide)

- Increased prevalence because **obesity** is epidemic in US
- **↑ risk in GDM pts of:** gestational HTN, preeclampsia, and cesarean delivery
- **Outcome:** typically resolve after delivery but 50% women will develop DM type 2 later in life
- **Screening:**
  1. **All pregnant** women should be screened between **24-28 wks of gestation**
  2. Pts with ↑ risk factors (eg BMI >/=30 kg/m^2, previous GDM, excessive weight gain during pregnancy, FH of diabetes, Hispanics, African Americans, and Native Americans) or symptomatic

(polyuria, polydipsia)—should be screened at 1st prenatal visit with HbA1c and fasting blood glucose and rescreened between 24-28 wks if initial screen is negative

- **Rx:** dietary modification—evenly distributed carbs, protein, and fat intake over 3 meals and 2-4 snacks daily.

FETAL AND NEONATAL COMPLICATIONS FROM MATERNAL DIABETES MELLITUS



- Because of fetal hyperinsulinemia→ fetus in constant anabolism→↑metabolic demand→hypoxemia
- Polycythemia is dangerous→viscous blood→risk of sludging, ischemia, and infarction of vital organs
- Newborns require close monitoring of CBC and signs of perfusion
- **Hypocalcemia**—typical in infants of diabetic mothers due to parathyroid hormone suppression. Neonates—usually asymptomatic but should be monitored for hypocalcemic seizures
- **Small left colon syndrome:** infants of pre-gestational and gestational diabetic mothers are at risk for small left colon syndrome→ transient inability to pass meconium and resolves spontaneously. Not related to intussusception

Contents

SARCOIDOSIS

Common features of sarcoidosis	
Epidemiology	• Young adults • **African Americans**

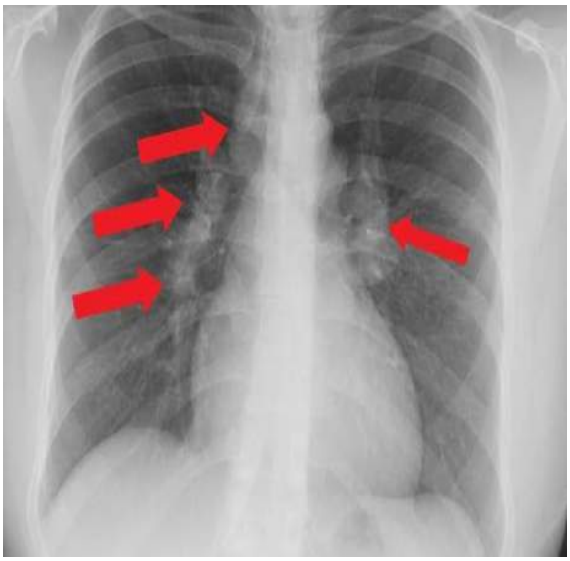
Clinical	• Constitutional symptoms
	• **Cough**, **dyspnea** & chest pain
	• Extrapulmonary findings
	  ○ Skin lesions
	  ○ Anterior/posterior uveitis
	  ○ Lofgren syndrome

Imaging	• **Bilateral hilar adenopathy** • Pulmonary reticular infiltrates
Laboratory	• Hypercalcemia/hypercalciuria • Elevated serum ACE level
Pathology	• Biopsy shows **noncaseating granulomas** that stain negative for fungi & acid-fast bacilli

ACE = angiotensin-converting enzyme.

Hypercalciuria occurs more frequently than hypercalcemia and can lead to nephrolithiasis

Manifestations of sarcoidosis	
Pulmonary	• Bilateral hilar adenopathy • Interstitial infiltrates
Ophthalmologic	• Anterior uveitis (iridocyclitis or iritis) • Posterior uveitis
Reticuloendothelial	• Peripheral lymphadenopathy • Hepatomegaly • Splenomegaly
Musculoskeletal	• Acute polyarthritis (especially the ankle joints) • Chronic arthritis with periosteal bone resorption
Central nervous system/endocrine	• Central diabetes insipidus • Hypercalcemia
Lofgren syndrome	• Erythema nodosum • Hilar adenopathy • Migratory polyarthralgias • Fever



- Frequently incidental finding on CXR. Can present with fever, cough, weight loss, dyspnea and fatigue
- May involve kidneys—interstitial nephritis or nephrolithiasis rather than GN
- Cardiac sarcoidosis—myocardial infiltration and inflammation→ conduction defects (AV blocks most common), **restrictive** & dilated cardiomyopathy, valvular dysfunction and heart failure. Can also cause sudden cardiac death
- **Definitive diagnosis**: consistent radiographic and clinical findings, and biopsy demonstrating non-caseating granuloma. Bronchoscopy with transbronchial biopsy is done to obtain tissue. Can be obtained from other sites which are involved like skin and peripheral lymph nodes etc
- Pts with incidental b/l hilar lymph nodes without symptoms are monitored without biopsy unless symptoms develop
- **Rx:** asymptomatic pts are monitored without medicine cox of high rate of remission. Symptomatic pts are treated with systemic glucocorticoids. Rule out infectious causes of granulomatous disease (TB and histoplasmosis) before starting glucocorticoids

GRANULOMATOSIS WITH POLYANGIITIS

(formerly known as Wegener granulomatosis)

Granulomatosis with polyangiitis	
Clinical manifestations	• Upper respiratory: Sinusitis/otitis, saddle-nose deformity • Lower respiratory: Lung nodules/cavitation • Renal: Rapidly progressive GN • Skin: Livedo reticularis, nonhealing ulcers

Diagnosis	• ANCA: PR3 (~70%), MPO (~20%)
	• Biopsy:
	  ○ Skin (leukocytoclastic vasculitis)
	  ○ Kidney (pauci-immune GN)
	  ○ Lung (granulomatous vasculitis)

Management	• Corticosteroids & immunomodulators (eg, MTX, cyclophosphamide)

May be accompanied by alveolar opacities

Or rituximab may also be used

ANCA = antineutrophil cytoplasmic antibody; **GN** = glomerulonephritis; **MPO** = myeloperoxidase; **MTX** = methotrexate; **PR3** = proteinase-3.

- A vasculitis of small and medium sized vessels- most commonly affecting white men and women age 30-50 yo

Upper respiratory tract—most commonly involved—present as chronic rhinosinusitis -
;LRT → narrowing and ulceration of trachea involved

auditory canal ulceration

- May be accompanied by anemia of chronic disease and mild leukocytosis
- HIV ↑ the chance of false positive result of ANCA and should be ruled out
- Pt with clinical Sx & +ve ANCA→ start treatment before confirmatory biopsy

BREATH SOUNDS ON AUSCULTATION

Normal breath sounds:

- Percussion: resonant
- Auscultation: vesicular breath sounds—quiet inspiratory phase and almost inaudible expiratory phase

Bronchial breath sounds:

- Louder and have prominent expiratory phase provided airway is patent. If airway is blocked, breath sounds over consolidated area would be decreased
- In case of interstitial lung disease, fine crackles will be heard at the end of inspiration

Egophony:

- Ask the pt to say letter E and listen with steth→ if sounds like A with nasal or bleating quality (egophony)→consolidation
- Egophony can also sometimes be present in pleural effusion at the area of fluid accumulation due to transmission of air through collapsed area of lung

Pulmonary auscultation examination findings				
Condition	**Auscultation**	**Tactile fremitus**	**Percussion**	**Mediastinal shift**
Consolidation (eg, lobar pneumonia)	• Crackles • Bronchial breath sounds • Bronchophony, egophony, pectoriloquy	Increased at consolidation site	Dullness (large consolidation)	None
Pleural effusion	Decreased breath sounds	Decreased	Dullness	Away from effusion (for large effusion)
Chronic obstructive pulmonary disease	Decreased breath sounds vesicular	Decreased	Hyperresonant (especially if large bullae)	None
Pneumothorax	Decreased breath sounds	Decreased	Hyperresonant	• Small: None • Tension: Away from pneumothorax

- Sound travels faster in solids than air and hence fremitus which is palpable vibration is ↑ in consolidation
- Consolidation also leads to bronchial breath sounds due to over- transmission of sound over chest wall

ACUTE BRONCHITIS

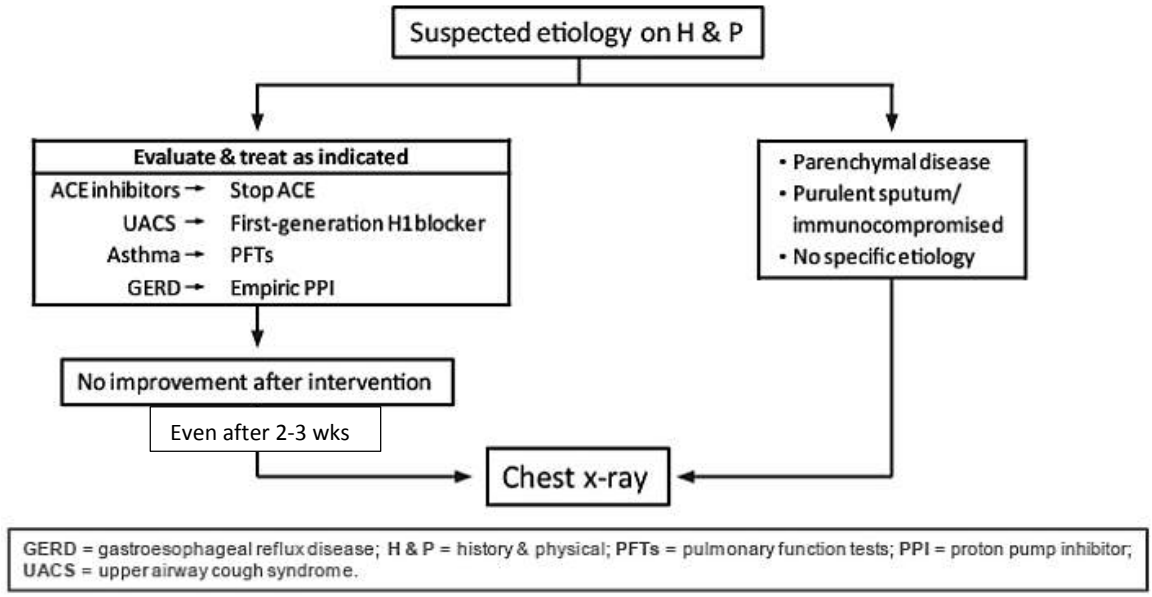
- Usually viral
- Afebrile
- Cough productive of purulent sputum after a recent URTI. Epithelial sloughing can make sputum yellow and purulent and is not a sign of bacterial infection. Can be blood-tinged due to erosion of small blood vessels from inflammation and epithelial damage—not alarming
- Mild wheezing—reflect airway involvement
- Rhonchi that improve with cough—suggest airway secretions that can easily be mobilized
- Clear lungs on CXR
- Supportive care

Cough lasting >5 days following URTI is characteristic of acute bronchitis

- No further evaluation is needed for small volume, new onset blood and no risk factors for malignancy or bronchiectasis (recurrent infections)
- Recurrent bleeding, high risk of malignancy and abnormal CXR or stable pt but active bleeding estimated to be >30ml→ high resolution CT (HRCT)

COUGH

Evaluation of subacute (3-8 weeks) or chronic (>8 weeks) cough



GERD = gastroesophageal reflux disease; H & P = history & physical; PFTs = pulmonary function tests; PPI = proton pump inhibitor; UACS = upper airway cough syndrome.

Common etiologies of chronic cough

- Upper airway cough syndrome (postnasal drip)
- Asthma and cough-variant asthma
- Gastroesophageal or laryngopharyngeal reflux
- Post respiratory tract infection
- ACE inhibitors
- Chronic bronchitis
- Chronic sinusitis
- Bronchiectasis
- Lung cancer
- Non asthmatic eosinophilic bronchitis

Chronic nonproductive cough is a common side effect of ACE inhibitors that is likely due to increased circulating levels of kinins, substance P, prostaglandins, and thromboxane.

CHRONIC COUGH

- 3 most common causes of chronic cough (>8 wks): upper airway cough syndrome (post-nasal drip), GERD and asthma
- **Upper airway cough syndrome** can occur after recent infection. Cough occurs at night, caused by chronic rhinosinusitis conditions which include: allergic and perennial non-allergic and vasomotor rhinitis; acute nasopharyngitis and sinusitis. Diagnosis confirmation and treatment: improvement of nasal discharge and cough with 1st gen antihistamines like chlorpheniramine or combination anti-histamine-decongestant (brompheniramine and pseudoephedrine)

NON-ALLERGIC AND ALLERGIC RHINITIS

	Nonallergic rhinitis	Allergic rhinitis
Clinical features	• Nasal congestion, rhinorrhea, sneezing, postnasal drainage • Later onset common (age >20) • No obvious allergic trigger • Perennial symptoms (may worsen with season changes) • Erythematous nasal mucosa	• Watery rhinorrhea, sneezing, eye symptoms • Earlier age of onset • Identifiable allergen or seasonal pattern • Pale/bluish nasal mucosa • Associated with other allergic disorders (eg, eczema, asthma, eustachian dysfunction)
Treatment	• **Mild**: Intranasal antihistamine or glucocorticoids • **Moderate to severe**: Combination therapy	• Intranasal glucocorticoids • Antihistamines

- NAR is also known as vasomotor rhinitis
- Dx is mainly clinical. Routine allergy testing is not necessary prior to empiric therapy. Plain radiographs are performed if symptoms suggest chronic sinusitis
- NAR pts with prominent rhinorrhea and post nasal drip (dry cough) sometimes respond to 1st gen. antihistamines (eg chlorpheniramine) but they rarely respond to anti-histamines without anticholinergic properties (eg loratadine).

best managed by Topical intranasal antihistamines include azelastine, olopatadine -

VENTILATOR

- PaO2—measure of oxygenation. Mainly influenced by FiO2 and PEEP
- PaCO2—measure of ventilation—affected by respiratory rate and tidal volume
- Normal **FiO2** at sea level=0.21 or 21%. Pts are often provided a high FiO2 (>/=80% or 0.8) initially in mechanical ventilation, pending the result of first ABGs. Ventilator setting can then be changed based on results. (Goal PaO2 >/=60). An important early goal in initial ventilator management should be to decrease the FiO2 to non-toxic values. No strict cut-off FiO2 values for oxygen toxicity, but levels below 50-60% are desirable. ↓ FiO2 when PaO2 is increased. Add PEEP if adequate oxygenation is not achieved with high FiO2
- Assist control mode of mechanical ventilation delivers a predetermined tidal volume with every breath. Inspiratory cycles can be initiated by the pt., but if the pt fails to breathe at a set minimum rate, then the ventilator will deliver tidal volume on its own
- **Normal tidal volume delivered:** 6ml/kg of ideal body weight.
- In pts with ARDS, mechanical ventilation improves oxygenation by providing an ↑ fraction of inspired oxygen (FiO2) and by providing PEEP to prevent alveolar collapse. When FiO2 is decreased below 60%, PEEP can be ↑ed to maintain adequate oxygenation

- If respiratory alkalosis (↑pH, ↓pCO2 and ↑pO2) develops at appropriate tidal volume being delivered, respiratory rate should be lowered (reductions in tidal volume can trigger ↑ ventilatory rate→ exacerbation of situation) Qid: 3048

ARDS

Acute respiratory distress syndrome	
Risk factors	• Infection, trauma, massive transfusion, acute pancreatitis
Pathophysiology	• Lung injury → fluid/cytokine leakage into alveoli • Impaired gas exchange, decreased lung compliance, PHTN
Diagnosis	• New/worsening respiratory distress within 1 week of insult • **Bilateral lung opacities** (pulmonary edema) *not* due to CHF/fluid overload • Hypoxemia with **PaO_2/FiO_2 ratio ≤300 mm Hg**
Management	• Mechanical ventilation (eg, low TV, high PEEP, permissive hypercapnia)

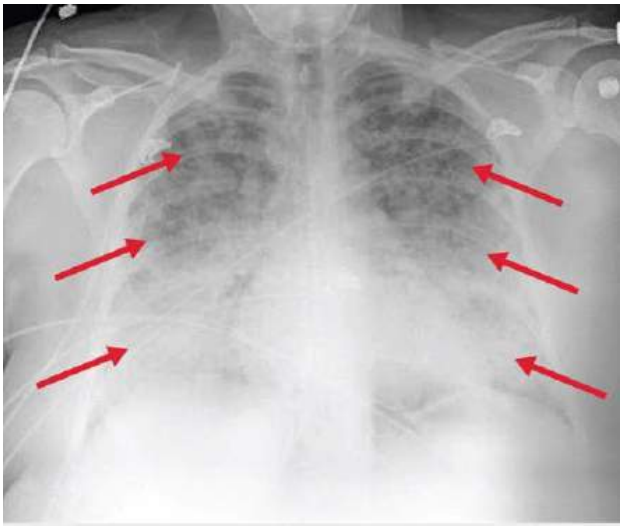
CHF = congestive heart failure; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure; PHTN = pulmonary hypertension; TV = tidal volume.

Hypoxemia: partial arterial pressure of oxygen <60 mm Hg.

- Normal PCWP

Leakage of bloody and proteinaceous material into alveoli, alveolar collapse due to loss of surfactant and diffuse alveolar damage leads to:

- Gas exchange is impaired due to ventilation-perfusion mismatch
- **Lung compliance** (ability to expand) is decreased (stiff lungs) due to both loss of surfactant and increased elastic recoil of edematous lungs
- Pulmonary arterial pressure is increased (pulmonary hypertension) due to hypoxic vasoconstriction, destruction of lung parenchyma, and compression of vascular structures from positive airway pressure in mechanically ventilated patients



Criteria for acute respiratory distress syndrome

- New or worsening respiratory symptoms during past week or within 1 week of known clinical insult
- Bilateral lung opacities on imaging consistent with pulmonary edema
- No signs of cardiac failure or fluid overload
- Objective assessment (eg, echocardiography) to definitively exclude hydrostatic pulmonary edema in patients without ARDS risk factors
- Severity of hypoxemia as defined by PaO_2/FiO_2 ratio (PF) ≤300 mm HG with PEEP ≥5 cm H_2O
  - **Mild:** PF 200-300 mm HG
  - **Moderate:** PF 100-200 mm Hg
  - **Severe:** PF ≤100 mm Hg

- In case of pancreatitis→ ↑ circulating pancreatic enzymes→ breakdown of endothelial membrane, ↑ circulating inflammatory cytokines, diffuse alveolar damage→ impaired gas exchange, ↓ lung compliance, pulmonary HTN requiring invasive mechanical ventilation
- Diffuse crackles on lung examination
- Diagnosis of exclusion—exclude cardiac cause of pulmonary edema

HYPOXEMIA

- **Causes:** ↓ inspired oxygen tension, hypoventilation, diffusion limitation, shunt and V/Q mismatch.
- **A-a gradient** can help to determine specific cause of hypoxemia. It is a measure of oxygen transfer from alveoli to blood. **Normal value <15**. Values increase with age but any value >30 at any age is considered abnormal.
- **Calculation of alveolar oxygen tension:**
  $PAO_2 = (FiO_2 \times [P_{atm} - P_{H2O}]) - (PaCO_2/R)$
  $= (0.21 \times [760-47]) - (PaCO_2/0.8)$

HYPOVENTILATION

- High PaCO2 (50-80 mmHg) and low PaO2 → alveolar hypoventilation+ respiratory acidosis
- **Causes:**
  1. **Pulmonary/ thoracic disease:** COPD, OSA, obesity hypoventilation, scoliosis
  2. **Neuromuscular diseases:** Myasthenia gravis, Lambert- Eaton syndrome, Guillain- Barre' syndrome
  3. **Drug- induced hypoventilation:** anesthetics, narcotics, sedatives
  4. **Primary CNS dysfunction:** brainstem lesion, infection, stroke
- **A-**a gradient is normal in hypoventilation and reduced inspired oxygen tension

EFFECT OF ARTERIAL OXYGENATION AND VENTILATION IN VARIOUS ENVIRONMENTS

Effect of arterial oxygenation & ventilation in various environments				
	Example	A-a gradient	P_aCO_2	Corrects with supplemental O_2?
Reduced inspired oxygen tension	High altitude	Normal	Normal	Yes
Hypoventilation	CNS depression	Normal	↑	Yes
Diffusion limitation	Interstitial lung disease	↑	Normal	Yes
Shunt	Intracardiac shunt, extensive ARDS	↑	Normal	No
V/Q mismatch	Obstructive lung disease, atelectasis, pulmonary edema & pneumonia	↑	Normal or ↑	Yes

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea	
Pathophysiology	• Relaxation of pharyngeal muscles leads to closure of airway • Loud snoring with periods of apnea
Symptoms	• Daytime somnolence • Non-restorative sleep with frequent awakenings • Morning headaches • Affective & cognitive symptoms
Sequelae	• Systemic hypertension • Pulmonary hypertension & right heart failure

Tx:
1. weight reduction, avoidance of sedatives and alcohol, and avoidance of supine posture during sleep
2. CPAP

- Occur alone or with OHS
- OSA→ hypoventilation only at night with transient hypoxia and hypercapnia that resolve while awake
- Men>women, ↑ incidence with age till 65 years, obesity, small mandible, ↑ soft tissue, tonsillar hypertrophy are risk factors
- **Complications:** Depression, accidents due to daytime somnolence, impotence
- **Dx:** nocturnal polysomnography—gold standard. 2 types of abnormal ventilation during sleep: apnea (cessation of breathing for >/= 10 sec) and hypopnea (↓ airflow causing SaO2 to decrease >/=4%)

- **Diagnostic criteria:** experiencing >/=15 obstructive respiratory events (apnea or hypopnea) per hour is diagnostic

OBSTRUCTIVE SLEEP APNEA AND OBESITY HYPOVENTILATION SYNDROME

- OSA+OHS→ morbid obesity, neck fat, fatigue, sleep disturbances, and progressive dyspnea on exertion
- OHS→ physical restriction of thoracic cavity caused by excess thoracic tissue continues throughout the day→ chronic hypoxia and hypercapnia (resp. acidosis)→to maintain pH, kidneys ↑ bicarb retention and ↓ chloride reabsorption→ compensatory metabolic alkalosis→↓ventilatory response to ↑ CO2→ hypoventilation

- Chronic hypoxia→pulmonary HTN due to hypoxic vasoconstriction→ cor pulmonale
- Isolated OSA and OSA+OHS→hypoxia→sympathetic NS→↑catecholamines→ systemic HTN

Obesity hypoventilation syndrome	
Diagnostic criteria	• Obesity with BMI ≥30 kg/m^2 • Awake daytime hypercapnia ($PaCO_2$ >45 mm Hg) • No alternate cause of hypoventilation
Workup	• ABG on room air (hypercapnia, normal A-a gradient) • No intrinsic pulmonary disease on chest x-ray • Restrictive pattern on PFTs • Normal TSH • Polysomnography
Treatment	• Nocturnal positive-pressure ventilation as first-line therapy • Weight loss (bariatric surgery in select cases) • Avoidance of sedative medications • Respiratory stimulants (eg, acetazolamide) as last resort

ABG = arterial blood gas; PFT = pulmonary function test.

SUMMARY:
Patients with obesity hypoventilation syndrome and obstructive sleep apnea can develop chronic hypoxia and hypercapnia (with a compensatory metabolic alkalosis), secondary erythrocytosis, pulmonary hypertension, and cor pulmonale.

PULMONARY EMBOLISM

DVT

- Common sources of pulmonary embolism:
  - The deep veins of the lower extremities are the most frequent source. Lower extremity deep vein thrombosis (DVT) is divided into 2 categories:
    - Proximal/thigh (eg, iliac, femoral, popliteal): These are the source of >90% of acute PEs, probably due to their large caliber and proximity to the lungs
    - Distal/calf: These are less likely to embolize and more likely to spontaneously resolve

FAT EMBOLISM

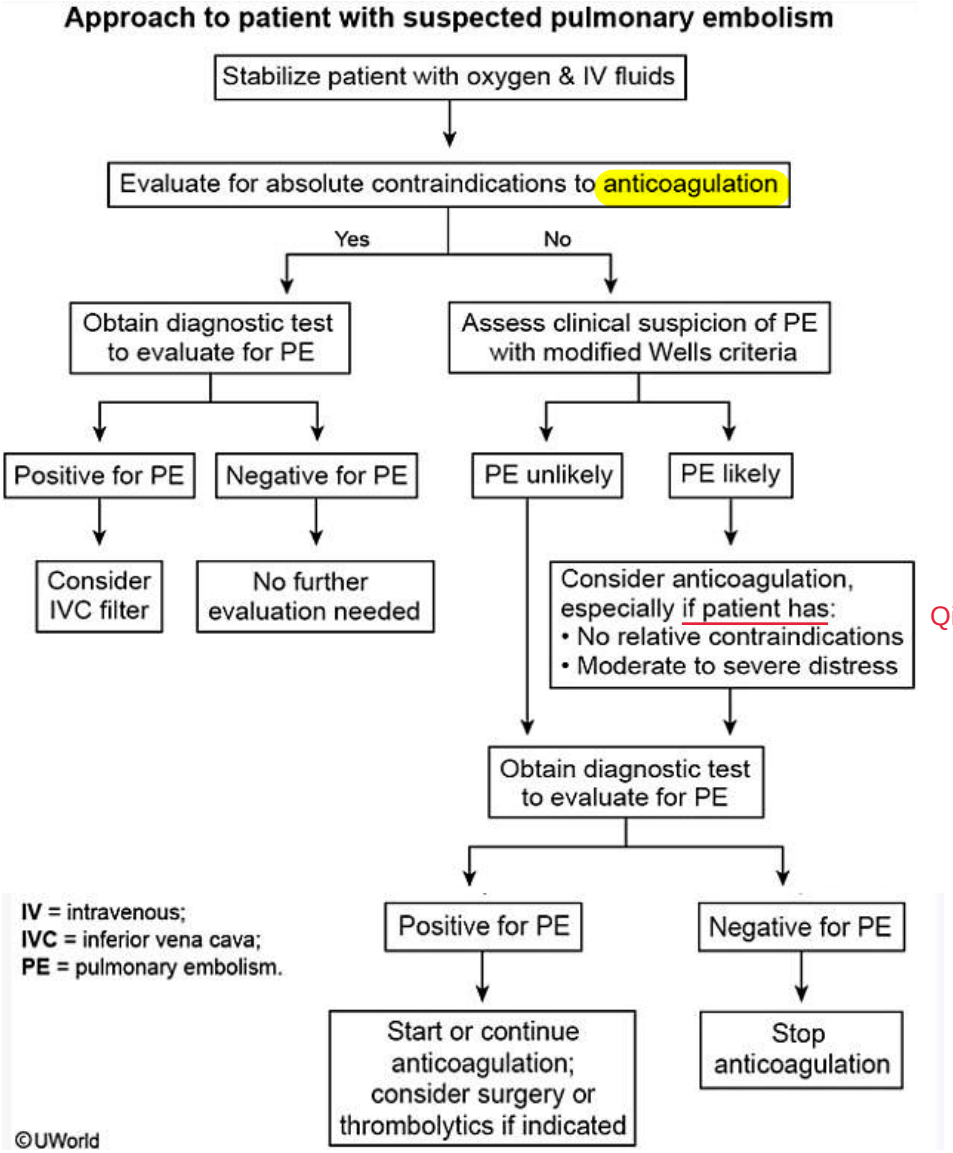
- Common in pts with polytrauma, esp. after multiple fractures of long bones—may occur 12-72 hours after trauma
- **S/S:** severe resp. distress, petechial rash, subconjunctival hemorrhage, tachypnea, tachycardia and fever. CNS manifestations: initially confusion and agitation but can progress to stupor, seizures or coma and frequently unresponsive to correction of hypoxia
- **Dx:** presence of fat droplets in urine or intra-arterial fat globules on fundoscopy. Thrombocytopenia, anemia and hypofibrinogenemia are non-specific findings
- **Serial X-rays:** increasing diffuse b/l pulm. Infiltrates within 24-48 hours of onset of clinical findings

- **Rx:** prompt resp. support. Use of heparin, steroids and low molecular weight dextrin is controversial

AMNIOTIC FLUID EMBOLISM

- Occurs immediately after rupture of membranes and not during pregnancy generally

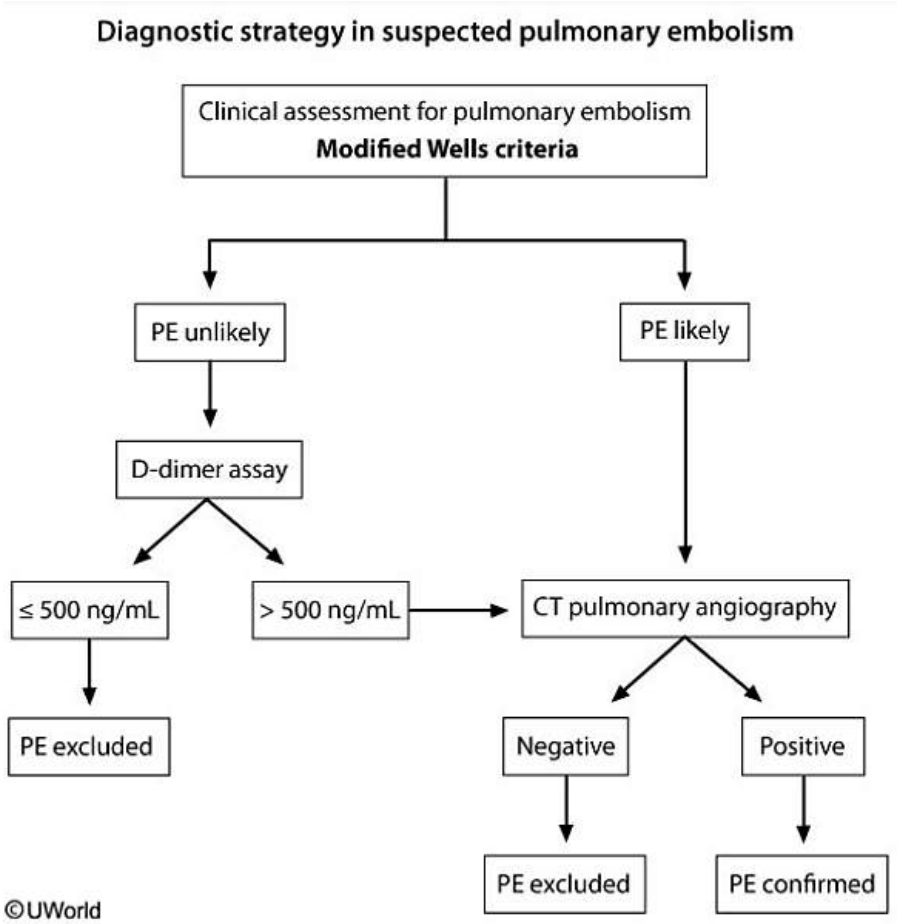
MANAGEMENT



Qid: 3717

- S/S: acute dyspnea and pleuritic chest pain most common, hemoptysis, DVT, tachypnea, tachycardia, and low grade fever
- Acute PE can cause b/l wheezing due to cytokine release in response to hypoxia and infarction
- ECG may show prominent S wave in lead I, Q wave in III and inverted T wave in lead III (S1Q3T3)
- CXR: Hampton's hump, Westermark sign—less common
- Atrial fib—due to atrial strain from ↑ right atrial pressure.
- Low oxygen saturation and atrial fib are poor prognostic signs

- Hemoptysis is a result of pulmonary **infarction.**
- Low-grade fever and mild leukocytosis are also common with PE.
- Chest CT scan showing a **wedge-shaped infarction** is virtually pathognomonic for pulmonary embolism.
- Contrast CT scan, the PE itself will appear as a pulmonary artery **filling defect**.
- PE is a common cause of both transudative and exudative pleural effusion.



- CT angiography is diagnostic test of choice
- V/Q mismatch is checked in those with significant renal impairement, morbid obesity and/or contrast allergy. Echocardiography can be done in pts highly unstable to tolerate CTA to look for changes in left ventricule
- V/Q mismatch→ A-a gradient ↑ more than expected A-a. PAO2 is calculated by:

$$PAO2 = (FiO2 \times [Patm - PH2O]) - (PaCO2 \div 0.8)$$

Simplified for pts breathing room air at sea level

$$PAO2 = 150 - (PaCO2 \div 0.8)$$

- Expected A-a gradient is calculated by:

$$\frac{patient\ age}{4} + 4 = expected\ A - a\ gradient$$

Or

$$2.5 + [patient\ age * 0.21] = expected\ A - a\ gradient$$

- D-dimers assay—to exclude PE in those who are unlikely to have PE but negative test cannot be used to exclude PE in those who are likely to have PE

WELL'S CRITERIA

Modified Wells criteria for pretest probability of PE

Score +3 points

- Clinical signs of DVT
- Alternate diagnosis less likely than PE

Score +1.5 points

- Previous PE or DVT
- Heart rate >100
- Recent surgery or immobilization

Score +1 point

- Hemoptysis
- Cancer

Total score for clinical probability

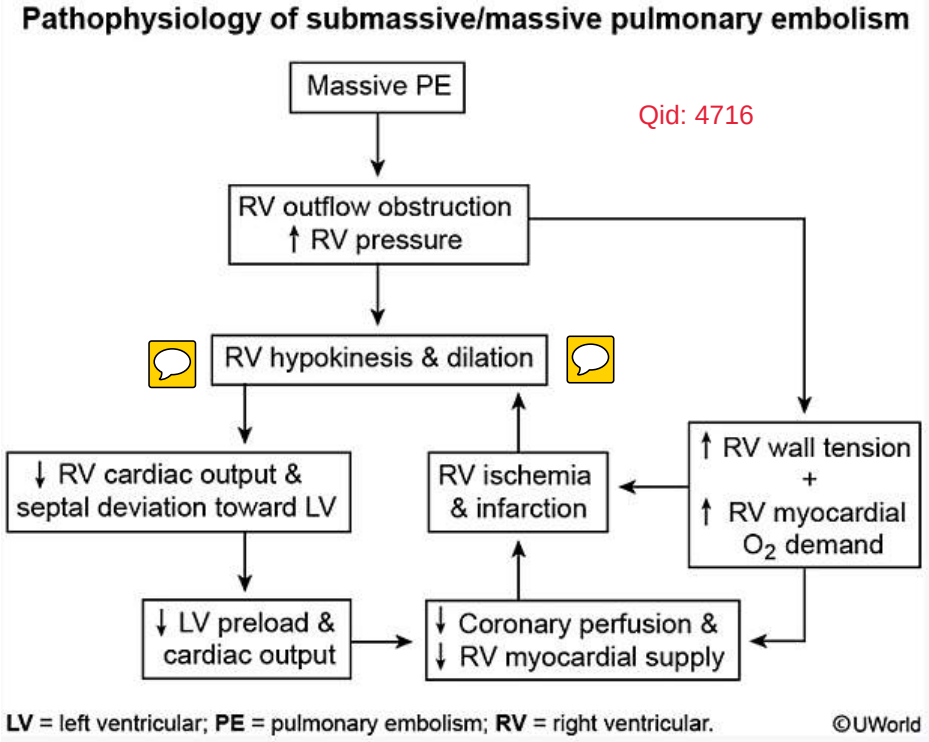
≤ 4 = PE unlikely

> 4 = PE likely

TREATMENT

- Immediate anticoagulation unless CI
- Many options are available: low molecular weight heparin (enoxaparin), oral factor Xa inhibitor (rivaroxaban) and injection factor Xa inhibitor (fondaparinux)→these 3 can't be used in severe renal insufficiency with GFR <30ml/min/1.73m2 as reduced renal clearance leads to increased anti-Xa activity and ↑ bleeding risk. Unfractionated heparin is used in these pts as its therapeutic levels are easily monitored with aPTT. Once heparin produces therapeutic anticoagulation (1.5-2times normal PTT), warfarin is started→ takes 5-7 days to reach therapeutic levels→after reaching therapeutic INR, heparin can be stopped and warfarin continued long term

MASSIVE PULMONARY EMBOLISM



Qid: 4716

treatment is **tPA** thrombolytic or surgery

Normal PCWP

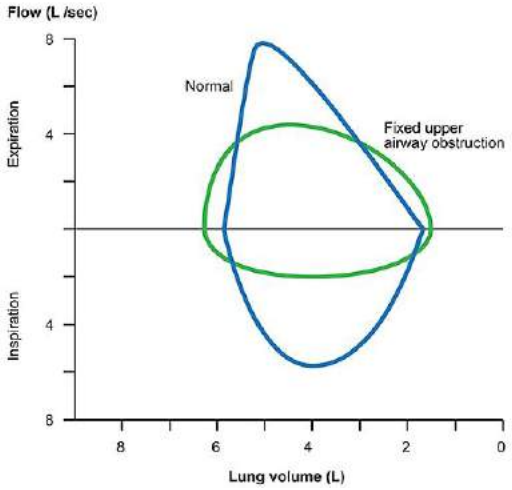
Inc. RA pressure
Inc. pulmonary artery pressure

- Significant dyspnea, hypoxia, tachycardia (bradycardia in complete heart block), clear lungs, chest pain, syncope, hemodynamic collapse, elevated JVP
- Septal deviation occurs cox RV pressure rises more than LV pressure
- Right ventricular dysfunction and elevated BNP and troponin→ ↑ mortality

FLOW VOLUME CURVES

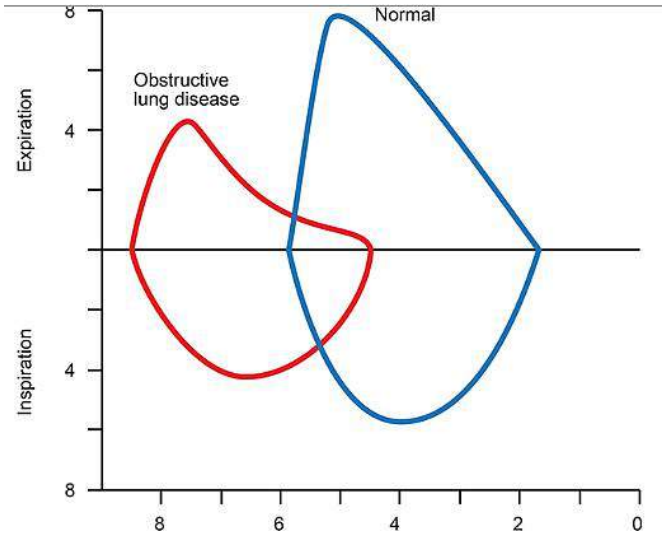
FIXED UPPER AIRWAY OBSTRUCTION

- Limits airflow during inspiration and expiration→flattening of flow volume loop
- Can be caused by laryngeal edema which can be 2^{o} to food allergy→ Rx: epinephrine, systemic corticosteroids, and antihistamines



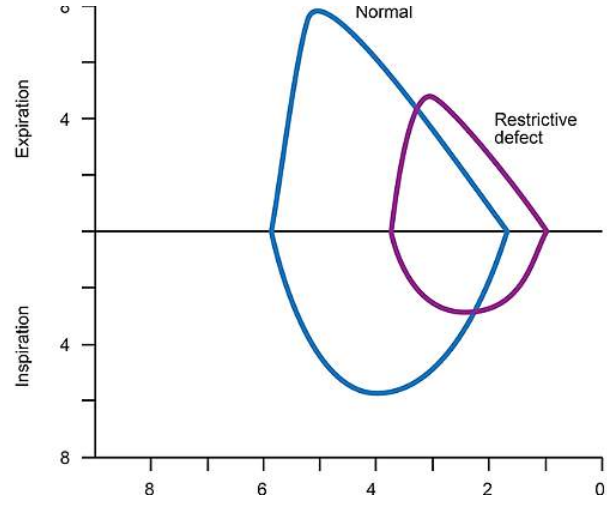
OBSTRUCTIVE PATTERN

- Causes intrapulmonary airway obstruction via bronchoconstriction→↓ airflow during effort independent phase of exhalation→ scooped out pattern during exhalation on flow volume loops

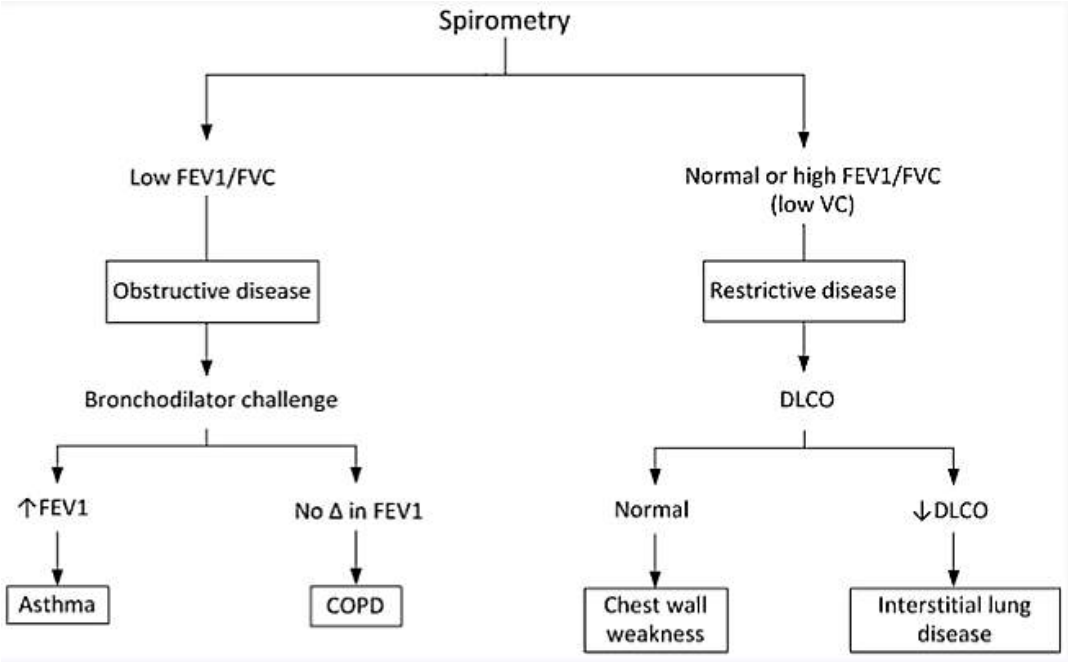


RESTRICTIVE PATTERN

- Pneumothorax→↓ lung ventilation by preventing complete expansion of affected lung→ restrictive pattern on flow volume loop
- Pulmonary edema→↓ lung compliance→↓ lung ventilation→ restrictive pattern



SPIROMETRY



OBSTRUCTIVE LUNG DISEASES

COPD

- Combination of :
  - Chronic bronchitis→ cough with sputum production for >/= 3months in 2 successive years and abnormality of tracheobronchial tree, prominent bronchovascular markings, mildly flattened diaphragm, normal DLCO
  - Emphysema→ thin e' severe dyspnea, hyperinflated chest, ↓ vascular markings, ↓ DLCO due to alveolar damage and moderate oxygen desaturation—usually centriacinar
- Either of these can be predominant

THERAPIES THAT PROLONG SURVIVAL

- Smoking cessation, supplemental oxygen and lung reduction surgery in certain patients

Long term home oxygen therapy

Progressive hypoxemia is common in patients with advanced chronic obstructive pulmonary disease (COPD), and studies have shown survival benefit of **long-term home oxygen therapy** (LTOT) in those with significant **chronic hypoxemia**. The criteria for initiating LTOT in patients with COPD include:

1. Resting arterial oxygen tension (PaO_2) **≤55 mm Hg** or pulse oxygen saturation (SaO_2) **≤88%** on room air
2. PaO_2 ≤59 mm Hg or SaO_2 ≤89% in patients with cor pulmonale, evidence of right heart failure, or hematocrit >55%

The dose of supplemental oxygen should be titrated so that SaO_2 is maintained at >90% during sleep, normal waking, and at rest. Survival benefits of home oxygen therapy are significant when it is used for ≥15 hours a day.

- Roflumilast—phosphodiesterase inhibitor with anti-inflammatory properties→ ↓mucociliary malfunction and pulmonary remodeling→used in maintenance therapy of COPD but not acute exacerbation

REMAINDER THERAPIES

- Given to ↓ respiratory symptoms, improving quality of life, and ↓ hospitalizations
- Include: inhaled bronchodilators esp. anti-cholinergics e.g. ipratropium, tiotropium—mainstay of treatment, may be combined with short acting beta agonists like albuterol
- Inhaled steroids and long acting beta 2 agonists—for more severe COPD

ACUTE EXACERBATION OF COPD

Acute exacerbation of chronic obstructive pulmonary disease	
Cardinal symptoms	• Increased dyspnea • Increased cough (more frequent or severe) • Sputum production (change in color or volume)
Diagnostic testing	• Chest x-ray: Hyperinflation • ABG: Hypoxia, CO_2 retention (chronic &/or acute)
Management	• Oxygen (target SpO_2 of 88%-92%) • Inhaled bronchodilators • Systemic glucocorticoids • Antibiotics if ≥2 cardinal symptoms • Oseltamivir if evidence of influenza • NPPV if ventilatory failure • Tracheal intubation if NPPV failed or contraindicated

Diagnosed by >/= one of these

ABG = arterial blood gas; **NPPV** = noninvasive positive-pressure ventilation; **SpO_2** = peripheral oxygen saturation.

- Often triggered by recent upper respiratory tract infection
- JVD may be observed esp. during expiration because of ↑ intrathoracic pressure
- Systemic glucocorticoids→↓ inflammation associated with COPD exacerbation, improve lung function and hypoxemia and ↓ risk of relapse, treatment failure, and length of hospital stay→administered for 5 days as oral prednisone or IV methylprednisolone. IV used in more severe exacerbations but no significant benefit over oral
- Inhaled glucocorticoid→ no role in acute exacerbation→ may ↓ exacerbation frequency and improve Sx. Do not affect mortality or lung function
- Long acting beta 2 agonists are used in long term maintenance
- Antibiotics are considered if:
  - >/=2 cardinal Sx present
  - Mechanical ventilation is needed (NPPV or endotracheal intubation)

  Sputum cultures—not recommended unless pt is at high risk of P. aeruginosa infection. Antibiotics are given to cover common respiratory pathogens (eg S. pneumonia, Moraxella cattarhalis, H. influenza)—include macrolides (azithromycin), respiratory fluoroquinolones (levofloxacin,

moxifloxacin) and penicillin/beta-lactamase inhibitors (amoxicillin/clavulanic acid)—duration of Rx 3-7days

➔ COPD is associated with formation of blebs, which can rupture and cause spontaneous pneumothorax. Pneumothorax must be considered in COPD pt with sudden decline in respiratory function. More acute than acute exacerbation. (bronchiectasis is not associated with blebs and pneumothorax)

NPPV

Noninvasive positive-pressure ventilation	

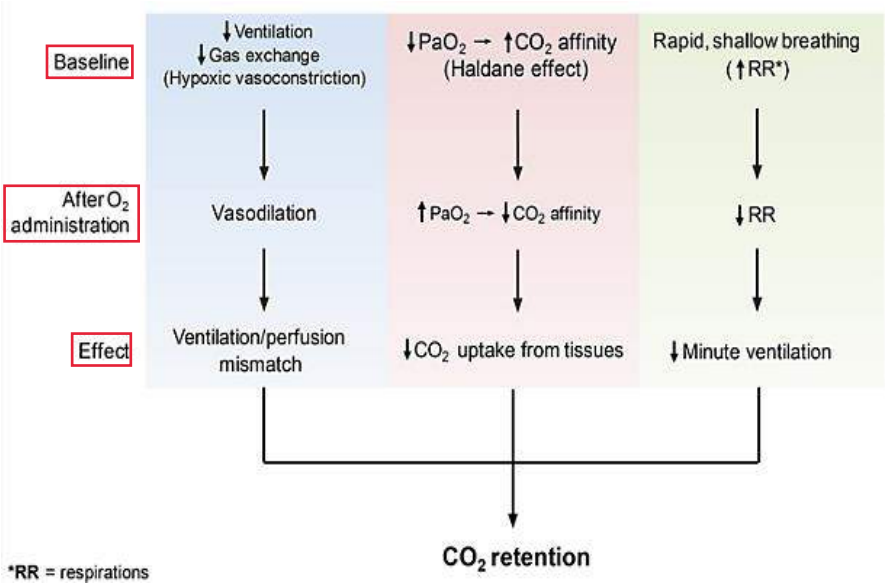
Indications (strongest evidence)	• COPD (severe exacerbation, prevent extubation failure)
	• Cardiogenic pulmonary edema
	• Acute respiratory failure
	  ○ Postoperative hypoxemic respiratory failure
	  ○ Immunosuppressed patients
	• Facilitate early extubation

Contraindications	**Medical instability**
	• Cardiac or respiratory arrest (or impending arrest)
	• Severe acidosis (pH <7.10)
	• Acute respiratory distress syndrome
	• Non-respiratory organ failure
	  ○ Unstable cardiac arrhythmia/hemodynamic instability
	  ○ Encephalopathy (Glasgow Coma Score <10)
	  ○ Gastrointestinal bleed
	Inability to protect airway
	• Uncooperative or agitated
	• Inability to clear secretions/high aspiration risk
	Mechanical issues
	• Recent esophageal anastomosis
	• Facial or neurological surgery, deformity, or trauma
	• Upper airway obstruction

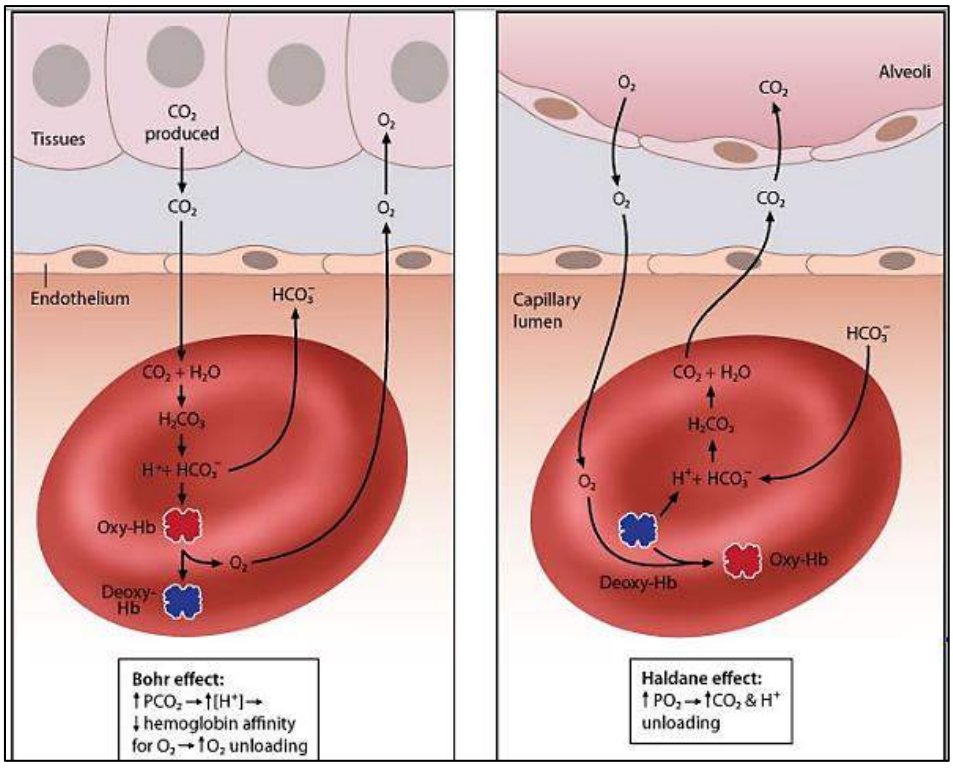
- NPPV is ventilatory support given by facemask rather than endotracheal tube; delivered in **different methods:** CPAP and bilevel positive airway pressure→ ↓ work of breathing, improve alveolar ventilation and preferred method of ventilatory support in pts with acute exacerbation of COPD (AECOPD)
- **Physiologic benefits**: ↓ RR and PaCO2, ↑ tidal volume, minute ventilation, PaO2
- **Benefits**: ↓ need of intubation, mortality, treatment failure, length of hospital stay and incidence of nosocomial infections
- **A** trial of NPPV must be given before intubation unless CI as in severe COPD, weaning and extubation will be more challenging→ failure after 2 hours of trial (hypoxia, acidosis)→ intubation

OXYGEN INDUCED CO2 RETENTION IN COPD

Supplemental oxygen worsens hypercapnia by following mechanisms:

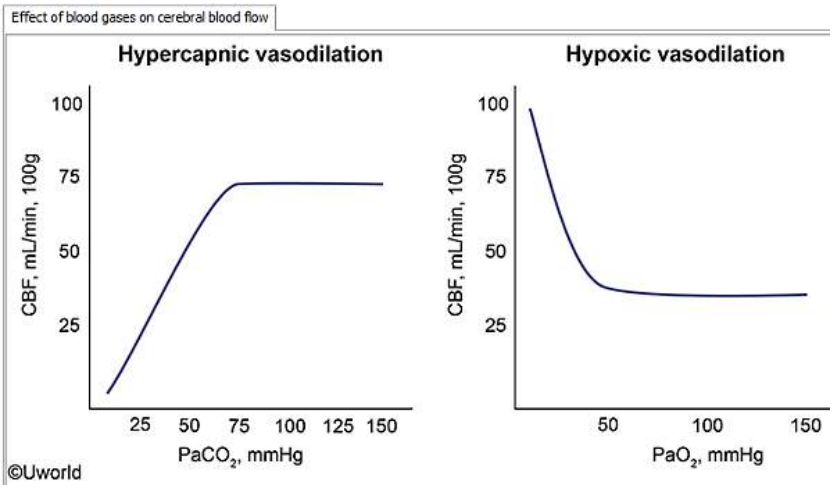


- Destruction of terminal bronchioles and alveoli→V/Q mismatch→local hypoxia and hypercapnia→ selective vasoconstriction→ redirects blood flow to better ventilated area→O2 therapy→ vasodilation→ ↑ blood flow to the affected area→ V/Q mismatch worsen
- ↑ oxyhemoglobin→↓ uptake of CO2 from tissues by Haldane effect



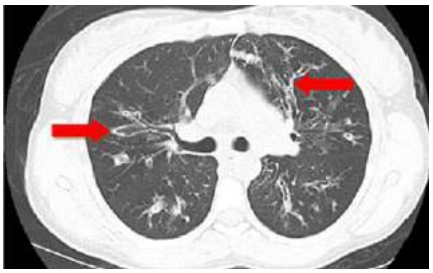
- ↓ respiratory drive→↓ RR→↓ minute ventilation
- Acute ↑ in CO2→ acidosis→↑ brain GABA and glutamine and ↓ glutamate and aspartate→ change in level of consciousness
- Hypercapnia→reflex cerebral vasodilation → seizures
- Hence, O2 should be given cautiously with a goal SaO2 of 90-93% or PaO2 60-70mmHg
- Pts who develop significant acidosis or have severely reduced level of consciousness require mechanical ventilation

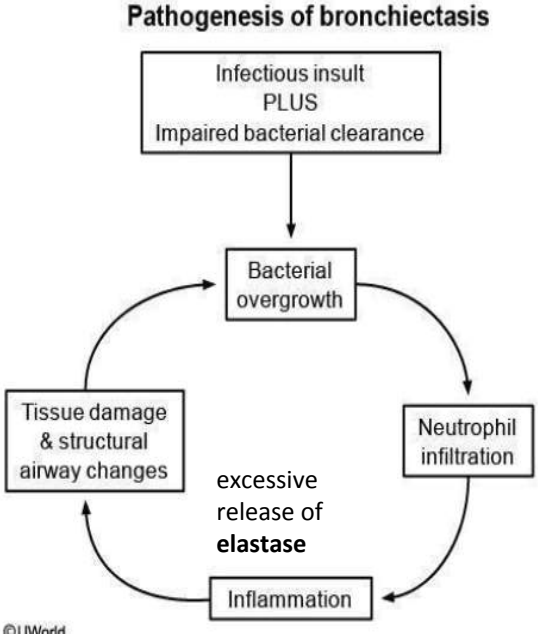
absence of marked acidosis in COPD despite CO2 retention is The body compensates for chronic hypercapnia by **increasing renal bicarbonate retention** and creating a compensatory metabolic alkalosis.



BRONCHIECTASIS

Clinical features of bronchiectasis	
Symptoms/Signs	• Cough with sputum production most days of the week • Rhinosinusitis • Dyspnea, hemoptysis, pleurisy • Wheezing, crackles, digital clubbing
Etiologies	• Airway obstruction • Congenital (eg, cystic fibrosis, alpha-1 antitrypsin, etc.) • Immunodeficiencies (eg, hypogammaglobulinemia) • Post-infectious (eg, *Aspergillus*, viral, TB) • Rheumatic and systemic diseases (eg, RA, Sjögren's) • Toxic inhalation/aspiration
Evaluation	• CBC with differential • Immunoglobulin quantification • Sputum culture/smear for bacteria, fungi, TB • High resolution CT • Pulmonary function tests





- C/F: mucopurulent sputum >100ml/day, recurrent fever, fatigue, weight loss. Rhonchi, wheezing and crackles are more common in bronchiectasis than COPD. COPD is more common in smokers and bronchiectasis pts have history of recurrent respiratory tract infections
- CXR—not sensitive or specific for diagnosis of bronchiectasis→linear atelectasis, dilated and thickened airways, and irregular peripheral opacities.
- Confirm diagnosis with **HRCT** (bronchial dilation, airway thickening, and lack of airway tapering)→ confirmed→**sputum analysis** for bacteria and mycobacteria (TB and atypical)—in all pts→**bronchoscopy**— for focal disease to evaluate for localized airway obstruction→ rule out systemic disease—for diffuse involvement→treat etiology, corticosteroids and macrolides for inflammation, pharmacologic agents and chest physiotherapy to mobilize airway secretions. Exacerbation treated with

The clinical presentation is often similar to that of **chronic bronchitis**; however, sputum production is more prominent in **bronchiectasis,** and exacerbations are typically **bacterial** (usually **viral** in chronic bronchitis) and require antibiotics.

specific antibiotics tailored to microbiology results. Surgical resection and transplantation may be needed in severe cases.

- PFTs are done to monitor disease progression and not for diagnosis
- In contrast chronic bronchitis present with non-purulent expectoration. CXR is usually normal

ASTHMA

Types and treatment:

- There are four types of asthma based on severity

Mild intermittent

- Symptoms </= 2 days/week, nighttime awakenings </= 2x/month, use of beta agonist </=2 times/week, FEV1 and FEV1/FVC normal, no limitations on daily activities
- Rx: short acting beta agonist (eg albuterol) as needed (PRN), no need of daily controller meds

Mild persistent

- Symptoms >2 days/week but less than daily, nighttime awakenings 3-4x/month, FEV1 and FEV1/FVC normal, mild limitations of daily activities
- Rx: short acting beta agonist (eg albuterol) as needed (PRN), low dose inhaled corticosteroids as controller med

Moderate persistent

- Symptoms daily, nighttime awakenings weekly, FEV1 60-80% predicted
- Rx: short acting beta agonist (eg albuterol) as needed (PRN) + low dose inhaled corticosteroids+ long acting beta 2 agonists inhaler

Severe persistent

- Symptoms throughout day, frequent nighttime awakenings, FEV1 <60% predicted, extremely limited activities
- Rx: short acting beta agonist (eg albuterol) as needed (PRN) + long acting beta 2 inhaler+ high dose inhaled corticosteroids. Oral prednisone can also be used in cases of severe persistent asthma

Diagnosis of asthma

- PFTs/spirometry to assess bronchodilator response→ no response→ methacoline challenge test
- Nocturnal or early morning peak expiratory flow rates measurement—for those with nocturnal symptoms only
- Alternative approach: 2-4 wks treatment with inhaled glucocorticoids→ improved condition→ asthma diagnosed

Asthma and comorbid GERD

- Comorbid GERD is usually present in pts with asthma→microaspiration of gastric contents→ ↑ vagal tone and bronchial reactivity→ exacerbates asthma symptoms→ sore throat, morning hoarseness, ↑ cough only at night, ↑ need of albuterol inhaler after meals—may not be associated with typical GERD symptoms—↑ risk with obesity→ Rx: PPI improve asthma symptoms and peak expiratory flow rates in asthma pt

Aspirin- exacerbated respiratory disease

- Non-IgE mediated

- Can develop in asthma, chronic rhinosinusitis with nasal polyposis, or chronic urticarial pts→Sx: sudden worsening of asthma (cough, wheezing and chest tightness), nasal or ocular sx (eg nasal congestion, rhinorrhea, or periorbital edema) and facial flushing within 30 min- 3hours after ingestion of NSAIDS
- Rx: management of underlying asthma and nasal congestion, avoidance of NSAIDS, or desensitization to NSAIDS if use is required. Leukotriene inhibitors (zileuton) and leukotriene receptor blockers (like montelukast) can also improve nasal and respiratory symptoms

Indicator of severe acute asthma exacerbation

- Acute pulmonary insult such as acute exacerbation of asthma→↑ respiratory drive due to combination of hypoxemia, anxiety due to sensation of dyspnea and signals from thoracic neural receptors due to change in lung volume and presence of inflammatory chemicals (like PG, histamines)→ hyperventilation→ ↓PaCO2 and pH (primary respiratory alkalosis)
- Normal pH and normal or ↑PaCO2 indicate inability to maintain adequate ventilation in the setting of increased work of breathing→ caused by respiratory muscle fatigue and severe air trapping→ suggests impending respiratory collapse/failure
- Other signs of impending respiratory failure:
  - Markedly ↓ breath sounds
  - Absent wheezing
  - Altered mental status
  - Marked hypoxia with cyanosis

Treatment of asthma exacerbation

- **Mild to moderate exacerbation**: oxygen and inhaled short acting beta 2 adrenergic agonists (SABAs)→ usually respond→ if no response→ systemic corticosteroids
- **Severe exacerbation**: SABAs+ ipratropium nebulizer+ systemic corticosteroids (oral/IV—takes several hour to show effect) → no improvement after one hour of therapy→ one time dosing with IV magnesium sulfate (bronchodilation)→ signs of respiratory failure→ admit to ICU with endotracheal intubation

- Patients on high doses of beta-2 agonists may develop hypokalemia, which may present with muscle weakness, arrhythmias and EKG abnormalities. Other common side effects of beta-2 agonists include tremor, palpitations and headache.

- The most common adverse effect of inhaled corticosteroid therapy is oropharyngeal thrush (oral candidiasis).
high-dose inhaled steroids for prolonged period of time can lead to adrenal suppression (not cushing), cataract formation & Osteoporosis. (avoid these answers unless Qs is clearly wanting them)

- **Exercise-induced bronchoconstriction** (EIB)
Path: Bronchoconstriction occurs in response to mast cell degranulation triggered by the passage of high volumes of dry, cold air.
- **Tx:** 1st line: beta agonist 10-20 min before exercise few times a week (less than daily)
2nd line: ICS or antileukotriene agents can be used in patients who exercise daily. or for those unable to tolerate beta agonists.

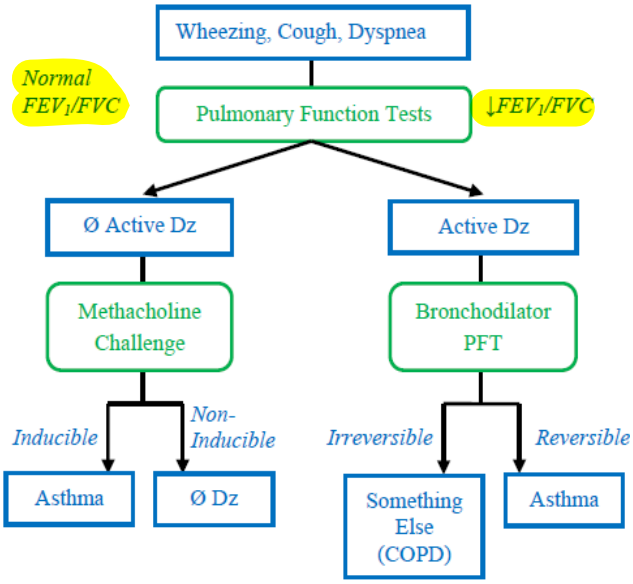
- Patients with an acute asthma exacerbation usually have **respiratory alkalosis** with a low $PaCO_2$ due to **hyperventilation.** A normal or elevated $PaCO_2$ is an alarming and extremely important finding that suggests impending respiratory failure.

- Asthma + acidosis + ↟CO2 = **intubation**

Adult onset asthma and difference between asthma and COPD

Asthma versus COPD			
	Asthma	**COPD**	**Late-stage COPD**
FVC	Normal/↓	Normal/↓	↓/↓↓
FEV_1	↓	↓	↓↓
FEV_1/FVC	↓	↓	↓↓
Bronchodilator response	Reversible	Partially/ nonreversible	Usually nonreversible
Chest x-ray	Normal	Normal	Hyperinflation, loss of lung markings
DLCO	Normal/↑	Normal/↓	↓

COPD = chronic obstructive pulmonary disease; DLCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.



	Obstructive lung disease	**Restrictive lung disease including obesity**
FEV_1	<80%	<80%
FEV_1/FVC	<70%	>70%
FVC	Normal to decreased	<80%

Normal FVC: 80% to 120%
TLC: 80% to 120%
FRC: 75% to 120%
RV: 75% to 120%
DLCO: 60% - 120%

- Asthma usually diagnosed in childhood or young adulthood but can develop in adults
- Hard to clinically differentiate COPD and adult onset asthma esp. in smokers→PFTs usually needed. Bronchodilators (usually albuterol) followed by spirometry—most effective test in differentiating asthma and COPD. Normal airflow after bronchodilator→ rules out COPD. Positive bronchodilator response= >12% increase in FEV1 is seen in asthmatics.
- COPD—never shows complete response to bronchodilators. DLCO—never ↑ in COPD.
- COPD and asthma must be differentiated: as COPD—mainly treated by long-acting anti-cholinergic inhalers and asthma—mainly treated by long-term steroid inhalers

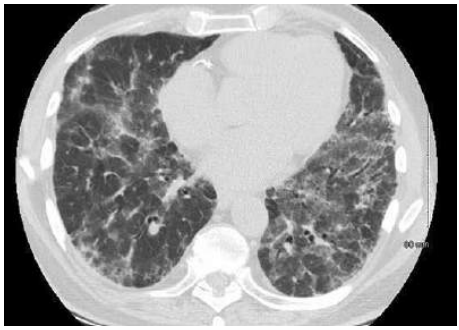
Theophylline toxicity

- Due to ↓ clearance and ↓ metabolism by cytochrome oxidase
- Due to inhibition of these enzymes by concurrent illness (eg cirrhosis, cholestasis, respiratory infection with fever) or drugs (eg cimetidine, ciprofloxacin, erythromycin, clarithromycin, verapamil)
- Sx: CNS stimulation effects (headache, insomnia, seizures), GI disturbance (N/V) and cardiac sx (arrhythmia)

RESTRICTIVE LUNG DISEASES

INTERSTITIAL LUNG DISEASE

Clinical features of interstitial lung disease	
Common etiologies	• Sarcoidosis, amyloidosis, alveolar proteinosis • Vasculitis (eg, granulomatosis with polyangiitis) • Infections (eg, fungal, tuberculosis, viral pneumonia) • Occupational & environmental agents (eg, silicosis, hypersensitivity pneumonitis) • Connective tissue disease (eg, systemic lupus erythematous, scleroderma) • Idiopathic pulmonary fibrosis, interstitial pneumonia • Cryptogenic organizing pneumonia
Clinical presentation	• Progressive exertional dyspnea or persistent dry cough • Pulmonary findings due to other underlying conditions (eg, silicosis, connective tissue disease) • >50% of patients with significant smoking history • Lung examination with fine crackles during mid-late inspiration, possible digital clubbing
Laboratory/ Imaging	• Chest x-ray can show reticular or nodular opacities • High-resolution chest computed tomography usually shows fibrosis, honeycombing, or traction bronchiectasis • **Pulmonary function tests:** Normal or ↑FEV1/FVC ratio, ↓DLCO, ↓TLC, ↓RV* • Resting arterial blood gas can be normal or show mild hypoxemia • Exertion usually causes significant hypoxemia due to V/Q mismatch
***FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion lung capacity of carbon monoxide; TLC, total lung capacity; RV, residual volume.**	



Idiopathic pulmonary fibrosis is due to excessive collagen deposition in peri-alveolar tissues. This leads to **decreased lung volumes** (low total lung capacity, functional residual capacity, and residual volume) with preserved or increased FEVl/FVC ratio. Patients have impaired gas exchange resulting in reduced diffusion capacity of carbon monoxide and increased alveolar-arterial gradient.

- Diagnosis: clinical, PFTs and imaging but biopsy may be needed in unclear cases
- **Idiopathic pulmonary fibrosis (IPF):** no known etiology→idiopathic
- **IPF:** extracellular matrix around alveoli→scarring→↓TLC, FRC, RV, ↑elastic recoil→impaired gas exchange→V/Q mismatch→↑A-a gradient (in all pts). Resting ABGs may be normal

HYPERSENSITIVITY PNEUMONITIS

- Inflammation of lung parenchyma caused by antigen exposure
- Common responsible antigens: aerosolized bird droppings (bird fancier's lungs) and molds associated with farming (farmer's lung)
- **Acute episode:** within 4-6 hours of exposure, fever, cough, breathlessness, malaise
- **Chronic exposure:** weight loss, clubbing, pulmonary fibrosis→restrictive pattern on spirometry→CXR: ground glass opacity, or "haziness" of lower lung fields, honeycombing

- **Best treatment:** Avoidance—can produce complete remission. Systemic steroids speed up recovery of acute symptoms and essential part of management of severe episodes but do not slow or reverse progression.

ASBESTOSIS

Clinical features of asbestosis	
Clinical presentation	• Prolonged asbestos exposure (shipyard, mining & construction workers, pipe fitters) • Symptoms develop ≥20 years after initial exposure • Progressive dyspnea (over months), bibasilar end-inspiratory fine crackles & clubbing • Increased risk for malignancies (lung cancer, malignant mesothelioma)
Diagnostic evaluation	• History & clinical findings of exposure (eg, **pleural plaques** on chest imaging virtually pathognomonic) • Interstitial fibrosis on imaging or histology &/or pulmonary function tests with restrictive pattern • Exclusion of other diseases

- Bronchogenic carcinoma is the most common malignancy diagnosed in patients exposed to asbestos. Smoking acts synergistically with asbestos to further increase the risk of lung cancer.

- Asbestosis is also the only known risk factor for malignant pleural mesothelioma. However, bronchogenic CA is more common in patients with asbestos exposure, especially smokers.

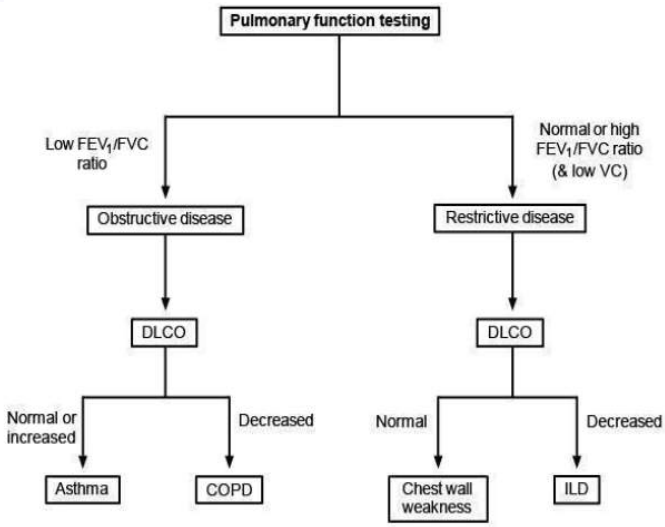
pleural mesothelioma typically presents as a **unilateral** pleural abnormality with a large pleural effusion on chest x-ray.

- Asbestos exposure is also common in: plumbers, electricians, carpenters, insulation workers
- Asbestosis and bronchogenic CA can present similarly
- Other findings on CXR: bibasilar reticulonodular infiltrates, honeycombing (cystic areas surrounded by interstitial infiltrates) and B/L pleural thickening
- HRCT: subpleural linear densities and parenchymal fibrosis
- Imaging can also show signs of bronchogenic CA

DLCO

Differential diagnosis based on carbon monoxide diffusing capacity of the lung			
	Obstructive pattern (FEV1/FVC <70% predicted)	**Restrictive pattern (FEV1/FVC >70% predicted, FVC <80% predicted)**	**Normal spirometry**
Low DLCO	• Emphysema	• Interstitial lung diseases • Sarcoidosis • Asbestosis • Heart failure	• Anemia • Pulmonary embolism • Pulmonary hypertension
Normal DLCO	• Chronic bronchitis • Asthma	• Musculoskeletal deformity • Neuromuscular disease	
Increased DLCO	• Asthma	• Morbid obesity	• Pulmonary hemorrhage • Polycythemia

DLCO = diffusion capacity of the lung for carbon monoxide.



- Normal DLCO→ means intact capillary and alveolar structures

PULMONARY HYPERTENSION

- Pulmonary arterial pressure >25mmgHg at rest and >30mmHg at exertion
- Pulmonary hemangiomatosis (disorder directly affecting pulm. Vasculature) can also cause pulm. HTN
- Initial Sx: dyspnea, weakness and fatigue. Later Sx: chest pain, hemoptysis, syncope or hoarseness (due to compression of recurrent laryngeal nerve). Signs of RHF develop late—Cor pulmonale
- PE: clear lung fields (crackles in pulm. Fibrosis)
- CXR: enlargement of pulm. Arteries with rapid tapering of distal vessels (pruning) and enlarged right ventricle

COR PULMONALE

Characteristic findings of cor pulmonale	
Common etiologies	• COPD (most common) • Interstitial lung disease • Pulmonary vascular disease (eg, thromboembolic) • Obstructive sleep apnea
Symptoms	• Dyspnea on exertion, fatigue, lethargy • Exertional syncope (due to ↓ cardiac output) • Exertional angina (due to ↑ myocardial demand)
Examination	• Peripheral edema • ↑ Jugular venous pressure with prominent *a* wave • Loud S2 • Right-sided heave • Pulsatile liver from congestion • Tricuspid regurgitation murmur
Imaging	• **Electrocardiogram (ECG)**: Partial or complete right bundle branch block, right axis deviation, right ventricular hypertrophy, right atrial enlargement • **Echocardiogram**: Pulmonary hypertension, dilated right ventricle, tricuspid regurgitation • **Right heart catheterization**: Gold standard for diagnosis showing right ventricular dysfunction, pulmonary hypertension & no left heart disease

- Cor pulmonale usually develop gradually but can be acute in case of PE
- COPD pts have distant heart sounds due to hyperinflated lungs (cardiac tamponade—distant heart sounds but more acute)
- End stage cor pulmonale present with hypotension, tachycardia, and signs of cardiogenic shock due to ↓ stroke volume
- CXR: may show central pulmonary artery enlargement and loss of retrosternal airspace due to right ventricular enlargement

- Right heart catheterization shows: ↑ CVP, right ventricular end diastolic pressure and mean pulmonary artery pressure >25mmHg without left heart disease
- Rx: optimization of right heart dynamics (preload, afterload and contractility) with supplemental oxygen, diuretics, treatment of underlying etiology and IV inotropes for severe decompensation

PLEURAL EFFUSION

Common causes of pleural effusions	
Transudate	**Exudate**
• Congestive heart failure • Cirrhosis • Nephrotic syndrome • Peritoneal dialysis	• Infections • Malignancy • Connective tissue diseases • Inflammatory disorders • Movement of fluid from abdomen to pleural space • Coronary artery bypass surgery • Pulmonary embolism (usually)

Lung CA, breast CA and lymphoma→75% of malignant pleural effusion

- When pleural effusion is suspected or diagnosed, 1st step is to determine the cause of pleural effusion and management starts with whether it is transudate or exudate
- 1st step: Perform diagnostic thoracocentesis (bedside, minimally invasive, permits rapid sampling, quantification, microscopic examination and visualization)—provide decision making info in 90% cases. However, if pt has established cardiogenic edema, then trial diuretic can be started
- If unclear cytology and lung mass +→ bronchoscopy
- If cytology shows malignant cells→ no need of bronchoscopy

LIGHT'S CRITERIA OF PLEURAL EFFUSION

Light's criteria for pleural effusions		
	Transudate	**Exudate**
Protein (pleural/serum)	≤0.5	>0.5
LDH (pleural/serum)	≤0.6	>0.6
	Pleural LDH ≤ two-thirds upper limit of normal serum LDH	Pleural LDH > two-thirds upper limit of normal serum LDH
Common causes	• Hypoalbuminemia (cirrhosis, nephrotic syndrome) • Congestive heart failure	• Infection (parapneumonic, TB, fungal, empyema) • Malignancy • PE

LDH = lactate dehydrogenase; PE = pulmonary embolism.

pH	7.45 - 7.55	7.30 - 7.40 empyema < 7.30

Undiagnosed pleural effusion is best evaluated with **thoracentesis,** except in patients with clear-cut evidence of congestive heart failure where a trial of a diuretic is warranted.

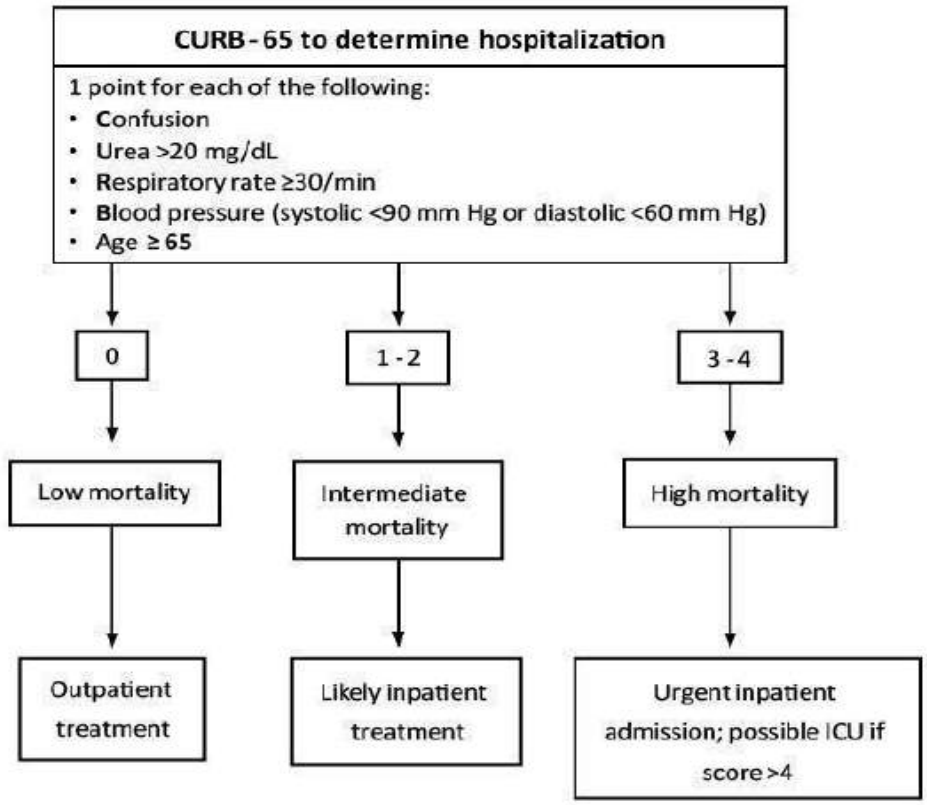
***Extremely high yield question for USMLE!!!**

- Normal pleural pH= 7.60. Transudate pH= 7.4-7.55 (need no further intervention except treatment of underlying disease). Exudate pH due to inflammation=7.30-7.45. pH<7.30 is due to excessive acid production by pleural fluid cells and bacteria (eg empyema) or decreased hydrogen ion efflux from pleural space (e.g. pleuritis, pleural fibrosis, tumor)
- **Exudative effusion** due to inflammation—release of cytokines→ ↑ capillary permeability. Glucose <60mg/dl—usually due to rheumatoid pleurisy, lupus pleuritis, esophageal rupture + causes mentioned in table. <30mg/dl is almost always due to empyema or rheumatic effusion. Pancreatitis and esophageal rupture cause ↑ amylase in pleural fluid
- **Transudative**— ↓ pleural pressure, ↓ plasma oncotic pressure and ↑ hydrostatic pressure. In liver cirrhosis→ ↑ permeability of right hemidiaphragm→ right sided pleural effusion also known as hepatic hydrothorax
- In **CHF**—can meet exudative criteria in 25% cases if pt has received excessive diuretic therapy prior to thoracocentesis. Mostly B/L (61%), can be U/L on right side in 27% cases and on left side in 12% cases
- **Tuberculous effusion:** exudative, moderate pleural lymphocytosis, very high proteins (>4). CKD, DM and smoking ↑ risk of reactivation of tuberculosis
- **Malignant pleural effusion**—exudative but lymphocytosis >70% is uncommon
- Trauma/malignancy→Disruption of thoracic duct→chylothorax— exudative, high in cholesterol content and milky white in appearance—no fever, chest pain as chyle does not induce inflammation

PNEUMONIA

COMMUNITY ACQUIRED PNEUMONIA

- Most common organisms: S. pneumonia, Hemophilus and atypicals (eg Mycoplasma). Pts requiring ICU admission usually have other organisms like S. aureus, Legionella and gram negative organisms like Pseudomonas
- 1st step in treatment is risk assessment to know whether pt can be treated as outpatient or inpatient. Cardiopulmonary conditions, age and severity of symptoms affect risk for CAP



Score >/=2→ hospital admission
Score >/=4→ ICU admission

CAP setting	Recommended therapy
Outpatient	Healthy patients • Macrolide or doxycycline Comorbid conditions (e.g., diabetes, malignancy, etc.) • Fluoroquinolone or beta-lactam + macrolide
Inpatient (non-ICU)	Fluoroquinolone OR Beta-lactam + macrolide
Inpatient (ICU)	Beta-lactam + macrolide (IV) OR Beta-lactam + fluoroquinolone

- beta lactam for pneumonia is cephalosporin (eg, ceftriaxone).

- Respiratory fluoroquinolones (eg, levofloxacin, moxifloxacin) are required.

- These medications treat the most common bacterial CAP organisms - *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella*, and *Mycoplasma pneumoniae*.

PARAPNEUMONIC EFFUSION

Parameter	Uncomplicated parapneumonic effusion	Complicated parapneumonic effusion	Empyema
Etiology	Movement of fluid from pneumonia into visceral pleura	Persistent bacterial invasion into pleural fluid	Bacterial colonization, purulent fluid
Pleural fluid analysis	pH > 7.20, ↓ to normal glucose, LDH ratio > 0.6	pH < 7.20, ↓ glucose, LDH ratio > 0.6	pH < 7.20, ↓ glucose, LDH ratio > 0.6
Pleural fluid Gram stain	Negative	Negative	Positive
Pleural fluid culture	Negative	Usually negative	Usually positive
Treatment	Antibiotics	Antibiotics, usually requires chest tube drainage	Antibiotics + chest tube drainage

Pleuritic chest pain, productive cough (green phlegm) and fever

Glucose <60 mg/dL

In empyema, there is loculated pleural effusion on CXR, frank pus on paracentesis, unlike complicated

2-4 weeks of prolonged antibiotics

- **Pneumonia:** shortness of breath, low-grade fever
- **40% cases are associated** with parapneumonic effusion (pleural effusion). Usually **exudative** by Light criteria (at least one of the above 3):
  1. Pleural fluid protein/serum protein ratio >0.5 (due to increased microvascular permeability and cellular destruction)
  2. Pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio >0.6
  3. Pleural fluid LDH >2/3 of upper limit of normal (ULN) for serum LDH (i.e. 2/3*90=60 U/L)

empyema exudate

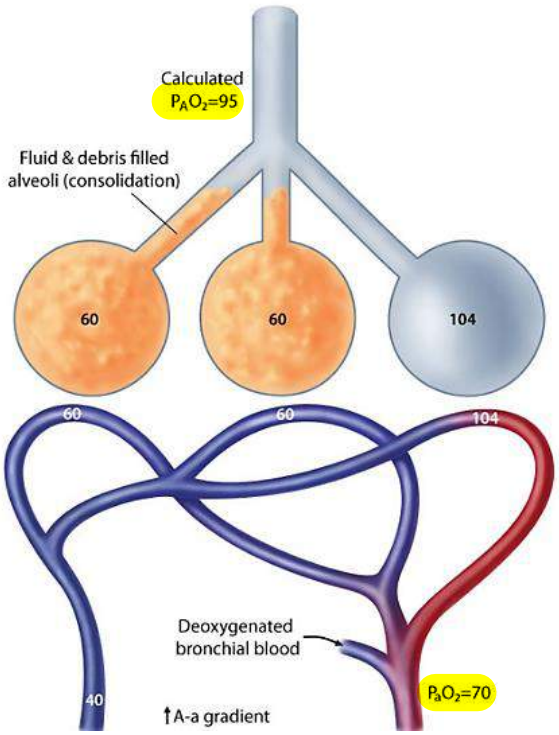
- **Low glucose** (<60 mg/dL) due to consumption (high metabolic activity) by activated neutrophils and bacteria
- **Low pH** (<7.2) due to anaerobic utilization of glucose by neutrophils and bacteria
- **High protein** due to increased microvascular permeability and cellular destruction

- Mostly are uncomplicated; small, sterile, free-flowing, and resolve with antibiotics. Immunocompromised pts are at ↑ risk of pneumonia complications

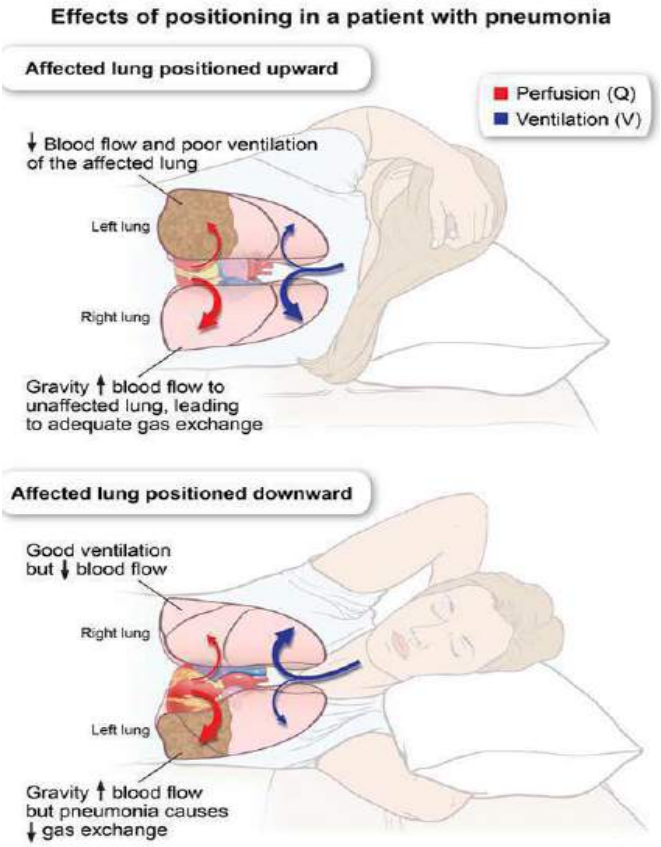
Drug induced lupus can cause exudative effusion with pH<7.2 and glucose <60mg/dl but with drugs like hydralazine, procainamide, isoniazid.

Pulmonary embolism is a common cause of exudative and transudative pleural effusion, bloody pleural effusion but does not cause low pH or glucose

V/Q mismatch in pneumonia:



A-a gradient= 95-70=25



- Alveoli in affected segment become filled with exudative material and cellular debris→consolidation→ ventilation=0 & normal perfusion→ V/Q= 0
- Lung bases have highest ventilation and perfusion and apex have least ventilation and perfusion due to gravity
- Assuming lateral position will ↑ blood flow and ventilation on dependent side. If lateral position opposite to that of consolidation is assumed, oxygenation will ↑ because more blood will flow to normal side and if position of consolidation side is assumed→↑ blood to affected side→↓ flow to normal side→ hypoxemia because of ↑ physiologic shunting (right to left shunting)

- Pneumonia causes hypoxemia due to **right-to-left intrapulmonary shunting** and an extreme **V/Q mismatch**. Increased concentration of inspired oxygen does **not** correct hypoxemia caused by intrapulmonary shunting.

- Positional changes that make the consolidation more gravity dependent worsen V/Q mismatch, increase intrapulmonary shunting, and lead to worsened hypoxemia.

CAUSES OF RECURRENT PNEUMONIA

Causes of recurrent pneumonia	
Involving same region of lung	**Local anatomic obstruction** • Bronchial compression (eg, neoplasm, mediastinal adenopathy, vascular anomaly) • Intrinsic bronchial obstruction (eg, bronchiectasis, retained foreign body, bronchial stenosis) **Recurrent aspiration** • Seizures • Ethanol or drug use • Gastroesophageal reflux disease, dysphagia, or achalasia
Involving different region of lung	• Sinopulmonary disease (eg, cystic fibrosis, immotile cilia) • Noninfectious (eg, vasculitis, bronchiolitis obliterans with organizing pneumonia) • Immunodeficiency (eg, HIV, leukemia, ↓immunoglobulins)

- Most important cause involving the same region→ bronchogenic carcinoma. Carcinoid (usually endobronchial) can also be the cause
- CT is indicated to look for underlying parenchymal disease→mass→bronchoscopy. Negative CT and high suspicion of endobronchial obstruction→ bronchoscopy
- Central mass on CT→ bronchoscopy
- Peripheral mass on CT→ CT-guided biopsy

ASPIRATION PNEUMONIA

Predisposing conditions for aspiration pneumonia
• Altered consciousness impairing cough reflex/glottic closure (eg, dementia, drug intoxication) • Dysphagia due to neurologic deficits (eg, stroke, neurodegenerative disease) • Upper gastrointestinal tract disorders (eg, GERD) • Mechanical compromise of aspiration defenses (eg, nasogastric & endotracheal tubes) • Protracted vomiting • Large-volume tube feedings in recumbent position

GERD = gastroesophageal reflux disease.

ASPIRATION SYNDROMES

Aspiration syndromes		
	Pneumonia	**Pneumonitis**
Pathophysiology	• Lung parenchyma **infection** • Aspiration of **oral** cavity microbes (anaerobes)	• Lung parenchyma **inflammation** • Aspiration of **gastric** contents with subsequent acid injury
Clinical features	• Present **days** after aspiration event • **Fever**, cough, ↑sputum • CXR infiltrate in dependent lung segment (classically **RLL**) • Can progress to **abscess**	• Present **hours** after aspiration event • Range from no symptoms to nonproductive cough, ↓O_2, respiratory distress • CXR infiltrates (one or both lower lobes) resolve without antibiotics
Management	**Antibiotics**: Clindamycin or β-lactam & β-lactamase inhibitor amoxicillin-clavulanate	Supportive (no antibiotics)

CXR = chest x-ray; O_2 = oxygen; RLL = right lower lobe.

- Aspiration pneumonia RF:
1. **Poor dentition**
2. upper airway instrumentation (eg, endotracheal or nasogastric tubes).
3. GERD
4. L.O.C

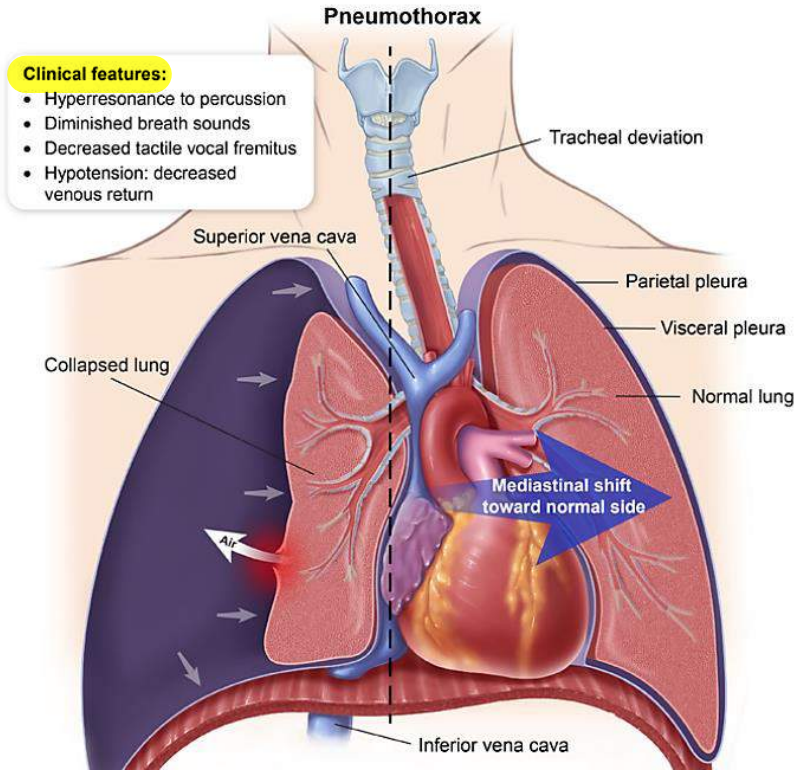
- Aspiration pneumonia location:
1. Supine: upper lobes and superior segments of the lower lobes.

2. Erect: lower lobes and the right middle lobe

Usually resolve rapidly within 24-48hours

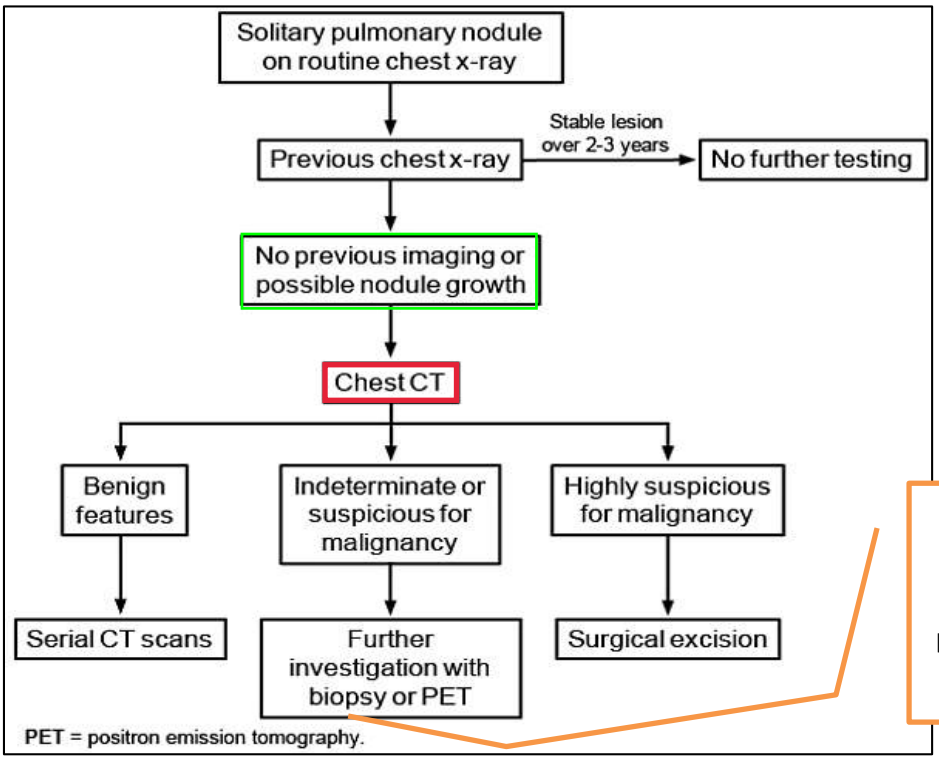
ARDS will typically involve entire lung fields and not specifically lower lung fields

PNEUMOTHORAX

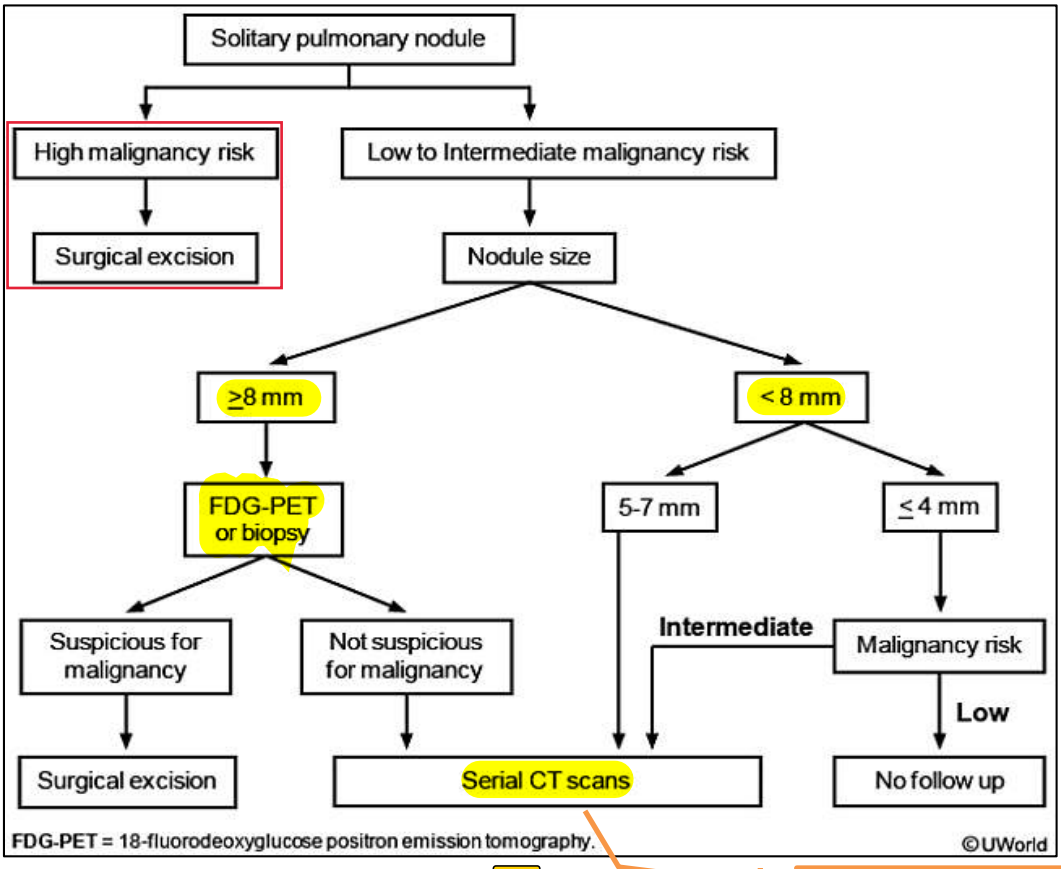


- Can be a complication of positive pressure ventilation (can also cause hypotension and alveolar damage esp. in pts with ARDS, pneumonia and obstructive airway disease) Qid: 2297

SOLITARY PULMONARY NODULE



Percutaneous biopsy is preferred. Bronchoscopy is not as sensitive as percutaneous biopsy unless lesion is >2cm



↑ growth→ surgical excision

DEFINITION OF SOLITARY PULMONARY NODULE: مهم

- Defined by following features:
  1. Rounded opacity
  2. <3cm
  3. Completely surrounded by pulmonary parenchyma
  4. No associated lymph node enlargement, pleural effusion, or atelectasis.
- Ground glass lesions have a higher malignancy risk and likely require yearly assessment, even with stable appearance and size

ASSESSMENT OF MALIGNANCY RISK IN SPN

Assessment of malignancy risk for solitary pulmonary nodule			
Variable	**Low risk**	**Intermediate risk**	**High risk**
Nodule size (cm)	<0.8	0.8-2.0	≥2.0
Age (yr)	<40	40-60	>60
Smoking status	Never smoked	Current	Current
Smoking cessation (yr)	>15	5-15	<5
Nodule margin characteristics	Smooth	Scalloped	Corona radiata or spiculated

CAUSES OF SOLITARY PULMONARY NODULE

Primary lung cancer	Squamous cell, adenocarcinoma, small cell, large cell & carcinoid
Metastatic cancer	Melanoma, breast, head & neck, renal cell, colon, germ cell & sarcoma
Benign infectious granulomas	Tuberculosis, histoplasmosis, atypical mycobacteria, coccidioidomycosis, *Cryptococcus* & blastomycosis
Benign neoplasms	Lipoma, hamartoma & fibroma
Vascular	Arteriovenous malformations

LUNG CANCER

Type of tumor	Incidence	Location	Clinical associations
Adenocarcinoma	40%-50%	• Peripheral	• Clubbing • Hypertrophic osteoarthropathy
Squamous cell carcinoma	20%-25%	• Central • Necrosis & cavitation	• Hypercalcemia
Small cell carcinoma	10%-15%	• Central	• Cushing syndrome • SIADH • Lambert-Eaton syndrome
Large cell carcinoma	5%-10%	• Peripheral	• Gynecomastia • Galactorrhea

Due to PTHrP

(remember: sCa++mous)

- Adenocarcinoma is most common type in non-smokers.
- Stage at diagnosis is most imp. Prognostic factor with survival determined by resectability

LUNG CANCER SCREENING

Recommendations for lung cancer screening	
Recommended test	• Low-dose chest CT
Recommended interval	• Yearly
Age for screening	• 55-80
Eligibility for screening based on smoking history	• Patient has ≥30-pack-year smoking history **AND** • Patient is a current smoker or quit smoking within the last 15 years
Termination of screening	• Age >80 **OR** • Patient successfully quit smoking for ≥15 years **OR** • Patient has other medical problems that significantly limit life expectancy or ability/willingness to undergo lung cancer surgery

PARANEOPLASTIC SYNDROMES

Common paraneoplastic syndromes associated with lung cancer	
Endocrine	• Syndrome of inappropriate antidiuretic hormone* • Hypercalcemia due to increased parathyroid hormone-related protein • Cushing syndrome due to ectopic adrenocorticotropic hormone production*
Hematologic	• Hypercoagulability (eg, Trousseau's syndrome, deep vein thrombosis)
Neurologic	• Lambert-Eaton myasthenic syndrome* • Ataxia, autonomic or sensory neuropathy
Musculoskeletal	• Hypertrophic osteoarthropathy (clubbing) • Dermatomyositis & polymyositis
***Generally associated with small cell lung cancer**	

SIADH

- Small cell lung cancer, stroke, hemorrhage, pneumonia, or drugs→ ↑ADH→ SIADH→ ↓ plasma osmolality (hyponatremia) and ↑ urine osmolality >100 mOsm/kg H2O and urine sodium concentration→initially vague Sx→untreated→ significant hyponatremia→ seizures and coma→Rx: fluid restriction is most important in those who can tolerate it→ if severe symptomatic or non-responsive give hypertonic saline→ Demeclocycline is considered if fluid restriction and ↑ salt intake do not resolve the condition. Demeclocycline can be nephrotoxic as it works at collecting tubule to inhibit action of ADH.
- No role of thiazide diuretics. Loops + salt tablets can be given

Syndrome of inappropriate antidiuretic hormone	
Etiologies	• CNS disturbance (eg, stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Ectopic ADH secretion (eg, small cell lung cancer) • Pain &/or nausea
Clinical features	• Mild/moderate hyponatremia - nausea, forgetfulness • Severe hyponatremia - seizures, coma • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Serum osmolality <275 mOsm/kg H_2O (hypotonic) • Urine osmolality >100 mOsm/kg H_2O • Urine sodium >40 mEq/L
Management	• Fluid restriction +/- salt tablets • Hypertonic (3%) saline for severe hyponatremia

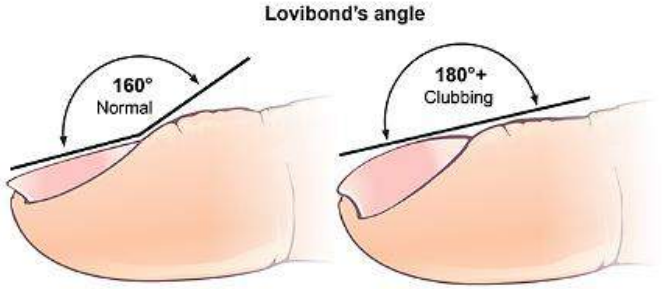
Secondary malignancy is common in patients with Hodgkin lymphoma treated with **chemotherapy** and **radiation.** The most common secondary solid tumor malignancies are **lung** (especially in smokers), breast, thyroid, bone, and gastrointestinal (eg, colorectal, esophageal, gastric tumors).
Qid: 4689

clubbing = Cancer / cystic fibrosis / cardiac shunt (top differentials)

DIGITAL CLUBBING Qid: 4521

Conditions commonly associated with digital clubbing	
Intrathoracic neoplasms	• Bronchogenic carcinoma • Metastatic cancers • Malignant mesothelioma • Lymphoma
Intrathoracic suppurative diseases	• Lung abscess • Empyema • Bronchiectasis • Cystic fibrosis • Chronic cavitary infections (eg, fungal, mycobacterial)
Lung disease	• Idiopathic pulmonary fibrosis • Asbestosis • Pulmonary arterio-venous malformations
Cardiovascular disease	• Cyanotic congenital heart disease

- Digital clubbing—bulbous enlargement and broadening of fingertips due to CT proliferation at nail bed and distal phalanx
- **Dx:** when angle between nail fold and nail plate is > 180^{o} (Lovibond angle)



- Can occur itself or in association with hypertrophic osteoarthropathy (i.e. painful joint enlargement, periostosis of long bones, and synovial effusions)
- May be hereditary, but is most often due to pulmonary or cardiovascular diseases
- Most common causes: **lung malignancies, cystic fibrosis,** and right to left cardiac shunt
- **Pathogenesis:** circulatory disruption from tumors, chronic lung inflammation→**megakaryocytes** skip normal route of fragmentation by pulmonary circulation→ megakaryocytes enter systemic circulation→ become entrapped in distal fingertips due to large size→secrete PDGF and VEGF→ CT hypertrophy, capillary permeability and vascularity→clubbing
- COPD (causing hypoxemia) alone in the absence of occult malignancy DOES NOT cause clubbing. COPD+ clubbing→ search for occult malignancy.

HYPERTROPHIC OSTEOARTHROPATHY (HOA)

- Digital clubbing+ sudden-onset arthropathy, commonly affecting wrists and hand joints

- Hypertrophic pulmonary osteoarthropathy (HPOA)—subset of HOA due to underlying lung disease. Usually due to adenocarcinoma
- CXR is appropriate initial study for underlying cause

MEDIASTINAL GERM CELL TUMORS

- Primary mediastinal germ cell tumors—common in young male pts, locally invasive
- Beta-hCG elevated in both seminomatous and non-seminomatous

NON-SEMINOMATOUS GERM CELL TUMORS

- Large mediastinal mass+ ↑ AFP (unlike seminomatous) and ↑beta-hCG (like seminomatous)→ vitually diagnostic
- C/f: cough, chest discomfort, dyspnea on exertion
- Confirm with biopsy
- Perform testicular USG to rule out small primary tumor as management and prognosis differ in both cases
- Almost all germ cell tumors in mediastinum are primary rather than metastatic

SEMINOMATOUS GERM CELL TUMORS

- Mediastinal mass + ↑ beta-hCG

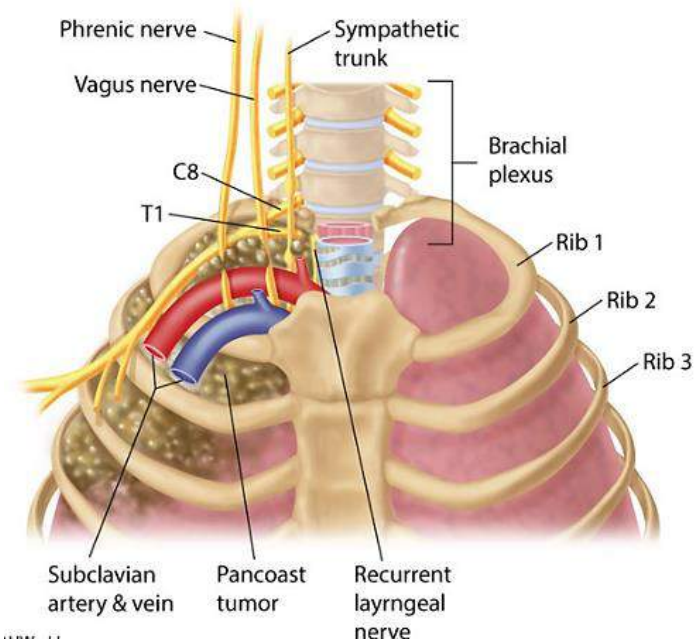
→Benign teratomas—from 3 germ layers—may also present as mediastinal mass—but do not produce tumor markers

PANCOAST TUMOR/SUPERIOR PULMONARY SULCUS TUMOR

Clinical presentation of Pancoast tumors

- Shoulder pain (most common)
- Horner's syndrome (ipsilateral ptosis, miosis, enophthalmos, and anhidrosis) from involvement of paravertebral sympathetic chain and inferior cervical ganglion
- C8-T2 neurological involvement
  - Weakness and/or atrophy of intrinsic hand muscles
  - Pain and paresthesias of 4th and 5th digits, medial arm, and forearm
- Supraclavicular lymph node enlargement
- Weight loss

- Pt can also develop ↑ sympathetic activity→ ↑flushing and sweating on contralateral side of face during exercise (Harlequin sign)
- Most pancoast tumors are non-small cell lung cancers
- Initial evaluation: chest imaging-CXR→ CT/MRI
- CT/MRI brain is also part of later evaluation cox of ↑ risk of brain mets



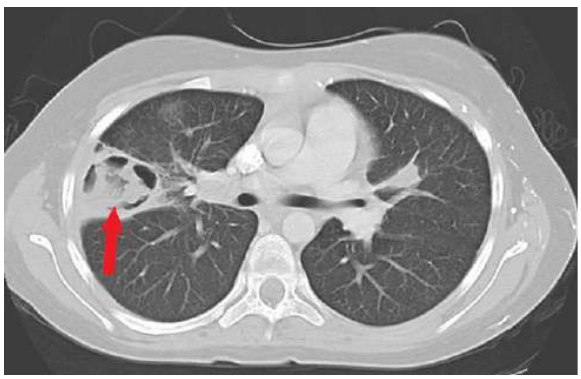
• Hoarseness due to recurrent laryngeal nerve involvement.

• Superior vena cava syndrome can occur also.

ASPERGILLOSIS

Pulmonary aspergillosis	
Risk factors	• Immunocompromised • Asthma, chronic obstructive pulmonary disease • Cavitary lung disease (eg, tuberculosis) • Sarcoidosis, malignancy
Clinical presentation	• Pleuritic chest pain • Dyspnea • Cough, hemoptysis classic triad of **fever, pleuritic chest pain**, and **hemoptysis.**
Laboratory/ imaging	• Positive *Aspergillus* IgG PLUS radiographic evidence: o Single/multiple nodules o Cavities (+/- fungal ball) o Consolidation o Peribronchial infiltrates
Treatment	• Aspergilloma: Surgical resection • Invasive aspergillosis: Voriconazole or caspofungin

- For treatment: itraconazole or bronchial artery embolization can also be used
- Other conditions like TB should be ruled out.
- Can also occur in bronchogenic cysts and bullae



	Invasive aspergillosis	Chronic pulmonary aspergillosis*
Risk factors	• Immunocompromise (**neutropenia**, glucocorticoids, HIV)	• Lung disease/damage (**cavitary tuberculosis**)
Findings	• **Triad** of fever, chest pain, hemoptysis • Pulmonary nodules with **halo sign** • Positive cultures • Positive cell wall biomarkers (galactomannan, beta-D-glucan)	• **>3 months:** Weight loss (>90%), cough, hemoptysis, fatigue • Cavitary lesion +/- **fungus ball** • Positive ***Aspergillus* IgG** serology
Management	• Voriconazole +/- caspofungin	• Resect aspergilloma (if possible) • **Azole** medication (voriconazole) • Embolization (if severe hemoptysis)

*Simple aspergilloma (fungus ball in preexisting lung cavity) is a form of chronic pulmonary aspergillosis but is usually quiescent with occasional hemoptysis.

ANKYLOSING SPONDYLITIS

Symptoms/signs of ankylosing spondylitis
• Low back pain (onset age <40, insidious onset, improves with exercise but not with rest, pain at night) • Hip & buttock pain • Limited chest expansion & spinal mobility • Enthesitis (inflammation at the site of insertion of a tendon to the bone) • Systemic symptoms (eg, fever, chills, fatigue, weight loss) • Acute anterior uveitis (unilateral pain, photophobia, blurry vision)

- Can also be associated with IBD and cardiac involvement with aortic regurgitation
- **PFTs:** may reveal mildly restrictive pattern: ↓VC and TLC but normal FEV1/FVC. FRC and RV are normal or ↑ due to fixation of rib cage in inspiratory position
- **AS** can also cause pulmonary fibrosis→ restrictive pattern

	Obstructive lung disease	Restrictive lung disease including obesity
FEV_1	<80%	<80%
FEV_1/FVC	<70%	>70%
FVC	Normal to decreased	<80%

FEV_1= forced expiratory volume in 1 second; FVC= forced vital capacity.

HYPOTHERMIA

Clinical features of hypothermia	
Classification	**Mild:** 32-35 C (90-95 F) • Tachycardia, tachypnea • Ataxia, dysarthria, **increased shivering** **Moderate:** 28-32 C (82-90 F) • Bradycardia, lethargy, hypoventilation, **decreased shivering**, atrial arrhythmias **Severe:** <28 C (82 F) • Coma, cardiovascular collapse, ventricular arrhythmias
Treatment	**General** • Warmed (42 C [107 F]) crystalloid for hypotension • Endotracheal intubation in comatose patients **Rewarming techniques** • **Mild hypothermia**: Passive external warming (remove wet clothing, cover with blankets) • **Moderate hypothermia**: Active external warming (warm blankets, heating pads, warm baths) • **Severe hypothermia**: Active internal rewarming (warmed pleural or peritoneal irrigation, warmed humidified oxygen)

- Tachycardia in mild—due to peripheral vasoconstriction
- Bradycardia and hypotension in moderate—due to ↓reactivity of pacemaker cells (hence unresponsive to atropine and cardiac pacing) and salt/water loss from cold induced diuresis

POINTERS

➔ Incentive spirometry given to prevent atelectasis in bed-bound pts, particularly following surgical procedures

➔ Chest physiotherapy is used in pt with pneumonia or atelectasis to loosen and promote expectoration of secretions. Pts with bronchiectasis need physiotherapy for long-term

➔ Alpha 2 adrenergic agonist dexmedetomidine is used for sedation in ICU

➔ Candida is extremely rare cause of pneumonia in any pt. colonizes bronchial epithelium and contaminates sputum culture—always look for something else—think candida if question says: esophagitis, endophthalmitis, endocarditis, hepatosplenic disease and meningitis

Contents

FOREIGN BODY ASPIRATION

Clinical manifestations of foreign body aspiration	
Signs & symptoms	• **History of choking** (80%-90% of cases) • Coughing • Sudden-onset respiratory distress • Cyanosis • Altered mental status
Physical examination findings	• **Focal monophonic wheezing** on affected side • **Diminished aeration on affected side** • Generalized wheezing • Inspiratory stridor • Hoarseness • Respiratory distress
Radiographic findings	• Hyperinflation or atelectasis of affected side • Visualization of foreign body

FB causing partial obstruction→air trapping in expiration→hyperinflation

Complete obstruction by FB→ atelectasis, post-obstructive pneumonia and /or localized bronchiectasis

- Common in ages 1-3 years
- Peanuts, popcorns and pieces of toys most common
- >1/2 end up in right main bronchus
- For both diagnosis and treatment: **immediate rigid bronchoscopy**

EPIGLOTTITIS

Epiglottitis	
Microbiology	• *Haemophilus influenzae* type b • Nontypable *H influenza* • *Streptococcus* • *Staphylococcus*
Clinical features	• **Distress** ("tripod" positioning, inspiratory stridor) • **Dysphagia** • **Drooling**
X-ray findings	• **"Thumbprint" sign** (enlarged epiglottis) • Loss of vallecular space
Management	• Keep child calm & comfortable • Emergency **endotracheal intubation** in the operating room

- High grade fever is also present
- Management should not be delayed for diagnostic studies. If diagnosis is unclear, perform chest xray
- If endotracheal intubation is unsuccessful due to inflammation, then perform **emergency tracheotomy**
- Cricothyroidotomy should not be performed in pre-pubescent pts, as upper portion of trachea in underdeveloped and children <12 yrs have ↑ risk of subglottic stenosis
- **Viral laryngeotracheobronchitis (croup)**→ "steeple sign" on xray, barking cough and inspiratory stridor→nebulized racemic epinephrine

BRONCHIOLITIS

Bronchiolitis	
Epidemiology	• Age <2 years • RSV most common cause
Clinical presentation	• Antecedent nasal congestion/discharge & cough • Wheezing/crackles & respiratory distress (eg, tachypnea, retractions, nasal flaring)
Treatment	Supportive care
Prevention	Palivizumab for infants with the following conditions: • Preterm birth <29 weeks gestation • Chronic lung disease of prematurity • Hemodynamically significant congenital heart disease
Complications	• Apnea (especially infants age <2 months) • Respiratory failure

RSV = respiratory syncytial virus.

In >2yo, mainly causes self-limited, mild, URTI (nasal congestion, rhinorrhea). In <2yo, cause LRTI

Can be waxing/waning—Sx peak at 5-7 days of illness—Dx: primarily clinical

e.g Hydration, saline nasal drops, nasal bulb suction

In addition, they tend to develop recurrent wheezing throughout childhood

- Also associated with ↑ risk of acute otitis media (upto 10%)

LARYNGOMALACIA

Laryngomalacia	
Pathophysiology	Increased laxity of supraglottic structures

Clinical presentation	• Inspiratory **stridor**
	  ◦ **Worsens when supine**, crying, or feeding
	  ◦ Improves in prone position
	• Begins in the neonatal period, peaks at **age 4-8 months**, resolves by age 12-18 months

Diagnosis	Flexible **laryngoscopy** showing collapse of supraglottic structures with inspiration & **omega**-shaped epiglottis
Management	• **Reassurance** for most cases • Supraglottoplasty for severe symptoms (eg, poor weight gain, apnea, cyanosis, rapidly worsening stridor)

Usually clinical—confirm with flexible fiber optic laryngoscopy

- Most pts have symptoms of gastric reflux like vomiting, arching of back with feeds, poor weight gain and treated accordingly e.g. upright positioning after feeds and acid reducers

ANAPHYLAXIS

- Severe allergic reaction, sudden in onset, affects >1 organ systems (oropharynx, lungs, GI, CVS) or pt collapses after exposure and can be fatal
- Common in pts with 1st degree relative with allergic disease
- **Rx:** IM epinephrine- proven to prevent and reverse progression to anaphylactic shock and death (beta 2 effect cause bronchodilation & inhibit the release of systemic inflammatory mediators and alpha 1 agonist cause vasoconstriction to raise BP and ↓ upper airway edema)

CYSTIC FIBROSIS

Clinical features of cystic fibrosis	
Respiratory	• Obstructive lung disease → bronchiectasis • Recurrent pneumonia • Chronic rhinosinusitis

Gastrointestinal	• Obstruction (10%-20%)
	  ○ Meconium ileus
	  ○ Distal intestinal obstruction syndrome
	• Pancreatic disease
	  ○ Exocrine pancreatic insufficiency
	  ○ CF-related diabetes (~25%)
	• Biliary cirrhosis

Reproductive	• Infertility (>95% men, ~20% women)
Musculoskeletal	• Osteopenia → fractures • Kyphoscoliosis • Digital clubbing

Cystic fibrosis	
Clinical features	• Chronic sinopulmonary disease (eg, bronchiectasis) • Gastrointestinal & nutritional abnormalities (eg, pancreatic insufficiency, meconium ileus, failure to thrive) • Salt loss syndromes (eg, acute salt depletion, chronic metabolic alkalosis) • Male urogenital abnormalities (eg, obstructive azoospermia)
Diagnosis	One or more clinical features **OR** History of cystic fibrosis in a sibling **OR** Positive newborn screening test **PLUS** Increased sweat chloride concentration ≥60 mmol/L on 2 or more occasions **OR** Identification of 2 cystic fibrosis mutations **OR** Abnormal nasal epithelial ion transport (potential difference)

- Inspissated mucus in developing fetal genital tract→obstructs developing vas deferens→congenital b/l absence of vas deferens→ transparent or no semen production →obstructive azoospermia
- In contrast, congenital aplasia of uterus and vagina (Mayer-Rokitansky-Kuster-Hauser syndrome) is rare. Female with CF are malnourished + amenorrhea +pubertal delay→subfertility. Viscous cervical mucus→inhibit sperm entry
- Gold standard test: quantitative pilocarpine iontophoresis is the gold standard test. Pilocarpine is applied to pt's extremity and chloride level is checked on 2 occasions→ abnormal or intermediate result→ DNA analysis → equivocal→ potential difference
- Pancreatic insufficiency can appear in infancy. 10% pts without pancreatic insufficiency in infancy and childhood develop recurrent pancreatitis in teens and 20s. Those with pancreatic insufficiency rarely develop pancreatitis
- High energy expenditure because of dyspnea and coughing→malnutrition→↑ risk of infections and respiratory failure
- Rx: high calorie diet, pancreatic enzymes and fat soluble vitamin replacement

NEONATAL RESPIRATORY DISTRESS

Common causes of neonatal respiratory distress			
Diagnosis	**Transient tachypnea of the newborn**	**Respiratory distress syndrome**	**Persistent pulmonary hypertension**
Pathophysiology	Inadequate alveolar fluid clearance at birth results in mild pulmonary edema	Surfactant deficiency results in alveolar collapse & diffuse atelectasis	High pulmonary vascular resistance results in right-to-left shunting & hypoxia
Clinical features	Tachypnea begins shortly after birth & resolves by day 2 of life	Severe respiratory distress & cyanosis after premature birth	Tachypnea & severe cyanosis
Chest x-ray	Bilateral perihilar linear streaking	Diffuse, reticulogranular (ground-glass) appearance, air bronchograms, low lung volumes	Clear lungs with decreased pulmonary vascularity

Should be suspected in all term and post-term infants

RDS

- Affected infants develop following features within minutes to hours:
  - Tachypnea (respiratory rate >60/min)
  - **Grunting** (to increase end-expiratory pressure)
  - **Nasal flaring** (decreases nasal airway resistance)
  - **Retractions** (intercostal muscles contract and pull in the compliant chest wall)
  - Hypoxia and cyanosis (reflects significant atelectasis)

- Rx: continuous positive airway pressure ventilation is the treatment of choice. Intubation, mechanical ventilation and exogenous surfactants are reserved for severe cases

MECONIUM ASPIRATION SYNDROME

- Term and post-term infants born through meconium-stained fluid
- Meconium obstructs airway and cause respiratory distress
- CXR: patchy infiltrates, coarse streaking of both lung fields and flattening of diaphragm

CONGENITAL DIAPHRAGMATIC HERNIA

- Left sided > right sided
- Left sided hernia of abdominal content→abnormal left sided lung development→↓left sided breath sounds→heart shift to right→ abnormal right sided lung development→↓ right sided breath sounds→hence, pulmonary hypoplasia and pulm. HTN→ concave abdomen and barrel shaped chest→ respiratory distress

- Sometimes diagnosed intranatally by USG
- Can cause→esophageal compression→polyhydramnios
- **Management:** secure airway, breathing and circulation (before diagnostic studies)→emergency intubation and cautious ventilation (blow-by oxygen and bag and mask ventilation are contraindicated—can introduce air in GI tract—exacerbate condition)→airway secured→ orogastric or nasal tube placed in connection with continuous suction to prevent bowel distention against lungs→ place umbilical artery line for continuous ABGs and BP monitoring→ place umbilical venous catheter for administration of fluids and meds
- **After stabilization→** perform imaging to check correct placement of tubes and for confirmation of diagnosis

APGAR SCORE

	Sign	0 points	1 point	2 points
A	Appearance/ color	Completely blue/pale	Body pink, extremities blue	Completely pink
P	Pulse	Absent	<100/min	>100/min
G	Grimace/ reaction	Absent	Grimace/ whimper	Cough/ sneeze/cry
A	Activity/ muscle tone	Limp	Some flexion	Active/ spontaneous
R	Respiratory effort	Absent	Slow, weak cry	Regular, good cry

- Score 10 is rare
- Score 7-9→ mostly, require no further intervention
- Score <7→ require further evaluation and resuscitation→ pulse oximetry monitoring and positive pressure ventilation. If heart rate <60→ chest compression may be given
- APGAR score at 5 min is useful in assessing response to preliminary intervention
- Most concerning factors are heart rate and respiration. Extremity cyanosis is common and may resolve in 1-2 days. Central body cyanosis raises concern for respiratory or cardiac problems
- Maternal factors that ↑ risk for resuscitation: very young maternal age, H/o DM or HTN and H/o substance abuse

Contents

PULMONOLOGY-SURGERY

FLAIL CHEST

- A condition that occurs when >/= 3 adjacent ribs are fractured in >/= 2 locations, causing a segment of ribs to lose its continuity with the remainder thoracic wall→ pain→ shallow breaths→ hyperventilation to compensate for hypoxemia. However, muscle splinting with recruitment of chest wall muscles can mask the motion of involved ribs and make it clinically difficult to diagnose early flail chest
- Can lead to pulmonary contusion—irregular non-lobar areas of opacification→ can lead to pneumonia and ARDS
- **Examination:** isolated thoracic wall segment exhibits **paradoxical** inward motion on inspiration and outward movement on expiration
- **Rx:** pain control and supplemental oxygen most imp early steps→intubation with mechanical positive pressure ventilation required in many pts→ positive pressure mechanical ventilation replaces the normal negative intrapleural pressure during spontaneous ventilation with positive intrapleural pressure→previously flail segment moves out normally with rest of rib cage during inspiration

PULMONARY CONTUSION

- Common after blunt chest trauma
- Lung parenchymal bruising
- Develop within 24 hours (usually few minutes-hours) as pulmonary edema sets in. Fluid challenge hastens the symptom appearance
- C/f: tachypnea, tachycardia, continued chest pain and dyspnea hours after MVA, hypoxia→ hyperventilation→hypocarbia and respiratory alkalosis
- PE: bruising of chest wall, ↓ breath sounds on side of contusion
- CXR: patchy irregular alveolar infiltrate or alveolar opacities over right and left lower lobes
- CT done to make early diagnosis
- D/D: ARDS→ develop 24-48 hours after trauma, usually b/l lung involvement
- Rx: close monitoring, intubation and mechanical ventilation in severe cases

PNEUMOTHORAX

Clinical features of pneumothorax	
Classification	• **Primary spontaneous pneumothorax**: No preceding event or history of lung disease • **Secondary spontaneous pneumothorax**: Complication of underlying lung disease (eg, COPD) • **Tension pneumothorax**: Life-threatening; trapped air with mediastinal shift & compromised cardiopulmonary function
Signs/ symptoms	• Chest pain &/or dyspnea • ↓ Breath sounds, ↓ tactile fremitus, ↓ chest movement • Hyperresonance to percussion on the affected side • Tachycardia, hypotension &/or tracheal deviation away from affected side (seen in TP)
Imaging	• Notable visceral pleural line • Air in hemithorax, contralateral mediastinal shift • Radiolucent costophrenic sulcus ("deep sulcus" sign)
Treatment	• **Small** (≤2 cm between lung & chest wall on chest x-ray): Observation & oxygen • **Large (stable)**: Needle aspiration or chest tube • **Clinically unstable or TP**: Urgent needle decompression, then chest tube placement (tube thoracostomy)

- Tracheal deviation to right can be due to: pneumothorax, hemothorax or right sided lung collapse
- Distended neck veins can be due to: pneumothorax and cardiac tamponade
- Untreated tension pneumothorax→ pulseless electrical activity and/or asystole
- Although 1st step is usually to intubate pt with respiratory distress but in pt with suspected tension pneumothorax, endotracheal intubation followed by positive pressure ventilation before needle thoracotomy can lead to worsening of symptoms
- Needle thoracotomy can be done in 2nd or 3rd intercostal space in midclavicular line or 5th intercostal space in midaxillary line
- Chest tube is placed in 5th intercostal space in midaxillary line.
- Pts with continued hemodynamic instability after needle decompression should have FAST (Focused Assessment with Sonography for Trauma) examination to look for pericardial tamponade
- Hemothorax—neck veins collapsed→ also require chest tube

POST-OP PULMONARY COMPLICATIONS

Postoperative pulmonary complications	
Complications	• Atelectasis, infection (eg, pneumonia) • Bronchospasm, exacerbation of chronic lung disease • Prolonged mechanical ventilation
Risk factors	• Age >50 years • Emergency surgery or surgery duration >3 hours • Heart failure, chronic obstructive lung disease • Poor general health (American Society of Anesthesiologists class >2)
Preoperative strategies (to reduce risk)	• Smoking cessation at least 8 weeks prior to surgery • Symptom control of chronic obstructive lung disease (eg, preoperative glucocorticoids if not well controlled) • Treatment of any respiratory infections prior to surgery • Patient education for lung expansion maneuvers (eg, chest physical therapy, coughing, deep breathing exercises, incentive spirometry)
Postoperative strategies	• Incentive spirometry • Deep breathing exercises • Epidural analgesia instead of parenteral opioids • Continuous positive airway pressure

- Intermittent positive airway pressure can also be used post-op
- Best strategy is incentive spirometry to prevent pneumonia—1st line
- CPAP—used in those who develop pulm. Complications in spite of incentive spirometry—as more expensive and has more complications

ATELECTASIS

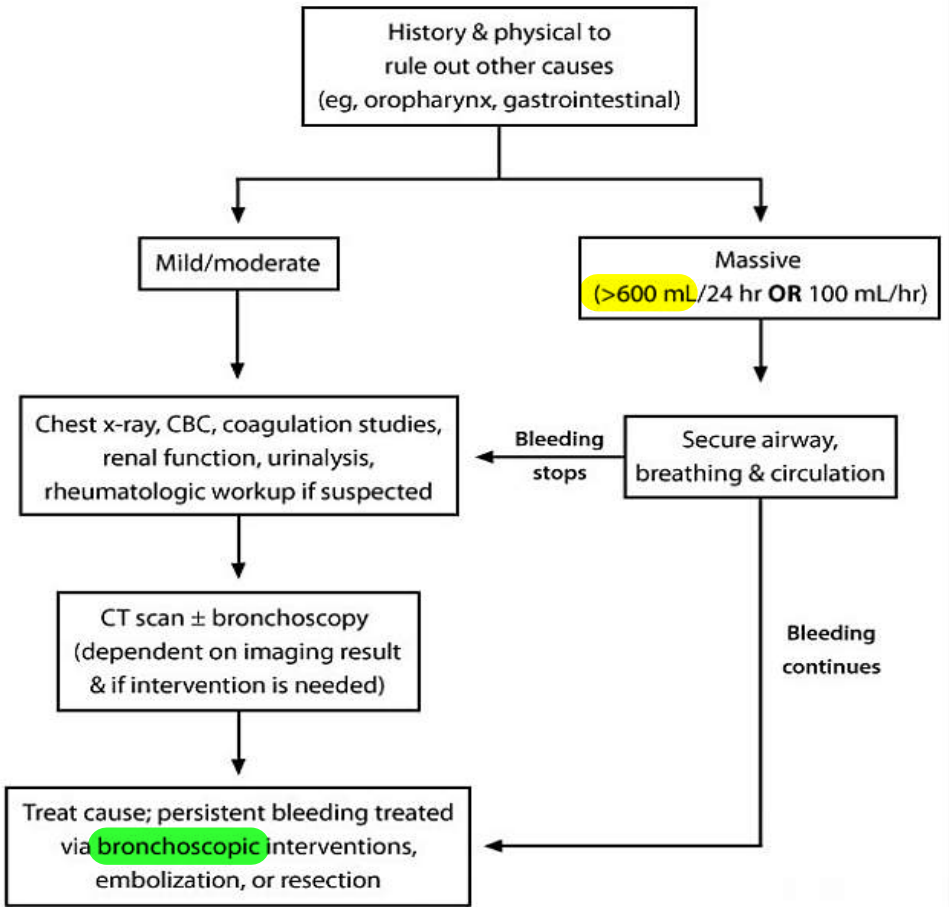
- Lobar or segmental collapse→↓ lung volume
- Classified based on pathophysiology (obstructive or non-obstructive), location and portion of lung involved
- Can occur post-operatively esp. after abdominal or thoracoabdominal surgery→ accumulation of pharyngeal secretions, tongue protruding posteriorly into pharynx, airway tissue edema, or residual anesthetic effect
- Post-op pain→ interfere with coughing and spontaneous deep breathing→↓functional residual capacity→ worsening of atelectasis
- Small area of atelectasis→ asymptomatic
- Large area of atelectasis→ significant ventilation perfusion mismatch→ hypoxemia→↑ work of breathing→ tachypnea and dyspnea→respiratory alkalosis and ↓PaCO2
- These manifestations start typically after pt has left post-anesthesia care unit, worse after 2nd post-op night to 5th post-op night
- Pulmonary embolism can also occur after surgery and present with similar symptoms

HEMOPTYSIS

COMMON CAUSES OF HEMOPTYSIS

Common causes of hemoptysis	
Pulmonary	• Bronchitis • Pulmonary embolism • Bronchiectasis • Lung cancer
Cardiac	• Mitral stenosis/acute pulmonary edema
Infectious	• Tuberculosis • Lung abscess
Hematologic	• Coagulopathy
Vascular	• Arteriovenous malformations
Systemic diseases	• Wegener granulomatosis • Goodpasture syndrome • Systemic lupus erythematosus, vasculitis

Most imp.



Massive hemoptysis

- Greatest danger in massive hemoptysis is not exsanguination but asphyxiation due to accumulation of blood in air passages
- Initial step is **securing ABC**, pt should be placed with bleeding lung in dependent position (lateral position) to avoid blood collection in airways of opposite lung
- **Bronchoscopy**—initial procedure of choice in massive hemoptysis—directly visualize the bleeding site, provide suctioning ability to improve visualization and provide other interventions (like balloon tamponade, electrocautery)→ bleeding not controlled→ perform **pulmonary arteriography** (precisely identify bleeding vessel and be used for **therapeutic embolization** to control bleeding)→ still not controlled→ **urgent thoracotomy and surgical intervention**
- FFP used for those with known coagulopathy (eg INR>1.5)

BURN INJURY

- **Initial management** is same as in all trauma pts—secure airway, breathing and circulation
- Burn victims are at high risk of resp. compromise as: supraglottic region which rapidly exchanges heat with inspired air, is very susceptible to direct thermal injury and acute obstruction by edema and blistering unlike subglottic region which is protected by reflexive closure of vocal cords upon exposure to extremely hot air
- **Indicators of thermal and smoke inhalation injury:** burns on face, singeing of eyebrows, oropharyngeal inflammation, blistering or carbon deposits, carbonaceous sputum, stridor, carboxyHb >10%, h/o confinement in burning building
- **Management:** all burn pts must be treated with high-flow oxygen via non-rebreather mask—maintain low threshold for intubation with physical evidence of thermal damage to upper airway—key reason for early intubation: progressive airway edema may preclude intubation later in course requiring emergent surgical airway

  Fluid replacement is also needed for fluid lost through wounds and injury related systemic inflammatory response (shock)

PULMONOLOGY-GYN/OBS

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism	
Risk factors	• Advanced maternal age • Gravida ≥5 (live births or stillbirths) • Cesarean or instrumental delivery • Placenta previa or abruption • Preeclampsia
Clinical presentation	• Cardiogenic shock • Hypoxemic respiratory failure • Disseminated intravascular coagulopathy • Coma or seizures
Treatment	• Respiratory & hemodynamic support • +/- Transfusion

- Can occur during pregnancy or shortly after delivery
- Amniotic fluid can enter circulation via endocervical veins, placental insertion site, area of uterine trauma→inflammatory response→vasopasm
- Diagnosed clinically after excluding other causes of cardiorespiratory failure (e.g. pulm. embolism, peripartum cardiomyopathy, eclampsia)
- Oxygen mask, intubation and mechanical ventilation can be used for hypoxemia and vasopressors for hemodynamic stability

Contents

RHEUMATOLOGY/ORTHOPEDICS & SPORTS-IM

- Active ROM= you yourself move
- Passive ROM= someone else moves

JOINT FLUID CHARACTERISTICS

Joint fluid characteristics				
	Normal	**Noninflammatory (eg, OA)**	**Inflammatory (eg, crystals, RA)**	**Septic joint**
Appearance	Clear	Clear	Translucent or opaque	Opaque
WBC count (mm^3)	<200	200-2,000	2,000-100,000	50,000-150,000
PMNs	<25%	25%	Often >50%	>80%-90%

OA = osteoarthritis; **PMN** = polymorphonuclear leukocytes; **RA** = rheumatoid arthritis; **WBC** = white blood cells.

HAND AND WRIST PAIN

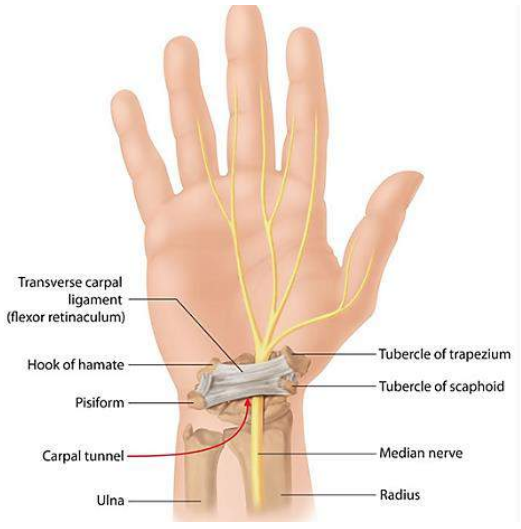
CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome	
Risk factors	• Obesity • Pregnancy • Diabetes • Hypothyroidism • Rheumatoid arthritis
Clinical presentation	• Pain & paresthesias in **median nerve** distribution (first 3½ digits) • Positive Phalen & Tinel tests • **Severe disease**: Weakness of thumb abduction & opposition, atrophy of thenar eminence
Confirmatory test	• Nerve conduction studies
Treatment	• Wrist splinting • Glucocorticoid injection • Surgery for severe or refractory symptoms

Symptoms are usually worse at night

If diagnosis is uncertain or severe symptoms prompt consideration for surgery—it shows slowing of median nerve conduction at wrist

- Carpal tunnel is made of carpal bones and transverse carpal ligament—contain median nerve and tendons of flexor digitorum profundus, flexor digitorum superficialis and flexor pollicis longus
- Electromyography is usually not done in case of CTS and rarely done to exclude other causes or in pts with weakness or severe cases
- Nocturnal wrist splinting holds the wrist in neutral position and prevents excessive flexion of hand during night



DE QUERVAIN TENOSYNOVITIS

- Most commonly occur in new mothers who hold their child with thumb outstretched (abducted/extended)

- Caused by inflammation of abductor pollicis longus and extensor pollicis brevis tendons as they pass through fibrous sheath at radial styloid process
- PE: tenderness can be elicited by direct palpation of radial side of wrist at the base of the hand
- Finkelstein test: passive stretching of affected tendons by grasping flexed thumb in palm with fingers→ elicit pain

TRIGGER THUMB

- Pain over palmar aspect of 1st metacarpophalyngeal and locking of thumb in flexion

FLEXOR CARPI RADIALIS TENOSYNOVITIS

- Pain with radial flexion of wrist and point tenderness of trapezium

ELBOW PAIN

RADIAL TUNEL SYNDROME

- S/S: similar to lateral epicondylitis and may occur in conjunction with that condition
- Tenderness overlie extensor tendon wad
- Examination: pain on flexing pt's long finger while pt actively extends fingers and wrists

LATERAL EPICONDYLITIS (TENNIS ELBOW)

- Caused by repetitive contraction of extensor muscles at lateral epicondyle—in activities that require repetitive forceful wrist extension and supination (backhand in tennis ad use of screwdriver)
- Tenderness +ve just distal to lateral epicondyle—worsened by use
- Pain elicited by passive wrist flexion and resisted wrist extension and supination
- Pathophysiology: degeneration of tendon of extensor carpi radialis brevis near lateral epicondyle

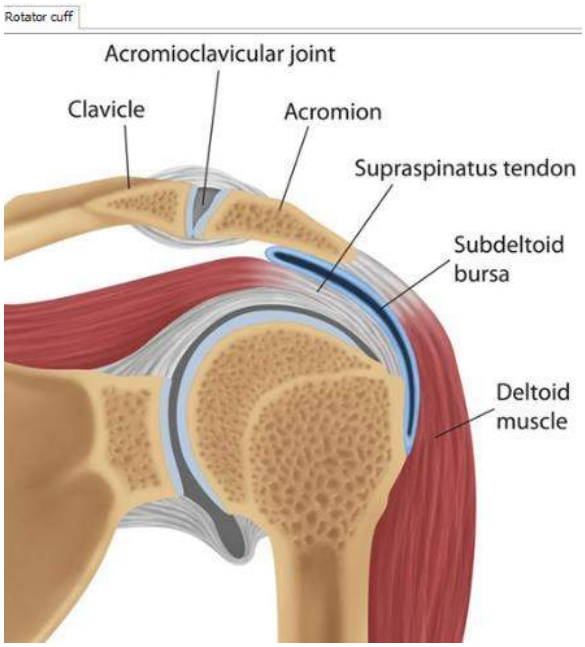
MEDIAL EPICONDYLITIS (GOLFER'S ELBOW)

- Tenderness over medial epicondyle
- Pain elicited by resisted wrist flexion and passive wrist extension

PANNER'S DISEASE

- Osteochondrosis of capitellum
- Typically in adolescent who is actively involved in sports that involve throwing
- Common complaint: chronic dull pain, crepitation and loss of supination and pronation

SHOULDER PAIN



COMMON CAUSES OF SHOULDER PAIN

Common causes of shoulder pain	
Rotator cuff impingement or tendinopathy	• Pain with **abduction, external rotation** • Subacromial tenderness • Normal range of motion with positive **impingement tests** (eg, Neer, Hawkins)
Rotator cuff tear	• Similar to rotator cuff tendinopathy • Weakness with external rotation • Age >40
Adhesive capsulitis (frozen shoulder)	• Decreased **passive & active** range of motion • More stiffness than pain
Biceps tendinopathy/rupture	• **Anterior** shoulder pain • Pain with lifting, carrying, or overhead reaching • Weakness less common
Glenohumeral osteoarthritis	• Uncommon & usually caused by **trauma** • Gradual onset of anterior or deep shoulder pain • Decreased active & passive abduction & external rotation

>Pain than stiffness

May show guarding with active movement but ROM otherwise is normal

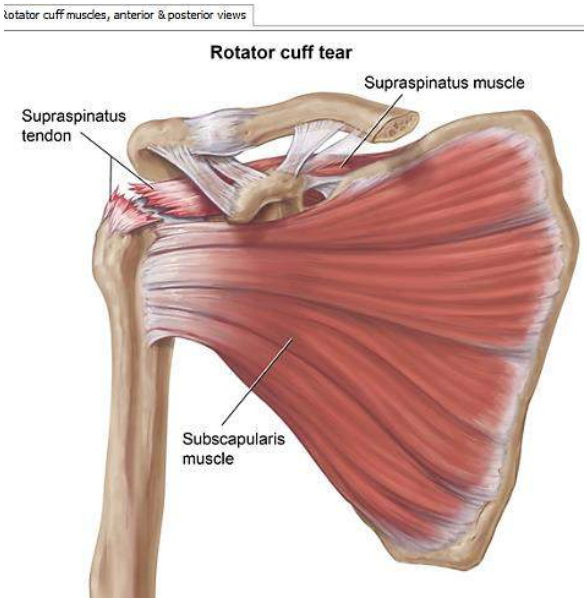
>Stiffness than pain

ROTATOR CUFF IMPINGEMENT/TENDINOPATHY (RCT)

- Occurs due to repetitive activity above shoulders
- Common in middle-aged and older individuals
- Chronic tensile loading and compression by surrounding structures→ microtears in rotator cuff tendons esp. supraspinatus→ fibrosis and inflammatory calcification
- Pain may also originate from subacromial bursa or long head of biceps, other than rotator cuff tendons

- Flexion or abduction→ ↓ space between humeral head and acromion→pressure on supraspinatus tendon and subacromial bursa→ compression of these soft tissues→ Impingement syndrome
- Neer test: pt.'s shoulder internally rotated and forearm pronated→ examiner stabilizes the scapula and flexes humerus→ reproduction of pain→ +ve test
- Chronic untreated rotator cuff tendinopathy→ ↑ risk of tear→ weakened abduction following a fall or minor trauma

ROTATOR CUFF TEAR



- Typically due to impingement of supraspinatus tendon
- Rotator cuff tendinopathy/tendinitis may present with pain but weakness will not be present in tendinitis without tear
- Rotator cuff tear usually occurs after a fall on outstretched arm in patients >40.
  - pain at lateral shoulder
  - Limited, painful active abduction, external rotation and raising arm above shoulder
  - Weakness but passive ROM is normal
  - X-ray: may show calcific tendinitis but has low sensitivity
  - MRI: visualize soft tissue around humeral head and most accurate to diagnose rotator cuff tear
  - Treatment: of acute tear is surgery with best results obtained if performed within 6 weeks of injury

ADHESIVE CAPSULITIS/ FROZEN SHOULDER SYNDROME

- Markedly ↓ ROM in multiple plains
- Glenohumeral joint loses its normal distensibility due to: chronic inflammation, fibrosis, and contracture of joint capsule
- Causes:
  - Idiopathic
  - Secondary to underlying conditions like: rotator cuff tendinopathy (most common), subacromial bursitis, paralytic stroke, DM or humeral head fracture
- Sx:
  - Gradual onset shoulder stiffness, with or without mild pain, that limits their ability to flex, abduct (eg reach overhead) or rotate the humerus

- Dx: confirmed on examination by >50% reduction in both passive and active ROM

RUPTURE OF TENDON OF LONG HEAD OF BICEPS

- Associated with overuse esp. in older patients
- Usually sudden onset pain, often with an audible pop and visible bulge
- May report weakness but normal passive ROM

POSTERIOR SHOULDER DISLOCATION

- **Causes:** Violent muscle contractions, as seen in a seizure or electrocution injury, are a common cause of posterior shoulder dislocation.
- **Presentation:** the shoulder is typically held in adduction and internal rotation, with visible flattening of the anterior aspect of the shoulder and prominence of the coracoid process
- **Radiographs** can reveal internal rotation of the humeral head with circular appearance (light bulb sign), widened joint space >6 mm (rim sign), or 2 parallel cortical bone lines on the medial aspect of the humeral head (trough line sign).
- **Management:** most are managed with closed reduction.

ANTERIOR SHOULDER DISLOCATION

- Most common form of shoulder dislocation
- Usually caused by a direct blow or fall on an outstretched arm.
- Patient holds the arm slightly abducted and externally rotated.

FOOT PAIN

D/D OF PAIN IN FOREFOOT:

- Arthritis, bursitis, stress fracture and Morton neuroma

Overview of running injuries of the foot & ankle	
Injury	**Clinical features**
Stress fracture	• Insidious onset • Focal pain in navicular or metatarsals • **Risk factors:** abrupt increase in intensity of training, poor running mechanics, female with eating disorder
Plantar fasciitis	• Plantar surface of the heel • Worse when initiating running or first steps of the day
Achilles tendinopathy	• Burning pain or stiffness 2-6 cm above the posterior calcaneus
Morton neuroma	• Numbness or pain between the 3rd & 4th toes • Clicking sensation when palpating space between 3rd & 4th toes while squeezing the metatarsal joints
Tarsal tunnel syndrome	• Compression of the tibial nerve at the ankle • Burning, numbness & aching of the distal plantar surface of the foot/toes

Mulder sign

ARTHRITIS

- Typically in metatarsophalangeal joints—not localized to single bony surface

BURSITIS

- Caused by wearing poor fitted shoes for prolonged period→ inflammation between metatarsal heads

MORTON NEUROMA

- Pain between 3rd and 4th toes on plantar surface
- Mulder sign: clicking sensation and pain that occurs when palpating this space and squeezing metatarsal joints simultaneously
- Commonly occurs in runners.
- Not a true neuroma, but a mechanically induced neuropathic degeneration of interdigital nerves→ numbness, pain and burning in the distal forefoot from the metatarsal head to the third and fourth toes→ worsened by walking on hard surfaces and wearing tight or high heeled shoes
- **Diagnosis**: primarily clinical
- **Treatment** involves metatarsal support with a bar or padded shoe inserts to decrease pressure on metatarsal heads. Surgery is usually reserved for patients who fail conservative treatment

PLANTAR FASCIITIS

- Burning pain on plantar surface of foot that worsens with 1st step in the morning
- Gradually improves during the day but usually worsens by the end of the day due prolonged weight bearing

- Common in runners with repeated microtrauma who develop local point tenderness on plantar surface of foot
- Examination: point tenderness at plantar surface of heel

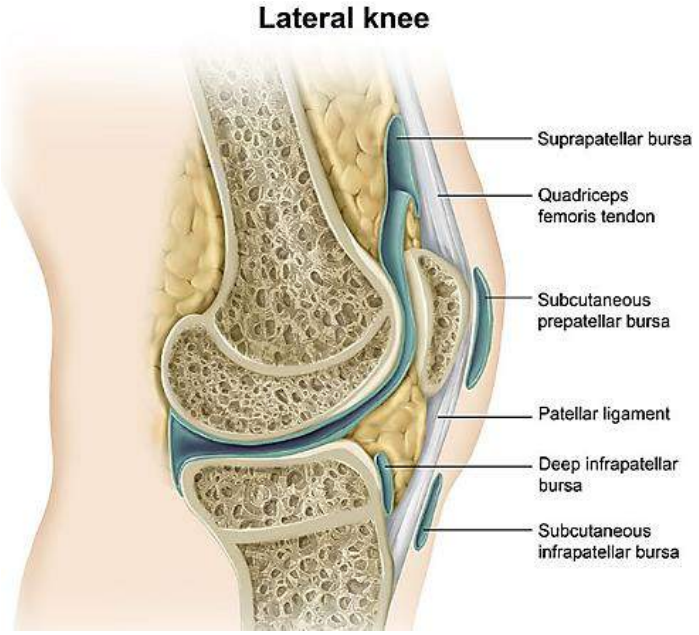
TARSAL TUNNEL SYNDOME

- Compression of tibial nerve as it passes through ankle
- Caused by fracture of ankle bones
- S/S: burning, numbness, aching of distal plantar (not dorsal) surface of foot/toes that sometimes radiate to calf

TENOSYNOVITIS

- Inflammation of tendon and its synovial sheath
- Usually in hands and wrists
- Due to overuse, following a bite or puncture wound
- Pain and tenderness along tendon sheath, particularly during flexion and extension

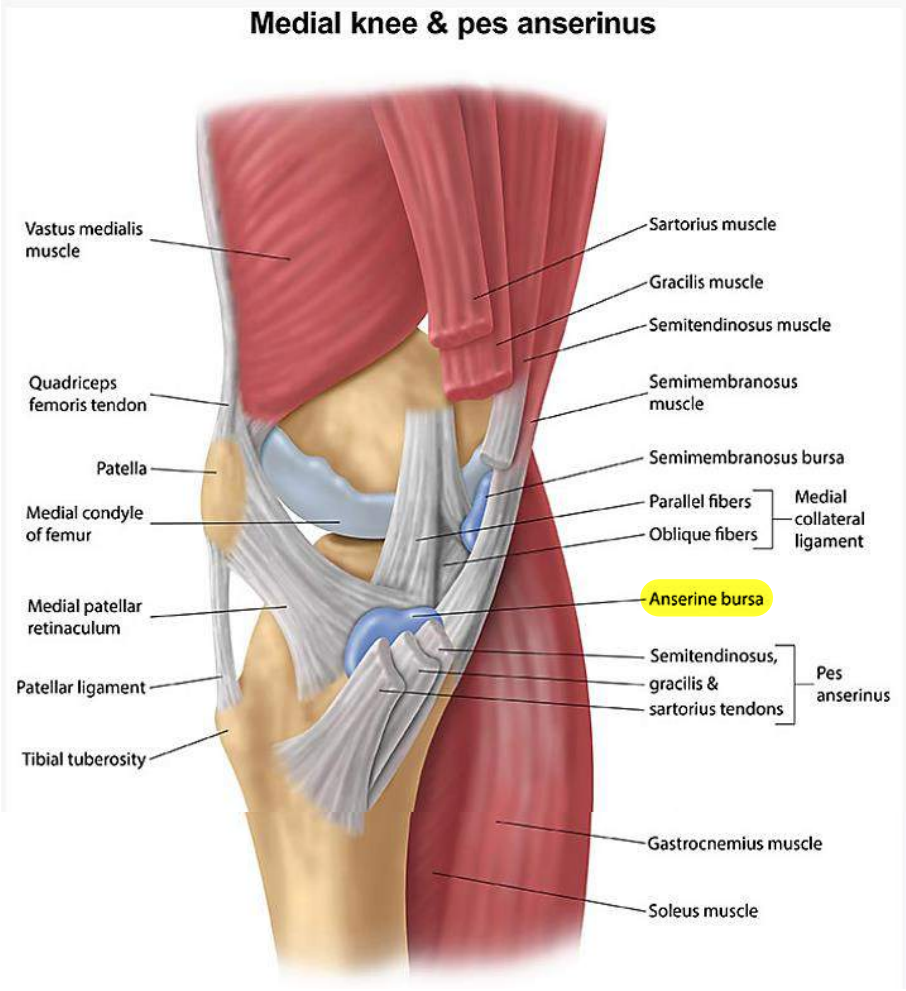
KNEE PAIN



BURSITIS

- Synovial sac—alleviates friction at bony prominences and ligamentous attachments
- Vulnerable to acute injury, infections, crystalline arthropathy and autoimmune disorders like RA
- **Sx:** pain and tenderness may be exquisite, swelling, erythema
- **PE:** active ROM decreased or painful. Passive ROM normal as causes less pressure on inflamed bursa

ANSERINE BURSITIS/PES ANSERINUS PAIN SYNDROME (PAPS)



- Most pts do not have true inflammation of bursa and pain may be contributed by multiple regional structures
- **Pes anserinus is formed by**: conjoined tendon of gracilis, sartorius and semitendinosus
- **Anserine bursa is located:** anteromedially over tibial plateau, just below joint line of knee and deep to pes anerinus
- **Causes**: abnormal gait, trauma or overuse
- **Sx:** Localized medial knee pain and focal tenderness over anteromedial tibia, just below joint line. Exacerbated by pressure from opposite knee while lying on side. Valgus stress test does not exacerbate the pain→ i.e. normal medial collateral ligament
- **Dx:** clinical grounds although x-ray can rule out concurrent osteoarthritis
- Doesn't cause locking and joint effusion

BAKER'S CYST

- Due to excess fluid production by inflamed synovium—in OA, RA and cartilage tears→ excess fluid accumulates in popliteal bursa→ expands→ creates tender mass in popliteal fossa.
- Occasionally burst→ release contents into calf→ resembles DVT

PREPATTELAR BURSITIS/HOUSEMAID'S KNEE

- Caused by chronic irritation of anterior knee in occupations requiring excessive kneeling

- While other bursitis are usually non-infectious, acute prepatellar bursitis is very commonly due to S. aureus infection—from penetrating trauma, repetitive friction or extension from local cellulitis
- **Examination**: Pain with direct pressure and superficial cytic swelling over patella with variable signs of inflammation
- **Dx:** should be confirmed by aspiration of bursal fluid for **cell count and Gram stain**
- **Rx:**
  - **Negative Gram stain and culture:** activity modification and NSAIDS
  - **Positive Gram stain and culture:** treated with drainage and antibiotics

DIFFERENTIAL DIAGNOSIS OF ANTERIOR KNEE PAIN IN YOUNG PATIENTS

Differential diagnosis of anterior knee pain in the young patient

Diagnosis	Patellofemoral syndrome	Patellar tendonitis	Osgood-Schlatter disease
Typical patient	Young female athletes	Primarily athletes ("jumper's knee")	• Preadolescent/ adolescent athletes • Recent growth spurt
Clinical features	• Subacute to chronic pain ↑ with squatting, running, prolonged sitting, using stairs • Patellofemoral compression test	Episodic pain & tenderness at inferior patella	• ↑ Pain with sports, relieved by rest • Tenderness & swelling at tibial tubercle

PATELLOFEMORAL PAIN SYNDROME

- **Risk factors**: overuse (most common), malalignment (eg angular deformities, weakness of hip abductors) and trauma

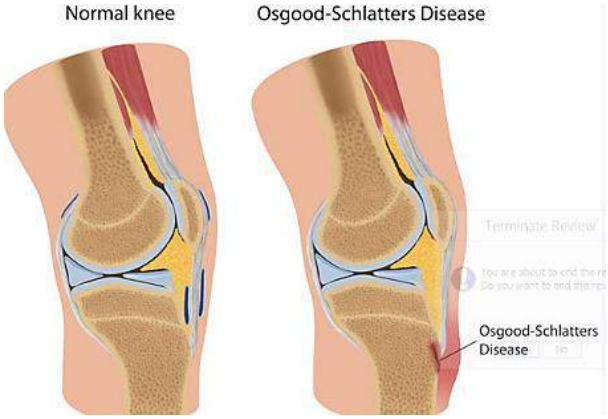
- Very common cause of chronic anterior knee pain in athletes and young women—worsened by prolonged sitting (due to flexion) or activity, climbing up or downstairs. May have crepitus with movement of patella.
- Presents with peripatellar pain (localized to patella)
- **Diagnosis:** challenging—mainly on history and physical examination. **Patellofemoral compression test:** pain elicited by extending the knee while compressing patella into trochlear groove and reproduction of pain with squatting are highly suggestive
- No separation of tibial tuberosity on x-ray. X-ray and MRI usually do not show any abnormality and usually needed only when diagnosis is in doubt or pt do not improve as expected
- **Rx:** primarily mechanical—**exercises to stretch and strengthen thigh muscles/quadriceps, knee extensors and hip abductors** and avoiding activities that aggravate pain, reduced intensity of exercise esp. running. NSAIDS often prescribed but not helpful. Persistence is often required on part of pt as improvement may take weeks to months

PATELLAR TENDINITIS

- Overuse syndrome from repetitive jumping and kicking and in occupations with repetitive forceful knee extension
- Presentation: episodic anterior knee pain after exercise
- Unlike Osgood, pt has point tenderness over inferior pole of patella and patellar tendon

OSGOOD SCHLATTER DISEASE

- Common cause of knee pain typically in adolescent male athletes



Etiology:

- During early adolescence (13-14 yrs in affected boys and 10-11 yrs in affected girls)→periods of rapid growth→ quadriceps puts traction apophysis of tibial tubercle where patellar tendon inserts→ sports like excessive running, jumping, kneeling→ traction apophysitis (Osgood Schlatter dis.)→ worsened by activity and relieved by rest. B/l in 1/4th cases

PE:

- Edema and tenderness over tibial tubercle
- Firm mass can sometimes be felt due to heterotopic bone formation
- Pain reproducible by extending knee against resistance

Radiographic findings:

- Non-specific—include anterior soft tissue swelling, lifting of tubercle from shaft, irregularity or fragmentation of tubercle

Rx:

- Activity restriction, stretching exercises and NSAIDS

TIBIAL OSTEOMYELITIS

- Usually bacterial

PE:

- Pain, swelling, tenderness, erythema
- Refusal to bear weight on affected extremity
- Systemic sx may also be present
- Pain does not remit with rest

PATELLAR FRACTURE

- Caused by direct blow or a sudden force under load (eg fall from height)
- Acute swelling, tenderness, and inability to extend knee

PATELLAR DISLOCATION

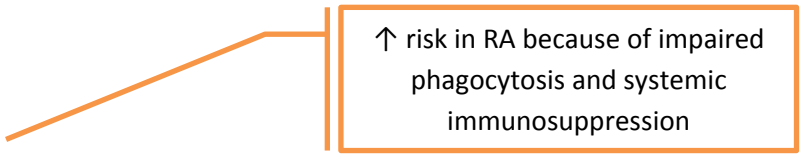
- Occur after quick lateral movements around flexed knee
- PE: flexed knee with patella displaced laterally

PATELLAR TENDON RUPTURE

- Rare. Although tears can occur with extreme loading in knee flexion→impaired knee extension

SEPTIC ARTHRITIS

- Involve joint space proper and not anterior tissue
- Cause acute pain, joint effusion and +/-fever, +/- chills and +/- leukocytosis. Pain on active and passive ROM. Onset occurs over days (and not hours like gout)
  - more commonly due to Gram +ve rather than Gram –ve and anaerobes
  - Fungal arthritis is usually due to Candida sp. Uncommon in non-immunocompromised pt. less acute and dramatic and usually preceded by recent invasive Candida infection



Septic arthritis	
Risk factors	• Abnormal joint: OA, RA, prosthetic joint, gout • Age >80 • Diabetes • IV drug abuse, alcoholism • Intra-articular glucocorticoid injections
Clinical features	• Acute monoarthritis: hot, swollen, decreased ROM • Fever • Elevated ESR & CRP
Diagnosis	• Blood cultures • **Synovial fluid analysis**: leukocytosis (>50,000/mm^3), Gram stain, culture
Initial treatment	• Gram-positive cocci: vancomycin • Gram-negative rod: third-generation cephalosporin • Negative microscopy: vancomycin (+ third-generation cephalosporin if immunocompromised)

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **IV** = intravenous; **OA** = osteoarthritis; **RA** = rheumatoid arthritis; **ROM** = range of motion.

Blood cultures are +ve in 50% cases and should be drawn prior to antibiotics

Prompt therapy with IV antibiotics and adequate joint drainage to prevent joint destruction

ILIOTIBIAL BAND SYNDROME

- Overuse injury
- Poorly localized pain at lateral knee
- Tenderness over lateral femoral condyle during flexion and extension
- Doesn't cause locking and joint effusion

SPECIAL TESTS FOR KNEE EXAMINATION

Special tests for knee examination	
MCL/LCL injury	**Valgus stress test** • Place 1 hand above knee along lateral thigh. Place the other along medial leg & apply outward pressure along calf • Laxity indicates MCL injury **Varus stress test** • Place 1 hand above knee along medial thigh. Place the other along lateral leg & apply inward pressure along calf • Laxity indicates LCL injury
ACL injury	**Anterior drawer test** • Have patient lie supine with knee flexed at 90 degrees • Grip proximal tibia with both hands & pull anteriorly **Lachman test** • Place knee at 30 degrees flexion • Stabilize distal femur with 1 hand & pull proximal tibia anteriorly with the other Significant anterior displacement of tibia with either test indicates ACL injury
PCL injury	**Posterior drawer test** • Flex knee to 90 degrees & stabilize foot • Grasp tibia with both hands & push posteriorly • Significant displacement indicates PCL injury **Posterior sag test** • Place patient supine with hips flexed to 45 degrees, knees flexed to 90 degrees & feet flat on table • PCL injury causes affected tibia to sag backward relative to femur
Meniscal tear	**Thessaly test** • Patient stands on 1 leg with knee flexed 20 degrees • Pain or locking with internal &/or external knee rotation suggests meniscal tear **Apley test** • With patient prone & knee flexed to 90 degrees, stabilize patient's thigh with examiner's knee or hand • Press patient's heel directly toward floor while internally & externally rotating foot • Focal pain with compression suggests meniscal tear **McMurray test** • Passive knee flexion & extension while placing examiner's thumb & index finger on medial & lateral joint lines • Clicking with passive movements or medial/lateral rotation suggests meniscal tear

ACL = anterior cruciate ligament; **LCL** = lateral collateral ligament; **MCL** = medial collateral ligament; **PCL** = posterior cruciate ligament.

Caused by forceful hyperextension of knee or a non-contact torsional injury during deceleration
Rapid onset hemarthrosis is typical

Can occur in athletes due to rapid direction changes—subacute or chronic locking or popping sensation—acute symptoms are usually mild—effusions possible but hemarthrosis is rare

Or locking may also be palpable

MEDIAL COLLATERAL LIGAMENT INJURY

- Caused by blow to lateral knee or forceful leg abduction and twisting/pivoting injuries.
- +ve medial knee tenderness and ecchymosis but absent catching during extension or rotation.
- Acute effusion/hemarthrosis usually absent unless ACL is also damaged
- MRI is the most sensitive test but reserved for pts being considered for surgery
- Rx: mostly non-operative with RICE (rest, ice, compression, elevation) and analgesics with progressive return to activity as tolerated

ANTERIOR CRUCIATE LIGAMENT INJURY

Features of anterior cruciate ligament injury	
Injury mechanisms	• Rapid deceleration or direction changes • Pivoting on lower extremity with foot planted
Symptoms	• Pain: rapid onset, may be severe • A "**popping**" sensation at the time of injury • Significant swelling (**effusion/hemarthrosis**) • **Joint instability**
Examination findings	• Anterior laxity of tibia relative to femur (anterior drawer test, Lachman test)
Diagnosis	• Magnetic resonance imaging
Treatment	• RICE (rest, ice, compression, elevation) measures • +/- Surgery

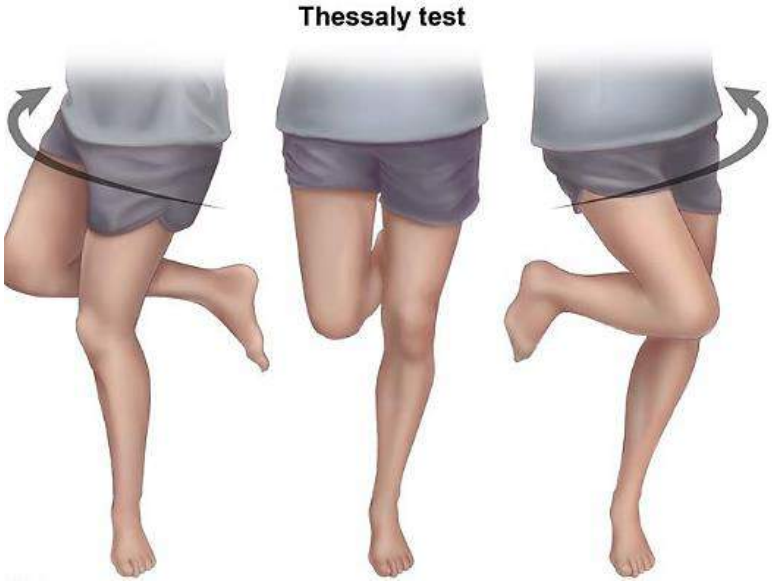
MENISCAL TEAR

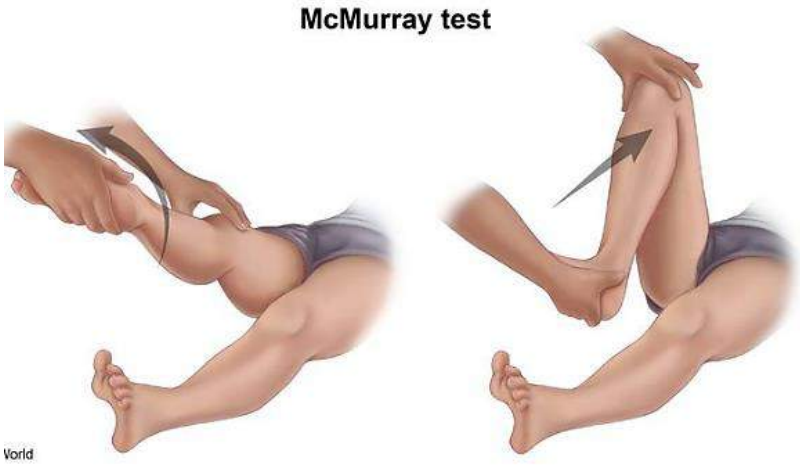
Meniscal tears	
Etiology	• **Younger patients**: Rotational force on planted foot • **Older patients**: Degeneration of meniscal cartilage
Symptoms	• Acute "popping" sensation • Catching, locking, reduced range of motion • Slow-onset joint effusion
Examination	• Joint line tenderness • Pain or catching in **provocative tests** (Thessaly, McMurray)
Diagnosis	• **MRI** • Arthroscopy
Management	• Mild symptoms, older patients: Rest, activity modification • Persistent symptoms, impaired activity: **Surgery**

And NSAIDS

Symptoms lasting >3-4 weeks—surgery reduce the risk of further joint injury

- Medial meniscus tear more common than lateral
- Reduced extension, sensation of instability and knee effusion—as meniscus is not directly perfused, hence, effusion is not apparent for several hours





- **X-ray:** older pt with tear due to joint degeneration will show signs of osteoarthritis but normal xray in young adults with traumatic tear
- **Dx:** confirmed with MRI or arthroscopy

HIP PAIN

- Superior gluteal nerve→ innervates gluteus medius and minimus→ weakness can be due to neuromuscular disease, impingement/trauma of nerve, inflammatory myopathies→ positive Trendelenburg sign and gait

AVASCULAR NECROSIS

Avascular necrosis	
Etiology	• Steroid use • Alcohol abuse • Systemic lupus erythematosus • Antiphospholipid syndrome • Hemoglobinopathies (eg, sickle cell) • Infections (eg, osteomyelitis, HIV) • Renal transplantation • Decompression sickness
Clinical manifestations	• Groin pain on weight bearing • Pain on hip abduction & internal rotation • No erythema, swelling, or point tenderness
Laboratory findings	• Normal white blood cell count • Normal ESR & CRP
Radiologic imaging	• Crescent sign seen in advanced stage • MRI is most sensitive modality

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

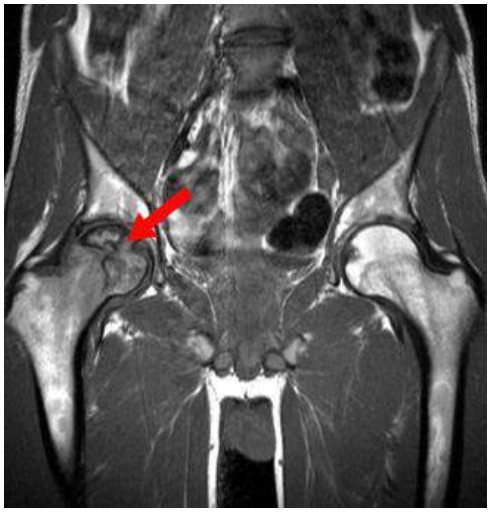
Steroids→ effect on osteocytes→ trabecular thinning and collapse over months to years
and
abnormal lipid levels→ microemboli→ osteonecrosis

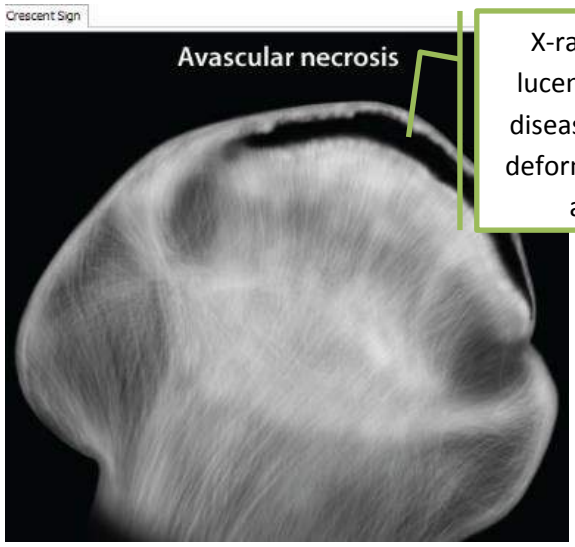
Progressive hip or thigh pain. Pain worse after activity but rest and night pain often present in advanced disease alongwith joint instability and ↓ ROM

Normal physical findings and X-ray initially

MRI visualize boundary between normal and ischemic bone, as well as zone of hypervascularity

- Caused by occlusion of end-arteries (micro-occlusion) supplying femoral head, abnormal endothelial function or ↑ intra-osseous pressure→ necrosis and collapse of periarticular bone and cartilage
- Femoral head is supplied by 2 main sources—ascending arteries and foveal artery which lie within ligamentum teres—foveal artery is patent in early life but may become obliterate later in life→ children less prone to avascular necrosis as compared to adults
- Sickle cell disease→ occlusion of microcirculation in bone by sickling and ↑ intraosseous pressure due to bone marrow hyperplasia→ osteonecrosis





X-ray= Subchondral lucency—in advanced disease—femoral head deformities also seen in advanced dis

TROCHANTERIC BURSITIS

- D/d of u/l hip pain in middle aged patients include: infection, arthritis, bursitis, trauma and radiculopathy

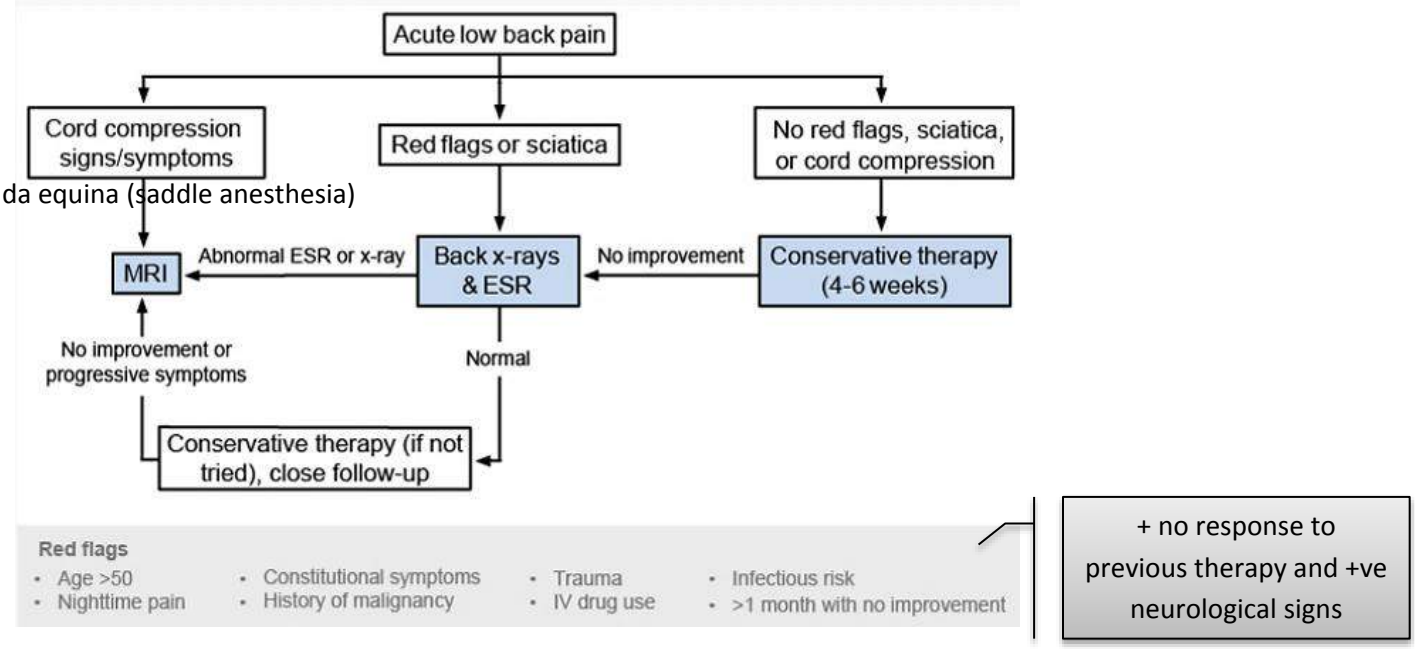
- Trochanteric bursitis is inflammation of bursa surrounding insertion of gluteus medius on greater trochanter of femur due to friction of tendons of gluteus medius and tensor fascia lata over greater trochanter of femur
- Causes: excessive frictional forces due to overuse, trauma, joint crystals or infection
- S/S: hip pain when pressure is applied (sleeping on side), external rotation or resisted abduction

MERALGIA PARESTHETICA

- Due to compression of lateral femoral cutaneous nerve at waist→ burning pain and paresthesia at lateral thigh
- Symptoms unaffected by motion

BACK PAIN

EVALUATION OF BACK PAIN



- Conservative therapy with NSAIDS—better than with acetaminophen in pts with no red flags
- Mostly lower back pain is musculoskeletal in origin, but red flags suggest systemic disease, herniated disc, or bony abnormalities (e.g lytic lesion or compression fractures) may be present
- MRI is done to look for disc disease, spinal infections and cancers. Common cancers that metastasize to bone: **breast, lungs, prostate, multiple myeloma, melanoma, renal and thyroid cancers**

CAUSES OF LOW BACK PAIN

Common causes of low back pain		
	Condition	**Clinical clues**
Musculoskeletal	Mechanical (muscle strain, spasm, degenerative arthritis)	• Normal neurologic examination • Negative straight leg raise • Possible paraspinal tenderness
	Herniated nucleus pulposus/ disk disease	• Radiculopathy (usually L4-L5) • Possible positive straight leg raise • Possible **neurologic deficits**
	Spinal stenosis	• Pseudoclaudication • Better with spine flexion • Worse with extension • **Older age**
	Compression fracture	• **Older age** • More common in women • **Trauma/fall** (may be minor)
Inflammatory	Ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease	• Better with activity or exercise • No improvement with rest • Gradual onset • **HLA-B27 present**
Malignancy	Metastatic cancer to bone	• **History of malignancy** • **Age >50** • Worse at night • Unintentional weight loss • Cauda equina syndrome (weakness, urine retention/incontinence, saddle anesthesia)
Infectious	Osteomyelitis, discitis, abscess	• Recent infection • **IV drug abuse** • Diabetes • **Fever, exquisite point tenderness**

Muscle strain pain can also radiate to buttocks and posterior thigh but pain below knee is characteristic of herniated disc

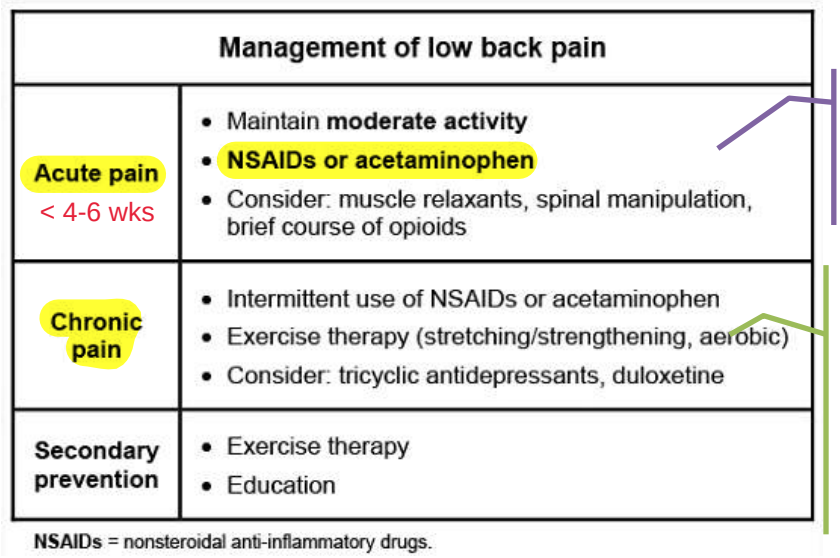
Radiation below the knee. Crossed straight leg raise test is also specific

Immune mediated disorder—Affects ligamentous insertion site (enthesitis)—gradual onset of LBP and progressive stiffness—causes destruction of articular cartilage esp. sacroiliac joint (sacroiliitis) and apophyseal joints of spine

Constant—not relieved by rest

Generally occurs in pts with recent overlying soft tissue infection or bacteremia—CRP and ESR usually ↑

MANAGEMENT OF LOW BACK PAIN



Management of low back pain	
Acute pain < 4-6 wks	• Maintain **moderate activity** • **NSAIDs or acetaminophen** • Consider: muscle relaxants, spinal manipulation, brief course of opioids
Chronic pain	• Intermittent use of NSAIDs or acetaminophen • Exercise therapy (stretching/strengthening, aerobic) • Consider: tricyclic antidepressants, duloxetine
Secondary prevention	• Exercise therapy • Education

NSAIDs = nonsteroidal anti-inflammatory drugs.

Acute= <4 weeks—most pts will have resolution without additional treatment

Chronic= >/=12 weeks and subacute= 4-12 weeks tend to persist or recur—exercise is the best treatment—initially supervised later transition to home exercise program

CERVICAL SPONDYLOTIC MYELOPATHY

- Degenerative changes in cervical spine in older pts
- Weakness, paresthesia and loss of fine motor control
- Neck and upper extremity symptoms are usually present and pts will usually show signs of b/l upper motor neuron weakness (hyperreflexia and upgoing plantar) and b/l sensory deficits
- MRI is used for diagnosis

CERVICAL SPONDYLOSIS:

- Affects 10% of people older than 50 years of age.
- H/o chronic neck pain is typical
- Limited neck rotation and the lateral bending—due to osteoarthritis and secondly muscle spasm.
- Sensory deficit do the osteophyte induced radiculopathy and isolated sneosry abnormalities are associated with good prognosis.
- **Typical radiographic findings**: bony spurs and sclerotic facet joints. Osteoarthritic changes are common in asymptomatic patients older than 50 years of age. Other findings may include narrowing of discs spaces and hypertrophic vertebral bodies

VERTEBRAL OSTEOMYELITIS

- **Risk factors:** IV drug abusers (high index of suspicion), recent h/o distant site infection, sickle cell anemia and immunosuppressed pts.
- Spine is a frequent site of osteomyelitic infection
- **Causative organism:** most commonly by S. aureus but also by Gram –ve organisms
- **Sx:** back pain not relieved by rest, fever is an inconsistent finding
- **PE:** tenderness to gentle percussion over involved spinous process is most imp. Clue
- **Labs:** leukocytosis is inconsistent, platelets ↑ as a marker of inflammation/stress, ESR ↑ usually >100mm/hr
- **MRI is the most sensitive diagnostic study**
- **Rx:** long-term IV antibiotics with or w/o surgery

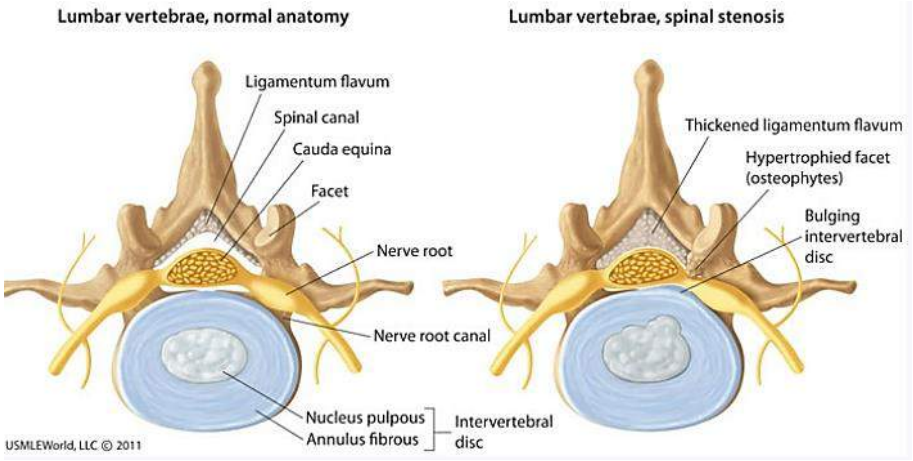
LUMBOSACRAL STRAIN

- most common cause of back pain—lifetime risk 80%
- S/S: acute onset back pain after physical exertion, no radiation, no neurologic deficits
- PE: local tenderness and contraction of paraspinal muscles. Normal neurologic exam and straight leg raise test
- Rx: NSAIDS and early mobilization
- **Prevention:** proper patient education is important. The education should emphasize the **importance of strengthening the supporting muscles** (including abdominal muscles) by regular exercise, choosing an **appropriate sleeping posture** (e.g. avoiding sleeping on the stomach)**,** and **learning proper techniques for bending and lifting objects**. Exercises with repetitive twisting and bending should be avoided**.** It is important to bend at the knees, not at the waist. While lifting an object, **one should also bend the knees, keeping the back straight**; this technique is very useful in preventing strains and back injuries. Warm-up exercises should be done before any sporting activities

LUMBAR DISC HERNIATION

- Acute back pain with/without radiation to unilateral lower leg usually (sciatica), recall inciting event, aggravated by activity and lumbar flexion, relieved by rest
- Spine not tender to palpation
- Rx: mostly spontaneous resolution of symptoms→ initial management focused on acute relief of symptoms. Nonsteroidal anti-inflammatory drugs and acetaminophen are the preferred first line drugs. Short term use of opioids or muscle relaxants can be considered in patients with persistent pain but is associated with significant sedation. Activity modification is often advisable, but patient should be encouraged to maintain moderate physical activity

LUMBAR SPINAL STENOSIS



- **Narrowing of spinal canal** with **compression of 1 or more spinal nerve roots (**not spinal cord compression). Due to narrowing of intraspinal (central) canal, lateral recess or neural foramen
- Primarily seen in **degenerative arthritis** with osteophyte formation affecting the facet joints (spondylosis).
- **Other factors**: hypertrophy of ligamentum flavum, bulging of intervertebral disc, degenerative disc disease and spondylolisthesis (displacement of one vertebral body relative to another)
- Mostly in pt >60yo

- **S/S:** Sx are **posture-dependent.** Back pain radiating to buttocks and thigh. Extension of lumbar spine (eg standing and walking upright) further narrows spinal canal and worsens symptoms and relieved by lumbar flexion (walking uphill and leaning on a cane).
- Onset of pain with walking is referred to as "**neurogenic claudication"** as it may resemble vascular claudication (pain with walking and relieved by rest). Neurogenic claudication—relieved by walking while leaning forward **("shopping cart sign")** and exercise with spine flexed (eg cycling) does not incite symptoms
- May be associated with numbness and paresthesia
- **Dx:** confirmed by **MRI**
- **Rx:** mostly conservative with physical therapy and exercise, some may require surgical intervention

NEUROGENIC VS VASCULAR CLAUDICATION

Neurogenic & vascular claudication		
	Neurogenic claudication (pseudoclaudication)	**Vascular claudication**
Symptoms	• Posture-dependent pain • Lumbar extension worsens pain (eg, walking downhill) • Lumbar flexion relieves pain (eg, walking while bent forward) • Lower-extremity numbness & tingling • Lower-extremity weakness • Low back pain	• Exertionally dependent pain • Pain relieved with rest, but not with bending forward while walking • Lower-extremity cramping/tightness • No significant lower-extremity weakness • Possible buttock, thigh, calf, or foot pain
Examination	• Normal pulses • Frequently normal examination	• Decreased pulses • Cool extremities • Decreased hair growth • Pallor with leg elevation
Diagnosis	• MRI of the spine	• Ankle-brachial index

IMPINGEMENT OF LUMBAR NERVE ROOTS:

- Can cause pain at posterior hip, thigh and lower leg
- Hip mobility is normal but may have exacerbation of pain on hip flexion and knee extension (straight leg raise)

VERTEBRAL COMPRESSION FRACTURE

Clinical features of vertebral compression fracture	
Etiologies	• Trauma • **Osteoporosis**, osteomalacia • Infection (eg, osteomyelitis) • Bone metastases • Metabolic (eg, hyperparathyroidism) • Paget disease
Clinical presentation	**Chronic/gradual VCF** • Painless • Progressive kyphosis • Loss of stature **Acute VCF** • Low back **pain** & **decreased spinal mobility** • Pain increasing with standing, walking, lying on back • Tenderness at affected level
Complications	• Increased risk for future fractures • Hyperkyphosis, possibly leading to protuberant abdomen, early satiety, weight loss, decreased respiratory capacity

VCF = vertebral compression fracture.

Most common cause of on-traumatic VCF—Can develop acute compression fracture with h/o minimal trauma like coughing, bending, lifting

Each VCF lead to >/= 1 cm decrease in height

- Neurological examination is typically normal (loss of DTRs is common in elderly esp. above 70yrs and not related to VCT)

SERONEGATIVE SPONDYLOARTHROPATHIES

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis	
Inflammatory back pain	• Insidious onset at age <40 • Symptoms >3 months • **Relieved with exercise** but not rest • Nocturnal pain
Examination findings	• Arthritis (sacroiliitis) • Reduced chest expansion & spinal mobility • Enthesitis (tenderness at tendon insertion sites) • Dactylitis (swelling of fingers & toes) • Uveitis
Complications	• Osteoporosis/vertebral fractures • Aortic regurgitation • Cauda equina
Laboratory	• Elevated ESR & CRP • **HLA-B27** association
Imaging	• **X-ray of sacroiliac joints** • MRI of sacroiliac joints

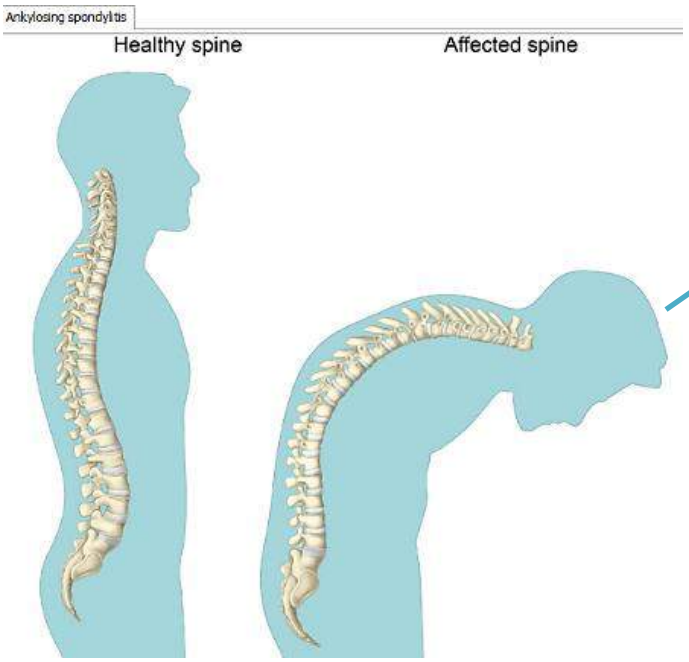
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Spinal rigidity ↑ the risk of vertebral fracture with minimal trauma. Additional findings: thoracic wedging and hyperkyphosis

Anterior uveitis (iritis) is the most common extraarticular manifestation—25-40% cases→ inflammation of uveal tract (iris, ciliary body and choroid)→ intense pain and photophobia in one eye

Osteopenia/osteoporosis→ ↑ osteoclast activity in the setting of chronic inflammation (mediated by TNF-a and IL-6)

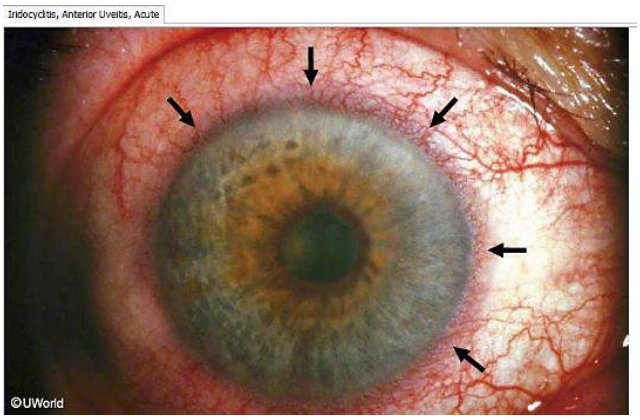
Due to scarring of valve cusps



X-ray showing sacroiliitis can confirm the diagnosis—may be –ve early→ MRI can confirm in such cases→ fusion of vertebral bodies with ossification of intervertebral discs (bamboo spine) also confirm the diagnosis

Enthesitis

- Inflammation and pain at the site where tendons and ligaments attach to bone
- Commonly due to tendon or ligament stress→ manifest as acute swelling and pain
- PE: tenderness at the site of tendon insertion
- Insertion of Achilles tendon at heel is the most common site of presentation→ worsens with activity (lower back pain improves with activity)
- Can involve costosternal junction, shoulders, elbows, hips, iliac crest, tibial tuberosity and other sites
- Chronic→ fibrosis and calcification
- Can be isolated like plantar fasciitis but characteristic finding in spondyloarthropathies such as ankylosing spondylitis (most common), psoriatic arthritis, reactive arthritis—can be present at multiple sites



PSORIATIC ARTHRITIS

Clinical features of psoriatic arthritis	
Arthritis	• DIP joints • Asymmetric oligoarthritis • Symmetric polyarthritis, similar to RA • Arthritis mutilans (deforming & destructive arthritis) • Spondylarthritides (sacroiliitis & spondylitis)
Soft tissue & nail involvement	• Enthesitis (inflammation at tendon insertion site to bone) • Dactylitis ("sausage digits") of toe or finger • Nail pitting & onycholysis • Swelling of the hands or feet with pitting edema
Skin lesions	• Arthritis precedes skin disease in 15% of patients • Skin lesions are present but not yet diagnosed in 15% of patients

DIP = distal interphalangeal; RA = rheumatoid arthritis.

i.e. separation of nail bed

i.e. white plaques with silvery scale

- Morning stiffness is present as in most inflammatory arthritides.
- Sausage digit→diffusely swollen finger
- **Rx:** options include: NSAIDS, methotrexate and anti-TNF agents

REACTIVE ARTHRITIS

- Type of seronegative spondyloarthropathy. Usually result from enteric or genitourinary infection by *Shigella, Salmonella, Yersinia, Campylobacter* or C. *difficile*
- Triad of non-gonococcal urethritis, asymmetrical oligoarthritis and conjunctivitis. Often involves knee and sacroiliac spine. In addition to the classic triad, mucocutaneous lesions and enthesitis (Achilles tendon pain) are common findings. Malaise and characteristic cutaneous findings (keratoderma blennorrhagica and balanitis circinata) are also present.
- Not all symptoms always present→ high suspicion for reactive arthritis in case of any asymmetrical oligoarthritis associated with the urethritis, conjunctivitis or mouth ulcers
- Synovial fluid analysis—usually sterile
- Rx: NSAIDS are first line during acute attack

ENTEROPATHIC ARTHRITIS

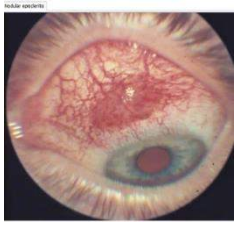
- In 10-20% pts with UC and Crohn disease
- Lower extremities and sacroiliac joints are mainly involved
- Symptoms wax and wane with symptoms of bowel disease
- These pts have prominent GI symptoms and other extraintestinal manifestations
- P-ANCA may be present in UC and ankylosing spondylitis despite the absence of vasculitis

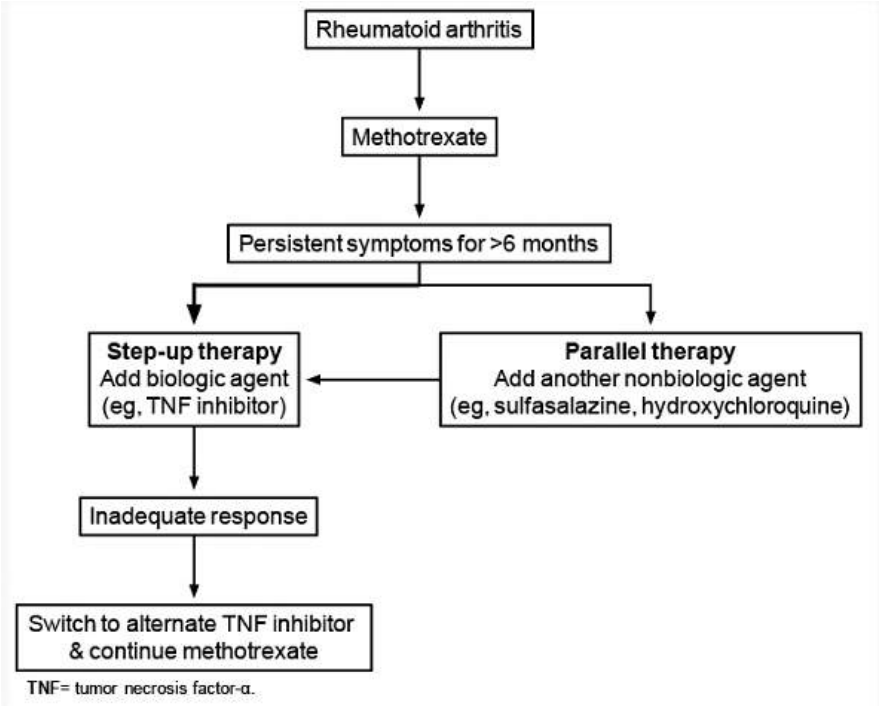
RHEUMATOID ARTHRITIS

Clinical features of rheumatoid arthritis	
Clinical presentation	**Symptoms** • Insidious onset, multiple joint pain, stiffness & swelling • Morning stiffness lasting hours, improves with activity • Small joints (eg, PIP, MCP, MTP) commonly involved • Monoarthritis (eg, knees, elbows) can also occur later • **Spares the DIP joint**, unlike osteoarthritis **Examination** • Affected joints are tender to the touch, swollen, with limited range of motion • Tenosynovitis of the palms → "trigger finger" • Rheumatoid nodules (especially on elbows) • Cervical joint involvement can lead to spine subluxation → spinal cord compression
Laboratory/ imaging studies	• Positive anti-CCP antibodies (diagnostic testing) • High IgM rheumatoid factor • High C-reactive protein & ESR correlate with disease activity • **X-ray**: Soft-tissue swelling, joint space narrowing & bony erosions

Anti-CCP = anti-cyclic citrullinated peptide; **DIP** = distal interphalangeal joints; **ESR** = erythrocyte sedimentation rate; **IgM** = Immunoglobulin M; **MCP** = metacarpophalangeal; **MTP** = metatarsophalangeal

- Peak incidence at 50-75 yo
- Reduced grip strength can occur occasionally and is a sensitive sign of early disease
- **Osteoporosis:** ↑ proinflammatory cytokines, corticosteroid therapy, and lack of physical activity→ local (around inflamed joint) and generalized loss of bone mass (↑ risk of osteopenia, osteoporosis, and bone fractures esp. if other risk factors (eg. low body weight, female sex, smoking, family history of osteoporosis, postmenopausal state, excessive alcohol intake, other comorbidities) are present—degree of bone loss correlates with **disease activity**
- **Strategies to prevent bone loss:** adequate physical activity, optimization of vitamin D and calcium intake, minimization of glucocorticoid dose, low threshold for starting bisphosphonates in RA pts.
- X-ray of long-standing, poorly controlled disease: periarticular osteoporosis, joint erosions and joint space narrowing
- **Episcleritis**—inflammation seen on white of the eye without involvement of uveal tract—most strongly associated with RA and IBD
- **Treatment:**





- Start DMARDS asap as joint damage begins early in the course. Methotrexate is preferred initial DMARD in moderate to severe RA due to efficacy and long term safety profile—test for TB, HBV and HCV before starting. Contraindications of Methotrexate: pregnant pt and those planning to become pregnant in near future, severe renal insufficiency, liver disease or excessive alcohol intake
- NSAIDS and COX-2 inhibitors—adjunctive therapies for symptomatic relief but do not reduce progression
- Glucocorticoids—can relieve symptoms and short-term radiographic progression—not effective in preventing eventual joint destruction

FELTY SYMDROME

- Felty syndrome is a clinical disorder seen in patients with severe, long-standing (>10 years) RA but rarely precedes the diagnosis.
- Characterized by neutropenia and splenomegaly. Splenomegaly without neutropenia can also occur in patients with RA, but the diagnosis of Felty syndrome should not be made in the absence of neutropenia
- Pts with FS have severe seropositive RA with ↑ risk of extra-articular manifestations
- More common in women—peak incidence in 4^{th} and 5^{th} decade
- Pathophysiology unknown
- Associated with HLA-DR4— ↑ incidence in pts with FH of RA—suggesting genetic component
- FS usually improves with treatment of underlying RA (eg. methotrexate)

Felty syndrome	

Clinical features	• Rheumatoid arthritis
	  ○ Severe erosive joint disease & deformity
	  ○ Rheumatoid nodules
	  ○ Vasculitis (mononeuritis multiplex, necrotizing skin lesions)
	• Neutropenia (ANC <1500/µL)
	• Splenomegaly

Diagnosis	• Anti-CCP & RF are positive in >90% of patients • Markedly elevated ESR, often >85 mm/hr • Peripheral smear & bone marrow biopsy to rule out other causes of neutropenia

ANC = absolute neutrophil count; **anti-CCP** = anti-cyclic citrullinated peptide; **ESR** = erythrocyte sedimentation rate; **RF** = rheumatoid factor.

OSTEOARTHRITIS

Osteoarthritis	
Risk factors	• Age >50 • Obesity • Prior joint injury • Diabetes
History	• Chronic, insidious symptoms • Minimal/no morning stiffness
Physical examination	• Knees/hips, DIP joints, cervical/lumbar spine • Hard, **bony enlargement** of joints • **Crepitus** with movement
Radiology	• X-rays: Narrowed joint space, osteophytes, subchondral sclerosis

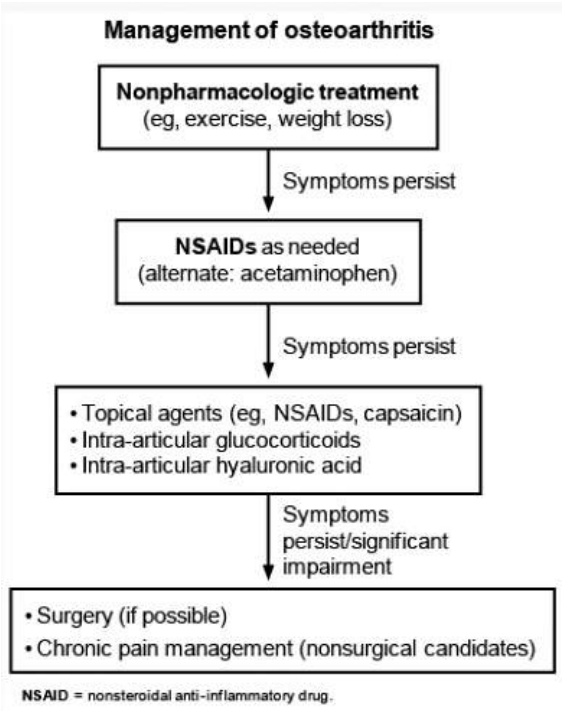
DIP = distal interphalangeal.

Prolonged rest may cause stiffness and pain but usually worse with activity

Diagnosis is usually clinical. X-ray confirms the diagnosis. Arthrocentesis is sometimes performed—show clear fluid without inflammatory cells

Osteoarthritis	
Age of onset	>40; increases with age
Joint involvement	• Knees • Hips • Distal interphalangeal joints • 1st carpometacarpal joint
Morning stiffness	None/brief (<30 min)
Systemic symptoms	Absent
Examination findings	• Hard, bony enlargement of joints • Reduced range of motion

- **Hip osteoarthritis**:
  - Pain in groin, buttock, or pelvis and can radiate to lower thigh or knee
  - ↓ external and internal rotation but synovitis (redness, warmth and tenderness) absent



- NSAIDS relieve pain but do not alter progression of disease

SYSTEMIC LUPUS ERYTHMATOSIS (SLE)

- Young African American, Hispanic and Asian women are at greatest risk

Manifestations of systemic lupus erythematosus	
Clinical symptoms	• **Constitutional**: Fever, fatigue & weight loss • Symmetric, migratory **arthritis** • Skin: **Butterfly rash** & **photosensitivity** • **Serositis**: Pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • Neurologic: Cognitive dysfunction & seizures

Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia
	• **Hypocomplementemia** (C3 & C4)
	• Antibodies:
	  ○ **ANA** (sensitive)
	  ○ **Anti-dsDNA** & **anti-SM** (specific)
	• Renal involvement: **Proteinuria** & elevated creatinine

Polyarticular—knees, carpal bones and joints of fingers most commonly involved—joint pain often exceeds objective findings—X-rays show no evidence of joint destruction/erosion

Can also cause stroke, headache (due to vasculitis)

And ↑ immune complexes

Hematologic manifestations of SLE:

Hematologic manifestations of systemic lupus erythematosus		
	Common mechanisms	**Uncommon mechanisms**
Anemia	• Anemia of chronic disease • Renal insufficiency from SLE nephritis • Iron deficiency anemia (gastrointestinal loss) • Autoimmune hemolytic anemia	• Medications • Hypersplenism • Microangiopathic hemolytic anemia • Aplastic anemia
Leukopenia	Autoimmune-mediated destruction	• Medications • Hypersplenism • Bone marrow dysfunction
Thrombocytopenia	Immune-mediated destruction	• Medications • Increased consumption due to thrombotic microangiopathy (thrombotic thrombocytopenic purpura)

GI blood loss e.g. peptic ulcer formation due to chronic NSAIDS use

- SLE can cause pancytopenia due to concurrent immune mediated destruction of all 3 cell lines. Bone marrow suppression can also cause pancytopenia. However, this is not usually due to SLE but rather

from other coincidental conditions like leukemia, drugs, myelodysplasia and malignant invasion of bone marrow. As a result, bone marrow biopsy is frequently done in SLE pts to exclude other causes

Renal manifestations of SLE:

- Immune complexes composed of ds-DNA and anti-ds-DNA antibodies deposit in mesangium and/or subendothelial space→ intense inflammatory response and complement activation→ lower C3 and C4 levels and nephritic syndrome
- Immune complexes may also deposit in sub epithelial space→ membranous glomerulonephritis→ nephrotic syndrome without hypocomplementemia

Clinical features:

- Fatigue, painless oral ulcers, nondeforming arthritis, renal abnormalities (hematuria, proteinuria, glomerulonephritis), cytopenias—most common manifestations of active disease
- Morning stiffness much shorter than RA

Initial screening:

1. Initial evaluation in pt. suspected of SLE should include blood counts to look for cytopenias, urinanalysis and creatinine to screen for nephropathy
2. ANA titers obtained early—sensitive but not specific→ if positive→ confirm with more specific Ab like anti-dsDNA and anti-Smith Ab (many pts will be negative for these even in presence of multi-system involvement)
3. Complement level, ESR and CRP should be assayed to assess ongoing disease activity

Monitoring disease activity in SLE:

- Periodic blood counts, inflammatory markers (eg ESR), complement levels and anti-dsDNA titers
- Regularly screen for lupus nephritis with urinalysis, serum creatinine, and urine protein assay

Treatment:

- Choice of drug depends on degree of organ involvement
- Most pts with active SLE benefit from **hydroxychloroquine**, a safe and well-tolerated medicine→can cause retinal toxicity rarely leading to irreversible vision loss→ common after 5-7 years of therapy→ perform baseline ophthalmologic evaluation, with annual reassessment starting after 5 years
- Cyclophosphamide is reserved for pts with significant renal or CNS involvement→ can cause acute hemorrhagic cystitis, bladder cancer, sterility and myelosuppression—acrolein is the bladder toxic metabolite→ drink plenty of water, void frequently and take MESNA to prevent renal complications

ANTI-PHOSPHOLIPID SYNDROME (APS)

Antiphospholipid antibody syndrome	
Clinical features	**Venous or arterial thromboembolic disease** • Deep venous thrombosis • Pulmonary embolism • Ischemic stroke/transient ischemic attack **Adverse pregnancy outcomes** • Unexplained embryonic or fetal loss • Premature birth due to placental insufficiency or preeclampsia
Laboratory findings	• **Lupus anticoagulant** effect: Paradoxical **aPTT prolongation** not reversed on plasma mixing studies • Presence of specific antiphospholipid antibodies o **Anticardiolipin** antibody o **Anti-beta2-glycoprotein-I** antibody

Thrombocytopenia

It prolongs PTT in vitro as it binds to phospholipids used in most assays—artifact and does not correlate with bleeding in vivo—indirect indicator of LA. Specific tests: diluted Russell viper venom test and kaolin clotting time

Diagnostic criteria for antiphospholipid antibody syndrome (1 clinical & 1 laboratory criterion must be met)	
Clinical	**Vascular thrombosis** • Arterial/venous thrombosis **Pregnancy morbidity** • ≥3 consecutive unexplained fetal losses before 10th week • ≥1 unexplained fetal loss after 10th week • ≥1 premature birth of normal neonate before 34th week due to preeclampsia, eclampsia, placental insufficiency
Laboratory	• Lupus anticoagulant • Anticardiolipin antibody (IgG/IgM – medium or high titer) • Anti-b2GP1 antibody (IgG/IgM – high titer)

Antiphospholipid syndrome	
Diagnosis	Vascular thrombosis (transient ischemic attack/stroke, deep venous thrombosis) **&/or** Pregnancy complication (eg, recurrent miscarriage) **PLUS** ≥1 of the following antibodies: • Anti-cardiolipin antibody • Lupus anticoagulant • Anti-beta2-glycoprotein antibody
Management	Anticoagulation (eg, heparin, warfarin)

- Some healthy pts may transiently become positive for APS antibodies, so all pts positive for these antibodies should have a repeat test for antibodies after 12 wks to confirm diagnosis
- Biggest risk factor for APS: SLE (in 40% cases of SLE) but can occur independently as well
- The APS-associated autoantibodies mediate a hypercoagulable state that may cause placental thrombosis. **Potential complications** include recurrent first-trimester miscarriage, fetal demise,
- preeclampsia, and fetal growth restriction
- **Rx:** Patients with APS require anticoagulation with low molecular weight heparin (LMWH) and low dose aspirin after acute thrombotic events or to prevent pregnancy loss or venous thromboembolism during pregnancy. Patients require long-term treatment with warfarin. Add hydroxychloroquine in pt with concomitant SLE.
- False positive RPR/VDRL is common in APS as syphilis antigen used in RPR contains cardiolipin

DMARDS

CLASSIFICATION

NON-BIOLOGIC AGENTS:

- Small-molecule drugs produced by conventional chemical synthesis→target inflammatory pathways eg. sulfasalazine, hydroxychloroquine, methotrexate, leflunomide, azathioprine

BIOLOGIC:

- Large molecule agents produced by biologic means, primarily recombinant DNA technology→ target cytokines and cell surface proteins eg. TNF inhibitors—etanercept, infliximab, adalimumab, tocilizumab, rituximab

Disease-modifying antirheumatic drugs

Agent	Mechanism	Adverse effects
Methotrexate	Purine antimetabolite	• Hepatotoxicity • Stomatitis oral ulcers • Cytopenias
Leflunomide	Pyrimidine synthesis inhibitor	• Hepatotoxicity • Cytopenias
Hydroxychloroquine	TNF & IL-1 suppressor	• Retinopathy
Sulfasalazine	TNF & IL-1 suppressor	• Hepatotoxicity • Stomatitis • Hemolytic anemia
TNF inhibitors • Adalimumab • Certolizumab • Etanercept • Golimumab • Infliximab	Anit-cytokines agents	• Infection • Demyelination • Congestive heart failure • Malignancy

TNF = tumor necrosis factor.

In moderate to severe SLE and RA—steroid sparing agent—LFTs are monitored frequently.

Other SE: alopecia, pulmonary toxicity, bone marrow suppression.

Folic acid supplementation→ ↓ SE. SE reversible usually on discontinuation but watch carefully for flare up

Neutropenia, infections (reactivation of latent TB, opportunistic infections)

RAYNAUD'S PHENOMENON

	Primary Raynaud's phenomenon	Secondary Raynaud's phenomenon
Etiology	• No underlying cause	• **Connective tissue diseases** • Occlusive vascular conditions • Sympathomimetic drugs • Vibrating tools • Hyperviscosity syndromes • Nicotine
Clinical presentation	• Usually women age <30 • No tissue injury • Negative ANA & ESR	• Usually men age >40 • Symptoms of underlying disease • **Tissue injury** or digital ulcers • Abnormal nail fold capillary examination
Management	• Avoid aggravating factors • **CCB** for persistent symptoms	• Evaluate & treat underlying disorder • **CCB** for persistent symptoms, **aspirin** for patients at risk for digital ulceration

ANA = antinuclear antibody; **ESR** = erythrocyte sedimentation rate; **CCB** = calcium channel blocker.

For example systemic lupus erythematosus, Scleroderma, thromboangiitis obliterans

Dilated or dropout vessels in nail-fold capillaries—predictive of future development or presence of CT disease

Dihydropyridine CCB like amlodipine and nifedipine are used

- **Primary RP:** ↑ vascular response to cold and emotional stress—symmetrical, episodic attacks—episodes may involve tingling, numbness, pain with color changes of pallor (white attack) or cyanosis (blue attack)
- **Treatment:** smoking cessation and avoidance of cold temperatures and emotional stress. Pharmacologic therapy includes dihydropyridine calcium channel blockers like nifedipine o amlodipine
- **Secondary RP:**
  Based on history and physical examination, workup for the patient with suspected secondary Raynaud's phenomenon may include:
  - CBC and metabolic panel,
  - Urine analysis
  - Antinuclear antibody and rheumatoid factor
  - ESR and complement levels (C3 and C4).
- If ANA is positive specific antibodies may be obtained

SYSTEMIC SCLEROSIS (SSc)

Clinical features of systemic sclerosis (scleroderma)	
Systemic	• Fatigue • Joint stiffness & pain
Skin	• Telangiectasia • Sclerodactyly • Digital ulcers • Calcinosis cutis
Vascular	• Raynaud phenomenon
GI	• Dysphagia, dyspepsia • Angiodysplasia of stomach (watermelon stomach) with GI bleeding • Malabsorption due to bacterial overgrowth
Pulmonary	• Pulmonary fibrosis • Pulmonary arterial hypertension
Renal	• Scleroderma renal crisis ◦ Acute onset oliguric renal failure with malignant hypertension ◦ Thrombocytopenia ◦ Microangiopathic hemolytic anemia
Cardiac	• Myocarditis, pericarditis, pericardial effusion

GI = gastrointestinal.

Classic early skin manifestations: thickening or hardening, edema and pruritis

Primarily affects esophagus→ smooth muscle atrophy and fibrosis in lower esophagus→choking, hoarseness. **Esophageal manometry:** hypomotility and incompetence in LES

Pulm. Complications are the most common cause of death in SSc. In 40% cases of diffuse SSc— most common pulm. complication

In 15% cases of limited SSc→ right heart failure

Before the advent of ACEi, renal crisis leading to HTN was the most common cause of death

- SSc—extreme heterogeneity in manifestations and severity—some degree of skin involvement in seen in almost all cases
- **Limited SSc:** sclerosis limited to skin of wrists, hand and face, may have esophageal dysmotility and vascular symptoms (eg Raynaud phenomenon)— but extradermal manifestations are limited in most cases
- **Diffuse cutaneous SSc:** with dermal thickening involving proximal extremities or trunk—more likely to cause extradermal manifestations and carries a more severe prognosis
- **Antibodies:** ANA in all patients, anti-topoisomerase I antibodies in diffuse. Anticentromere Ab in limited

SJOGREN SYNDROME

- More in females in 5th or 6th decade of life

Sjögren syndrome	
Primary SS	• No associated connective tissue disease
Secondary SS	• Comorbid connective tissue disease present (eg, SLE, RA, scleroderma)
Clinical features	• Ocular symptoms (eg, **dry eyes**, decreased tears) • Oral symptoms (eg, **dry mouth**, swollen salivary glands) • Objective signs of **decreased lacrimation** (eg, Schirmer test) • **Autoantibodies** to Ro (SSA) &/or La (SSB) • Salivary gland biopsy with focal lymphocytic sialoadenitis • Salivary gland involvement (eg, decreased salivary flow, delayed uptake on salivary scintigraphy)

RA = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **SS** = Sjögren syndrome.

+ dyspareunia

Enlargement and firmness to palpation of these glands

- Extraglandular manifestations may include: arthritis, LAD, Raynaud phenomenon, or vasculitis.
- Occasionally optic neuritis may be present
- Other antibodies that may be present: ANA, RF
- Dx: confirmed by subjective and objective evidence of dry mouth and eyes in the presence of either histologic presence of lymphocytic infiltration of salivary glands or serum autoantibodies directed against SSA (Ro) and/or SSB (La)

PARANEOPLASTIC SYNDROME

Paraneoplastic syndrome	Involved site	Clinical features
Myasthenia gravis	Acetylcholine receptor in postsynaptic membrane	Fluctuating muscle weakness • Ocular (ptosis, diplopia) • Bulbar (dysphagia, dysarthria) • Facial, neck & limb muscles
Lambert-Eaton syndrome	Presynaptic membrane voltage-gated calcium channels	• Proximal muscle weakness • Autonomic dysfunction (eg, dry mouth) • Cranial nerve involvement (eg, ptosis) • **Diminished or absent deep-tendon reflexes**
Dermatomyositis/ polymyositis	Muscle fiber injury	• Symmetrical & more proximal muscle weakness • Interstitial lung disease, esophageal dysmotility, Raynaud phenomenon • Polyarthritis • Esophageal dysmotility • **Skin findings** (eg, Gottron papules, heliotrope rash) in dermatomyositis

Muscle weakness and DTRS improve with repetitive isometric contraction

- Paraneoplastic syndromes are common in: cancers of lungs, ovaries, breast and lymphomas

DIFFERENTIAL DIAGNOSIS OF MYOPATHY

Differential diagnosis of myopathy			
Disorder	**Clinical features**	**ESR**	**CK**
Glucocorticoid-induced myopathy	• Progressive proximal muscle **weakness** & atrophy **without pain** or tenderness • Lower-extremity muscles are more involved	Normal	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in the shoulder & pelvic girdle • Tenderness with decreased range of motion at shoulder, neck & hip • **Responds** rapidly **to glucocorticoids**	↑	Normal
Inflammatory myopathies	• Muscle pain, tenderness & proximal muscle weakness • **Skin rash** & **inflammatory arthritis** may be present	↑	↑
Statin-induced myopathy	• Prominent muscle pain/tenderness with or without weakness • Rare rhabdomyolysis	Normal	↑
Hypothyroid myopathy	• Muscle pain, cramps & weakness involving the proximal muscles • Delayed tendon reflexes & myoedema • Occasional rhabdomyolysis • **Features of hypothyroidism** are present	Normal	↑

CK = creatine kinase; ESR = erythrocyte sedimentation rate.

GLUCOCORTICOID-INDUCED MYOPATHY

- Acute myopathy associated with high-dose glucocorticoid in critically ill pts is less common than chronic myopathy
- ↑ muscle catabolism and ↓ anabolism as a direct effect of glucocorticoids
- This risk of GIM rises with higher doses of glucocorticoids (generally >40 mg hydrocortisone daily or its equivalent).
- Muscle power ↑ after discontinuation but recovery takes weeks to months

FIBROMYALGIA/ POLYMYOSITIS/ PMR

Condition	Distinguishing clinical features	Laboratory/diagnosis
Fibromyalgia	• Usually **young-to-middle-aged women** • Widespread musculoskeletal **pain** in both sides of body, above & below waist • Fatigue when arising from sleep & mid-afternoon • Cognitive difficulties (eg, attention/tasks requiring rapid thought changes) • Nonspecific gastrointestinal symptoms (eg, diarrhea, constipation)	• **No abnormal laboratory studies** • Possible tender points on physical examination (eg, mid trapezius, lateral epicondyle, costochondral junction) • Symptoms >3 months with increased widespread pain index or symptom severity score
Polymyositis	• Symmetrical proximal **muscle weakness** • Increasing difficulty climbing stairs, getting up from a chair, carrying heavy groceries • Less prominent hip/shoulder involvement	• **Elevated muscle enzymes** (eg, creatine kinase, aldolase, lactate dehydrogenase, aspartate aminotransferase) • Possible autoantibodies • Electromyography abnormal
Polymyalgia rheumatica	• Age usually **>50** • Aching & morning stiffness > pain in shoulders, hips, neck, torso • Synovitis, bursitis, decreased range of motion • No significant muscle tenderness • Possible systemic symptoms	• Clinical diagnosis • Significantly **elevated erythrocyte sedimentation rate** • Symptoms improve with corticosteroids

And greater trochanter

FIBROMYALGIA

- Dx: history and exam findings. Revised 2010 American College of Rheumatology criteria suggest using widespread pain index and symptom severity score rather than trigger points for diagnosis of fibromyalgia→ better address cognitive problems, fatigue and severity of symptoms

Widespread pain index (score 0-19)	Symptom severity scale (0 = no problem, 1 = slight, 2 = moderate, 3 = severe)
• Neck • Jaw (left & right) • Shoulder (left & right) • Upper arm (left & right) • Lower arm (left & right) • Chest • Abdomen • Upper back • Lower back • Hip (left & right) • Upper leg (left & right) • Lower leg (left & right)	• Fatigue (0-3) • Waking unrefreshed (0-3) • Cognitive symptoms (0-3) • Somatic symptoms 0 = none 1 = few 2 = moderate 3 = many Final score between 0-12

- Diagnosis depends on tenderness in at least 11 of 18 defined trigger sites
- **Rx:**
  - Initial fibromyalgia treatment: emphasize patient education (i.e. fibromyalgia is a benign condition with a favorable prognosis), regular aerobic exercise and good sleep hygiene.
  - Pts perceive that their pain and fatigue worsen acutely during or after exercise (e.g. aerobic exercise, strength training, stretching).
  - Gradual and incremental low-impact exercises (eg swimming, fast walking and water aerobics)—improve pain and fatigue and improve long-term benefits. Water exercises can greatly reduce pain
  - Patients who do not respond to conservative measures may require medications. Tricyclic antidepressants for example amitriptyline are preferred first line drugs.
  - Serotonin and norepinephrine reuptake inhibitors (eg Duloxetine, milnacipran) and pregabalin are alternate therapies that may be useful for the patients who do not respond to tricyclic antidepressants.
  - Patients with persistent symptoms may require combination drug therapy, referral for supervised rehabilitation, pain management consultation or cognitive behavioral therapy.

POLYMYOSITIS

Polymyositis	
Clinical presentation	• Symmetrical proximal **muscle weakness** • No/mild pain or muscle tenderness
Diagnostic tests	• **Elevated muscle enzymes** (eg, CK, aldolase) • Autoantibodies (eg, ANA, anti-Jo-1) • **Biopsy**: Endomysial mononuclear infiltrate, patchy necrosis
Associated conditions	• Interstitial lung disease • Myocarditis • **Malignancy**
Treatment	• Systemic glucocorticoids • Glucocorticoid-sparing agents (eg, methotrexate, azathioprine)

CK = creatine kinase; **ANA** = antinuclear a

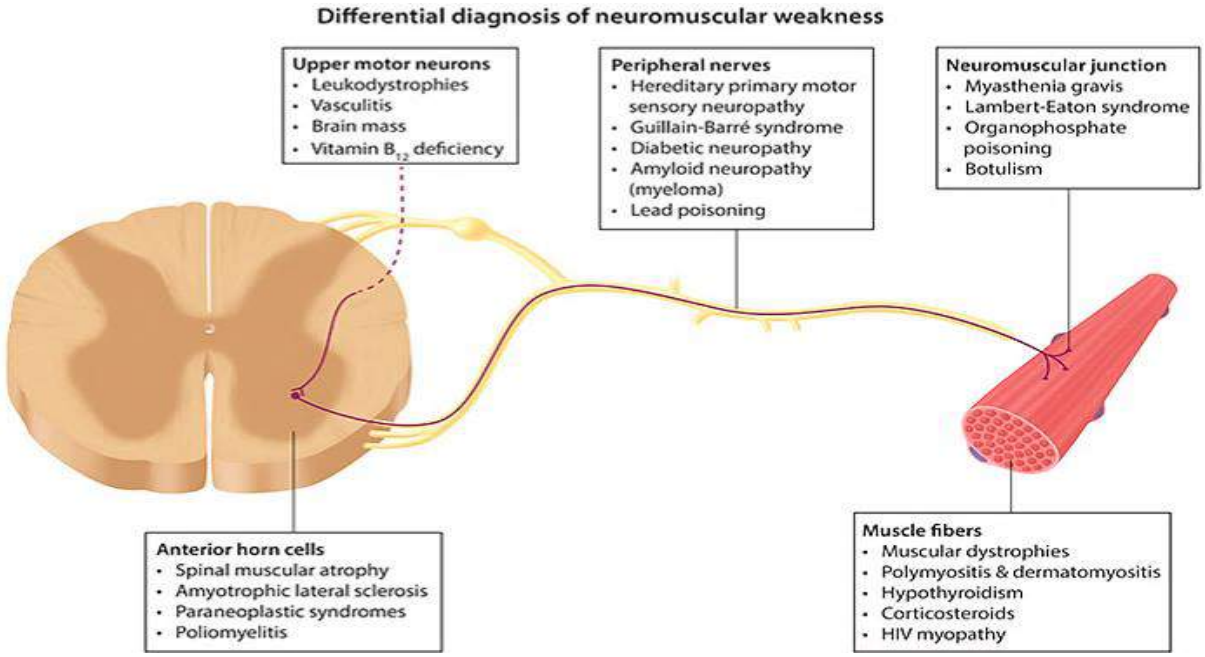
Invariably elevated

Definitive diagnosis—Mononuclear infiltrate surrounding necrotic and regenerating muscle fiber

Careful examination and age-appropriate screening is needed

Chronic disease—require long-term treatment→ high dose steroids are needed for remission

- Inflammatory disease of muscles—slowly progressive proximal muscle weakness of lower extremity (difficulty negotiating stairs or rising from seated position).
- Proximal arm weakness follows→ difficulty working with arms overhead.
- May develop dysphagia due to involvement of striated muscles of upper pharynx
- Mild pain or tenderness may be present but severe pain or lack of muscle weakness should prompt other diagnosis



- Electromyography is used for differentiating polymyositis from other causes of weakness but is non-specific

DERMATOMYOSITIS

Clinical features of dermatomyositis	
Muscle weakness	• Proximal, symmetric • Weakness in UE = LE
Skin findings	• Gottron's papules • Heliotrope rash
Extramuscular findings	• Interstitial lung disease • Dysphagia • Myocarditis

Diagnosis	• ↑ CPK, aldolase, LDH
	• Anti-RNP, anti-Jo-1, anti-Mi2
	• Diagnostic uncertainty
	  ○ EMG
	  ○ Biopsy (skin/muscle)

Management	• High-dose glucocorticoids **PLUS** glucocorticoid-sparing agent • Screening for malignancy

CPK = creatinine phosphokinase; EMG = electromyography;
LDH = lactate dehydrogenase; LE = lower extremity; UE = upper extremity.

Classically proximal extensor muscle inflammatory myopathy

Gottron's papules—pathognomonic
Eruption on chest and lateral neck known as shawl sign

Usually 10 times the upper limit—can lead to myoglobin induced acute kidney injury by causing damage to tubular cells

Regular, age-appropriate screening is essential

- Dermatomyositis 6 times more common in females
- Anti- Jo-1→ anti-synthetase antibody
- Anti-Mi2→ antibody against helicase
- 15% will have or will develop internal malignancy—most commonly: ovarian, pancreatic, lungs, stomach or colorectal cancers, and non-Hodgkin lymphoma

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica	
Clinical features	**Findings**

Symptoms	• Age >50
	• Bilateral pain & morning stiffness >1 month
	• Involvement of 2 of following:
	  ○ Neck or torso
	  ○ Shoulders or proximal arms
	  ○ Proximal thigh or hip
	  ○ Constitutional (fever, malaise, weight loss)

Physical examination	• Decreased active ROM in shoulders, neck & hips
Laboratory studies	• ESR >40 mm/h, sometimes >100 mm/h • Elevated CRP • Normocytic anemia possible • ~20% can have normal studies
Treatment	Response to glucocorticoids

CRP= C-reactive protein; **ESR** = erythrocyte sedimentation rate; **ROM** = range of motion.

Rapid and thorough relief is expected→ failure to improve→ diagnosis in question

- Physical examination is frequently unremarkable with patients having no focal tenderness or pain with active or passive ROM
- Pts have objectively normal muscle strength
- -ve signs of inflammation
- When asked to identify location of pain, patients typically indicate soft tissues and not the joints

CHARCOT JOINTS

Charcot joint (neurogenic arthropathy)	
Associated conditions	• **Vitamin B12 deficiency** • **Diabetes** • Peripheral nerve damage • Spinal cord injury • Syringomyelia • Tabes dorsalis (tertiary **syphilis**)
Clinical manifestations	• **Deformed** joints • Lacking/decreased sensation (proprioception, pain, temperature) with **loss of neurologic input** • Arthritis or arthropathy • **Mild pain** • Fractures (may be unsuspected by patient) • Degenerative joint disease & loose bodies on joint imaging
Management	• Treat underlying condition • Mechanical devices (assist in weight bearing, decrease further trauma) • X-rays (if trauma is present)

Osteophyte and loss of cartilage

- **Pathogenesis:** loss of neurologic input (loss of pain, temp, proprioception)→ repetitive trauma of weight bearing joints→ 2^{o} degenerative joint disease, joint deformation and functional limitation→X-ray: loose bodies, osteophytes and loss of cartilage. In diabetes, vasculopathy also contribute to disease

GOUT

Causes of gout	
Increased urate production	• **Primary gout** (idiopathic) • Myeloproliferative/lymphoproliferative disorders • Tumor lysis syndrome • Hypoxanthine guanine phosphoribosyl transferase deficiency
Decreased urate clearance	• Chronic kidney disease • Thiazide/loop diuretics

Hematologic malignancies and psoriasis

Risk factors for gout	
Increased risk	• **Medications** (eg, diuretics, low-dose aspirin) • Surgery, trauma, recent hospitalization • Volume depletion • **Diet**: High-protein (meat, seafood), high-fat, fructose or sweetened beverages • Heavy **alcohol** consumption • Underlying medical conditions (eg, hypertension, obesity, chronic kidney disease, organ transplant)
Decreased risk	• Dairy product intake • Vitamin C (≥1500 mg/day) • Coffee intake (≥6 cups/day)

Medications that raise (e.g thiazide diuretics, cyclosporine) or lower (e.g allopurinol)

- **Acute flares:** abrupt onset with maximal symptoms in 12-24 hours→ if gradual onset in more time then joint aspiration for cell count, Gram stain and culture done to check for septic arthritis otherwise typical gout flare typically treated- presence of crystals will not rule out septic arthritis as these will be present between attacks (in septic arthritis: cell count >50,000/mm3, Gram stain + → start empiric antibiotic until culture results are known)
- Upto 50,000 cell/mm3—negatively birefringent needle shaped crystals
- **X-ray in chronic gout**: punched out erosions with an over-hanging rim of cortical bone known as a "rat bite lesion"
- Urate lowering medications are not given after 1st attack—given in recurrent attacks and complicated disease (tophi, renal uric acid stones)
- **Allopurinol** inhibits uric acid production and used to prevent gout attacks in pts with hyperuricemia due to PV
- **NSAIDS, Glucocorticoids, or colchicine**—given in acute attack—short term glucocorticoids are also given in pts starting on urate lowering meds to prevent flare-ups—steroids are relatively CI in DM

Prevention of future gout attacks
• Weight loss to achieve BMI <25 kg/m^2 • Low-fat diet • Decreased seafood & red meat intake • Protein intake preferably from vegetable & low-fat dairy products • Avoidance of organ-rich foods (eg, liver & sweetbreads) • Avoidance of beer & distilled spirits • Avoidance of diuretics when possible

Ethanol ↑ uric acid production and ↓ clearance

- **Avoid** food containing fructose and other refined sugars
- **Obesity**, HTN, aspirin, beta blockers, diuretics and DM are risk factors for recurrence of gout
- **Smoking and ↑ coffee intake ↓** risk of gout.

PSEUDOGOUT

Pseudogout (acute calcium pyrophosphate crystal arthritis)	
Symptoms	• Acute mono- or oligoarticular arthritis • Peripheral joints (**knee** most common)
Diagnosis	• Inflammatory effusion (15,000-30,000 cells/mm^3) • **CPPD crystals** (rhomboid shape, positive birefringence) • **Chondrocalcinosis** on imaging
Treatment	• Intra-articular glucocorticoids • Nonsteroidal anti-inflammatory drugs • Colchicine

CPPD = calcium pyrophosphate dihydrate.

Age >65 years

Can affect knees, ankles, upper extremity large joints and may involve multiple joints concurrently

Hard to detect but diagnostic

- Common in hyperparathyroidism with chronic hypercalcemia, hypothyroidism, and hemochromatosis (pseudogout→ look for these causes)
- Acute attacks occur in the setting of trauma/overuse, surgery or medical illness
- Can also cause chronic inflammatory arthritis resembling rheumatoid arthritis and non-inflammatory degenerative arthritis resembling osteoarthritis
- X-ray is also useful for diagnosis→ chondrocalcinosis (indicator of CPPD-calcium pyrophosphate dehydrate crystal deposition disease)

HEREDITARY HEMOCHROMATOSIS

Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk of hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

Type 2 DM and not type 1

- **Dx:** serum iron studies→ confirm with genetic testing
- Liver biopsy generally not done but can be done to stage liver disease or confirm diagnosis if iron studies are suggestive and genetics not positive
- **Rx:** serial phlebotomy to deplete serum iron stores

SECONDARY AMYLOIDOSIS

Clinical features of secondary amyloidosis	
Epidemiology	• Extracellular deposit of insoluble polymeric protein fibrils in tissues & organs, elevated amyloid A • Can be secondary to chronic inflammatory conditions ◦ **Inflammatory arthritis** (eg, rheumatoid arthritis) ◦ **Chronic infections** (eg, bronchiectasis, tuberculosis, osteomyelitis) ◦ **Inflammatory bowel disease** (eg, Crohn's disease) ◦ **Malignancy** (eg, lymphoma) ◦ **Vasculitis**
Clinical presentation	• Asymptomatic proteinuria or nephrotic syndrome • Cardiomyopathy with heart failure • Hepatomegaly • Mixed sensory & motor peripheral neuropathy &/or autonomic neuropathy • Visible organ enlargement (eg, macroglossia) • Bleeding diathesis • Waxy thickening, easy bruising of skin
Diagnosis	• Abdominal fat pad aspiration biopsy
Treatment	• Treatment of underlying condition • Colchicine for prevention & treatment

AUTOIMMUNE HEPATITIS

- Anti-smooth muscle antibodies
- Variety of liver diseases— asymptomatic mildly elevated aminotransferases, acute liver failure and cirrhosis
- Associated with type 1 DM and not type 2.
- Joint complications are less common and cause arthralgia of small joints

WHIPPLE DISEASE

- Multi-system disease characterized by a multitude of possible manifestations.
- S/S: History of chronic malabsorptive diarrhea (steatorrhea, flatulence, abdominal distention), protein losing enteropathy, weight loss, migratory non-deforming arthritis, lymphadenopathy and a low-grade fever.
- Can cause damage to the eye, CNS and myocardium.
- Caused by infection with gram positive bacillus Trophyrema whippelii—unknown mechanism of transmission

- Dx: small intestinal biopsy and PCR in patient with clinical symptoms consistent with the disease. Biopsy→PAS+ve macrophages in the lamina propria containing non acid-fast gram positive bacillus

PAGET'S DISEASE OF BONE

Paget disease of bone	

Clinical features	• Most patients are asymptomatic
	• Bone pain & deformity
	  ○ **Skull:** Headache, hearing loss
	  ○ **Spine:** Spinal stenosis, radiculopathy
	  ○ **Long bones:** Bowing, fracture, arthritis of adjacent joints
	• Giant cell tumor, osteosarcoma

Pathogenesis	• Osteoclast dysfunction • Increased bone turnover
Laboratory testing	• Elevated **alkaline phosphatase** • Elevated bone turnover markers (eg, PINP, urine hydroxyproline) • Calcium & phosphorus are usually normal
Imaging	• X-ray: Osteolytic or mixed lytic/sclerotic lesions • **Bone scan**: Focal increase in uptake
Treatment	• **Bisphosphonates**

PINP = procollagen type I N propeptide.

Frontal bossing, cranial nerve dysfuncion

Also affects pelvis and clavicle

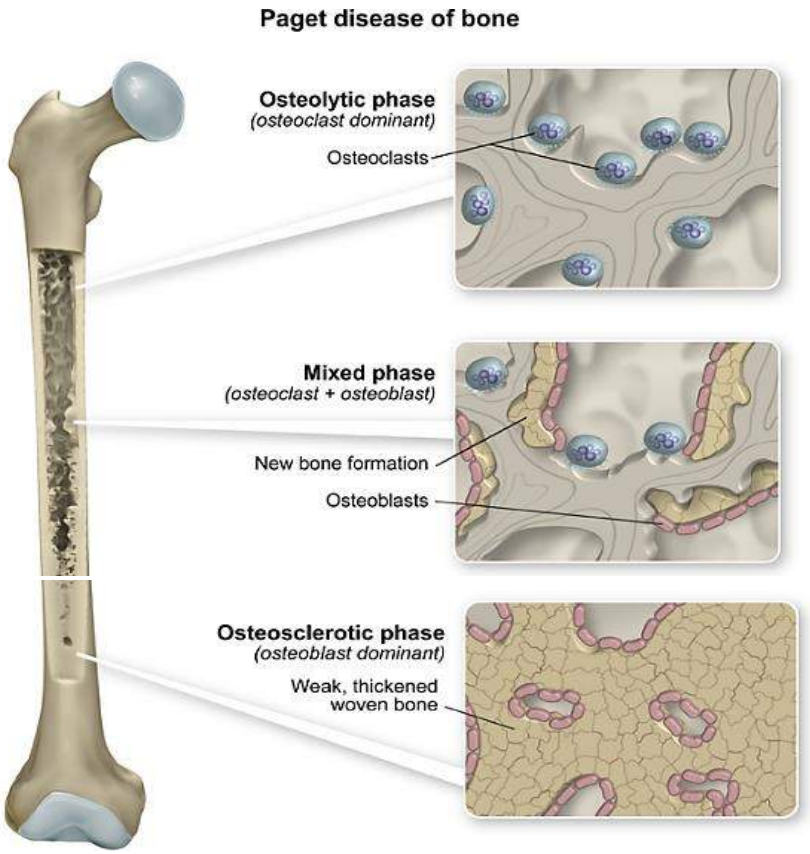
Serum calcium normal in the absence of other risk factors like prolonged immobility and hyperparathyroidism but urine calcium may be ↑

Cortical thickening

Radionuclide bone scan is used to fully stage the disease

Inhibit osteoclast function and decrease bone turnover

- **Alkaline phosphatase:**
  - Ubiquitous enzyme—highest expression in bone and hepatobiliary tissue. Useful marker of cholestatic liver disease (not hepatocellular in which there is elevation of transaminases) and diseases of bone causing increased bone turnover.
  - Most common cause of isolated, asymptomatic elevation of alkaline phosphatase in an elderly patient is **Paget disease of bone (osteitis deformans)**
  - Most commonly incidentally discovered on routine blood test, and alkaline phosphatase level can be strikingly elevated, often > 10 times upper limit of normal
  - Fractionation of alkaline phosphatase→ predominance of bone rather that liver isoenzymes
- Asymptomatic pts with minimal disease activity (incidental discovery of mildly ↑ alkaline phosphatase)—may be left untreated and observed
- Symptomatic pts and those with high-risk bone involvement (like skull and weight bearing long bones)—should be treated to ↓ pain and risk of complications



OSTEITIS FIBROSA CYSTICA

- Osteitis fibrosa cystica (Von Recklinghausen disease of bone)
- Presents with bony pain, is characterized by excessive osteoclastic resorption of bone, leading to replacement with fibrous tissue (brown tumors).
- Very rare
- Seen primarily in patients with parathyroid carcinoma. It can also occur in primary and secondary/tertiary (advanced renal disease) hyperparathyroidism.

INFECTIOUS ARTHRITIS

VIRAL ARTHRITIS

- Can present similar to RA. RF (+ve in RA, viral and bacterial arthritis and also in normal individuals) and ANA (sensitive for SLE, but may be positive in RA, HIV, hepatitis and normal individuals) may also be positive.
- Symmetric inflammatory arthritis that resolves in 2 mo is viral arthritis
- Causative organisms: parvovirus, hepatitis, HIV, mumps and rubella among many others
- Rx: NSAIDS for resolution of symptoms

LYME DISEASE

Stage	Clinical manifestations of Lyme disease
Early localized (days-1 month after tick bite)	• **Erythema migrans** (80% of patients) • Fatigue, malaise, lethargy • Mild headache & neck stiffness • Myalgias & arthralgias

Early disseminated (weeks-months after tick bite)	• **Carditis** (5% untreated patients)
	  ◦ Atrioventricular block, cardiomyopathy
	• **Neurologic** (15% untreated patients)
	  ◦ Unilateral or bilateral cranial nerve defects (usually VII), meningitis, encephalitis
	• **Muscular** (60% untreated patients): Migratory arthralgias
	• **Conjunctivitis** (10% untreated patients)
	• **Skin**: Multiple erythema migrans
	• Regional or generalized lymphadenopathy

Late or chronic (months-years after tick bite)	• **Muscular** (60% untreated patients): Arthritis • **Neurologic**: Encephalomyelitis, peripheral neuropathy

Can be monoarticular and oligoarticular—knee is most commonly involved joint—synovial fluid shows inflammatory profile→av. Leukocyte count 25,000 cells/uL. Diagnosis of Lyme arthritis confirmed by ELISA and Western blot→ Rx: oral doxycycline or amoxicillin in the absence of other manifestations of Lyme dis.

- Most prevalent in northeastern and upper mid-western states of US

OSTEOMYELITIS

- Fever, malaise, localized joint pain and swelling
- Chronic osteomyelitis: central lytic bone defect with surrounding sclerosis termed as Brodie's abscess

GONOCOCCAL ARTHRITIS

Disseminated gonococcal infection	
Clinical presentation	• Purulent arthritis without skin lesions **OR** Triad of: • Tenosynovitis (eg, wrist, ankles, fingers & knees) • Dermatitis (pustules, macules, papules & bullae) • Migratory asymmetric polyarthralgia without purulent arthritis
Diagnosis	• Blood cultures (2 sets) but may be negative • Synovial fluid analysis may show up to 50,000 cells/mm^3 • Urethral, cervical, pharyngeal or rectal cultures • Recommend HIV & syphilis screen • Recurrent DGI: check terminal complement activity
Treatment	• IV ceftriaxone 1 g/day for 7-14 days, switch to PO (cefixime) when clinically improved • Joint drainage for purulent arthritis • Empiric azithromycin (single 1-g dose) OR doxycycline for 7 days for concomitant chlamydial infection • Treat sexual partners

DGI = disseminated gonococcal infection; **HIV** = human immunodeficiency virus; **IV** = intravenous; **PO** = orally.

Nucleic acid amplification test

Or cefotaxime

- Septic arthritis in sexually active young adult is gonococcal arthritis until proven otherwise
- Gram stain of synovial fluid (+ve in25% cases), blood cultures (positive in 20-50% cases) and genital/ pharyngeal NAAT (+ve in 90% cases)→ used to confirm diagnosis

ARTERITIS

GIANT CELL ARTERITIS

Giant cell arteritis – clinical manifestations	
Systemic symptoms	• Fever, fatigue, malaise, weight loss
Localized symptoms	• **Headaches**: Located in temporal areas • **Jaw claudication**: Most specific symptom of GCA • **PMR** • Arm claudication: Associated bruits in subclavian or axillary areas • Aortic wall thickening or aneurysms • CNS: TIAs/stroke, vertigo, hearing loss
Visual symptoms	• Amaurosis fugax: Transient vision field defect progressing to monocular blindness • **AION**: Most common ocular manifestation
Laboratory results	• Normochromic anemia • Elevated **ESR** & CRP • Temporal artery biopsy
Treatment	• **PMR only**: Low-dose oral glucocorticoids (eg, prednisone 10-20 mg daily) • **GCA**: Intermediate- to high-dose oral glucocorticoids (eg, prednisone 40-60 mg daily) • **GCA with vision loss**: Pulse high-dose IV glucocorticoids (eg, methylprednisolone 1000 mg daily) for 3 days followed by intermediate- to high-dose oral glucocorticoids

Diminished pulses and/or bruits over axillary, brachial or femoral arteries and over supraclavicular and/or carotid areas

Follow by serial chest X-rays

Fundoscopy: swollen & pale disc with blurred margins

With a slow taper over several months

AION = anterior ischemic optic neuropathy; **CNS** = central nervous system; **CRP** = C-reactive protein; **ESR**= erythrocyte sedimentation rate; **GCA** = giant cell arteritis; **PMR** = polymyalgia rheumatica; **TIA** = transient ischemic attack.

Aortic aneurysm can happen in ppl with GCA.
UW:4460

TAKAYASU ARTERITIS

Takayasu arteritis	
Risk factors	• **Female** • Asian • Age 10-40
Symptoms	• Constitutional (eg, fever, weight loss) • **Arterio-occlusive** (eg, claudication, ulcers) in upper extremities • Arthralgias/myalgias
Examination findings	• Blood pressure discrepancies • Pulse deficits • Arterial bruits
Diagnosis	• Elevated inflammatory markers (eg, ESR, CRP) • Chest x-ray: Aortic dilation, widened mediastinum • **CT/MRI**: Wall thickening, narrowing of lumen
Treatment	• Systemic glucocorticoids

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

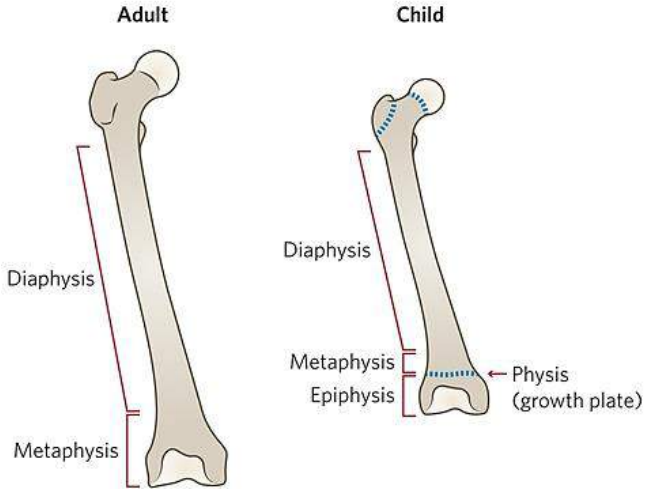
- Mononuclear infiltrates and granulomatous inflammation of vascular media→arterial wall thickening with aneurysmal dilation or narrowing and occlusion
- Initially non-specific symptoms—later arterio-occlusive symptoms develop
- Pts commonly have anemia

VASCULAR TUMORS

GLOMUS TUMORS

- Common benign vascular tumor
- Triad of: severe intermittent pain, tenderness and sensitivity to touch
- Subungual in 70% cases, other sites palm and wrist
- Common in fourth decade. Females> males

BONE TUMORS



OSTEOID OSTEOMA

- Benign bone forming tumor
- Common in adolescents and early adulthood esp. males
- Most commonly affects proximal femur, may also involve other long bones and spine
- **Sx**: increasing pain that worsens at night. No association with physical activity. Pain relieved by NSAIDS and strongly suggests diagnosis
- **PE: Children:** focal tenderness, swelling or deformities
- **PE: Adolescents:** often no focal findings on exam
- **Xray:** typical small, round, lucency with sclerotic margins and sometimes central ossification
- **Rx:** NSAIDS for symptomatic relief and serial examination and xray every 4-5 months to monitor lesion. Surgical resection reserved for those with refractory symptoms
- Most lesions resolve spontaneously over several years

OSTEOSARCOMA

- Most common primary tumor affecting children and young adults—boys b/w 13-16 yo are at higher risk
- **Location:** frequently occur at metaphysis of long bone such as distal femur, proximal tibia and proximal humerus
- **S/S:** Chronic localized pain. Constitutional Sx like weight loss, fever and malaise—usually absent
- **PE**: palpable tender soft-tissue mass
- **X-ray:** destruction of normal bone pattern with indistinct margins and a mixture of radiodense and radiolucent areas. Characteristic spiculated "sunburst" pattern and periosteal elevation known as Codman triangle
- **Labs:** ↑ alkaline phosphatase and lactate dehydrogenase—from turnover of damaged osteocytes—high levels=worse prognosis. ↑ ESR—non-specific marker of inflammation
- **Rx:** tumor excision and chemotherapy

EWING SARCOMA

- Highly malignant—early metastasis to lungs and lymph nodes
- Affects long bones of extremities. Lower limb> upper limb. Most commonly metaphysis and diaphysis of femur, followed by tibia and humerus

- Usually in white males in 1st/2nd decade of life (adolescent males)—rare, but 2nd most common primary bone tumor
- **S/S:** Pain and swelling for many weeks/months, deformity, erythema and warmth of local area sometimes seen→ misdiagnosed initially as osteomyelitis because of intermittent fever, leukocytosis, anemia and ↑ ESR. Cause extensive involvement of affected bone. Systemic symptoms in 20% pts
- May demonstrate multiple layers of new subperiosteal bone formation
- **Radiographs:** lamellated appearance or "onion skin" periosteal reaction—usually lytic, central and accompanied by endosteal scalloping→ followed with moth-eaten or mottled appearance and extension into soft tissue
- **Rx:** radiation, surgery, and multi-drug chemotherapy. Radiation and chemotherapy used preoperatively

CHONDROSARCOMA

- Occur in fifth or sixth decade of life
- People with multiple endochondromas and hemangiomas are at higher risk than general population
- Xray→ fusiform defect with scalloping

FIBROSARCOMA

- Malignant spindle cell neoplasm in 30-60yo
- Clinical picture: painful mass
- X-ray: osteolytic lesion whose margins are well-defined or ragged and moth-eaten

GIANT CELL TUMOR OF BONE

- Benign and locally aggressive seen in young adults
- S/S: pain, swelling, ↓ ROM around affected joint. 10-35% experience pathologic fractures due to thinning of bone cortex in weight bearing areas
- X-ray: typically present on xray of epiphyseal region of long bone, most commonly distal femur and proximal tibia. Show expansile and eccentric lytic areas
- MRI: show both hemorrhagic and cystic regions
- Pathology: sheets of interspersed large osteoclast giant cells that appear as round to oval polygonal or elongated mononuclear cells
- Treatment: surgery (eg intralesional curettage with or without bone grafting)—first line of GCTB

SCREENING STUDIES

OSTEOPOROSIS

Osteoporosis risk factors

- Advanced age
- Medical history of fracture with minimal trauma (fragility fracture)
- Low body weight (<58 kg [127 lb])
- Family history of hip fracture
- Current smoking
- Excessive alcohol intake
- Medications (eg, steroids, anticonvulsants)
  - Secondary causes of osteoporosis
  - Premature menopause
  - Hypogonadism
  - Malabsorption (celiac disease)
  - Inflammatory disorders (eg, inflammatory bowel disease, rheumatoid arthritis)
  - Hyperthyroidism & hyperparathyroidism
  - Cushing syndrome
  - Vitamin D deficiency
  - Chronic liver or renal disease

MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS
Hormonal factors like low estrogen	Female gender
Malnutrition	Advanced age
↓ calcium	Small body size
↓ vitamin D	Late menarche or early menopause
Meds like glucocorticoids or anticonvulsants	Caucasian/Asian ethnicity
Immobility (weight bearing exercise is preventive)	FH of osteoporosis
Cigarette smoking	
Excess alcohol intake (dose-dependent ↑ in risk of osteoporotic fracture—significantly ↑ risk if > 2 drinks/day)	
Strict vegan vegetarian diet (as it does not contain calcium in contrast to lacto-ovo vegetarian diet—includes foods fortified with calcium such as dairy products, orange juice, cereals and whole grains)	

- One time DEXA screening for osteoporosis in **all women >/=65 yo and younger pts who have other risk factors for osteoporosis.** Most significant risk factor in US is post-menopausal state
- **Interpretation of DEXA scan (of hip and spine):**
  - **>2.5 SD below mean (ie. T-score <-2.5)** for a young adult at peak bone density→significant fragility and risk of fracture
  - **1-2.5 SD below mean (ie T-score -1 to -2.5)→** osteopenia
- **Rules for follow-up DEXA and screening** are not well-established

PAP SMEAR:

- ↓ the risk of cervical cancer in young and middle-aged women
- Risk of cervical cancer ↓ with age. Women >65 or those who have cervix removed for reason other than cancer→ no need of further pap smear

COLONOSCOPY

- Start at 50 in ppl with normal risk and repeated every 10 years unless there is evidence of polyp
- Pt with high-risk polyp→ follow-up colonoscopies every 3-5years

CT CHEST

- X-ray does not ↓ mortality in pts with high risk of lung cancer
- Low-dose CT has shown to ↓ lung cancer related mortality in high-risk pts

PHARMACOLOGY

MEDICINES	USES	SIDE EFFECTS
Cisplatin, carboplatin	Treat ovarian, testicular, bladder cancer	Cochlear dysfunction
Aminoglycosides		Cochlear dysfunction
Cyclophosphamide		Acute hemorrhagic cystitis, bladder cancer, sterility, myelosuppression
Hydroxychloroquine		Optic neuritis
Ethambutol		Optic neuritis
Phenytoin, isoniazid, vincristine, heavy metals, chronic alcoholism		Peripheral neuropathy
Beta blockers, ergotamine		Digital vasospasm (Raynaud's)
Amiodarone, lithium		Thyroid dysfunction
Cyclosporine		Gout

Contents

RHEUMATOLOGY/ORTHOPEDICS & SPORTS-PAEDS

RADIAL HEAD SUBLUXATION (NURSEMAID'S ELBOW)

Radial head subluxation (nursemaid's elbow)	
Mechanism	• **Axial traction** on forearm with elbow extended (child pulled, lifted, or swung by arm)
Physical examination findings	• Arm held **extended & pronated** • No swelling, deformity, or focal tenderness
Treatment	• Supination of forearm & flexion of elbow **OR** • **Hyperpronation** of forearm

Attempted forearm supination→ child will resist and cry out in pain but otherwise usually not in distress

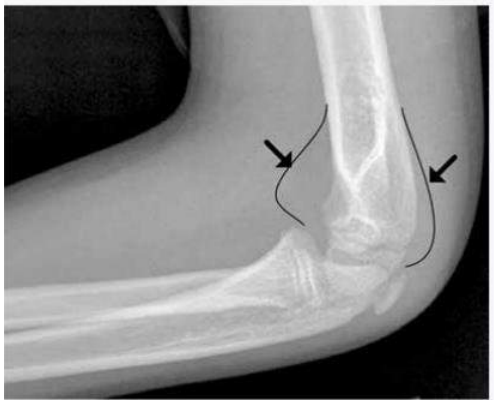
Also commonly performed but may be less successful

Pop may be heard on successful reduction

- Common in 1-5 yo children
- Response to treatment is also diagnostic
- No post-reduction films are needed when patient resumes full use of extremity

SUPRACONDYLAR FRACTURE OF HUMERUS

- Elbow fractures—almost 50% fractures of children
- Most common type is supracondylar fracture of humerus
- Commonly in ages 2-12 yo
- After a fall on outstretched arm with elbow extended
- Xray usually show large triangular anterior fat pad (lucency) and posterior fat pad (lucency)



- May be complicated by neurovascular injury or compartment syndrome
- Neurovascular injury→ frequently monitor pulses
- Compartment syndrome→ progressively increasing pain esp. with increasing swelling→ remove any bandage, measure compartment pressure and emergent orthopedic evaluation for possible fasciotomy

GROWING PAINS

- Growing pains are a common musculoskeletal complaint in children, occurring in approximately 10% to 30% of children aged 2 to 12 years.
- Unknown etiology, but they are unrelated to growth despite their name
- Diagnosis—clinically made in the absence of the systemic symptoms and abnormal examination findings.
- Laboratory studies and radiographs—not necessary

Growing pains	
Clinical features	• Occurs primarily at **night** & resolves by morning • Affects **lower extremities** (eg, thighs, calves), usually **bilateral** • **Normal** physical examination & activity
Treatment	• Parental education & reassurance • Massage, stretching exercises, heat & analgesics

- Followed closely to monitor for pain that increases in frequency or intensity, which may warrant further evaluation
- Children with Growing Pains often have a lower pain threshold and more depressive symptoms when compared to other children, but psychiatric evaluation is not required for these patients

CLUBFOOT/ TELIPES EQUINOVARUS

Definition:

- Equinus and varus of calcaneum and talus, varus of midfoot and adduction of forefoot

Etiology:

- **Congenital—**usually isolated and idiopathic
- **Teratogenic—**associated with neuromuscular disorder or a complex syndrome
- **Positional—**abnormal positioning of affected foot in utero

Treatment:

- **Immediate** non-surgical methods like stretching and manipulation of foot, followed by serial plaster casts, malleable splints or taping→ unsatisfactory response→ surgical repair preferably between 3-6months of age but always before 12 months
- Majority cases respond to conservative management without surgical repair
- Untreated cases→ further deformation, gait abnormality and development of ulceration

METATARSUS ADDUCTION

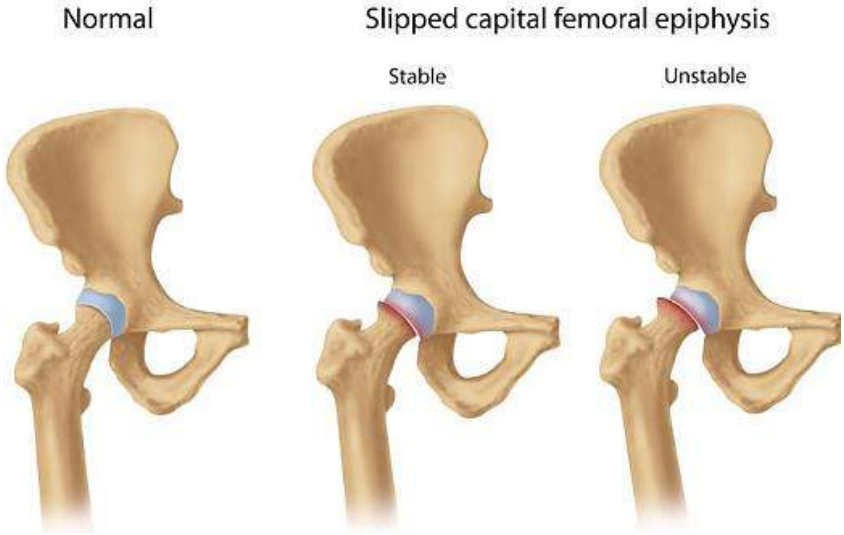
- Congenital foot deformity—common in 1st born child. No sexual predominance
- Adduction at tarsometatarsal joint and ↑ angle between 1st and 2nd metatarsals
- 10% cases associated with acetabular dysplasia; hence careful hip examination required
- **Three types:**

- **Type I:** mild metatarsus adduction characterized by feet that cause over-correction both passively and actively into abduction→ spontaneously correct themselves and do not need treatment
- **Type II:** that correct in to neutral position by passive or active movement→ Rx: orthotosis or corrective shoes, and sometimes plaster casts if initial treatment gives no result
- **Type III:** rigid feet and do not correct→Rx: managed with serial casts

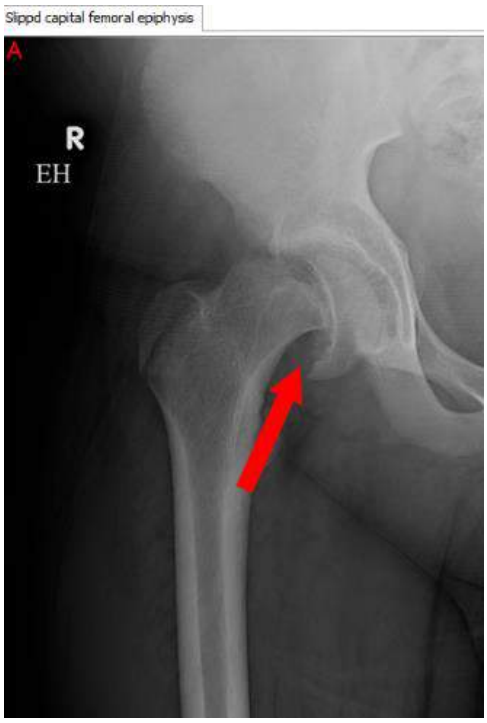
- Surgical correction may be needed if significant residual metatarsus adductus in 4yo

→ **Internal tibial torsion** is also a physiologic finding in newborns and spontaneous correction occurs in 95% cases

SLIPPED CAPITAL FEMORAL EPIPHYSIS

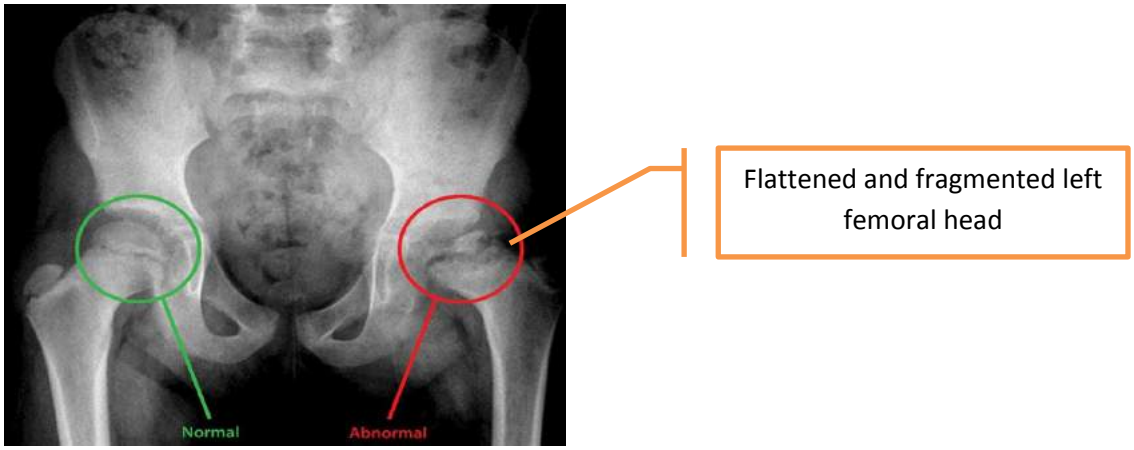


- Displacement of femoral head on femoral neck due to disruption of proximal femoral growth plate
- Typically in **obese** children 10-16 yo. The mean age of presentation is 12 years in girls and 13.5 years in boys. > in adolescent boys than girls.
- Physis (i.e. physical junction between femoral head and neck weakens during early adolescence due to rapid growth—it is cartilage and not as strong as bone—obesity worsens stress→ physis fracture and femoral disc slips
- Additional risk factors: endocrinopathies (eg hypothyroidism, growth hormone def.), renal failure and radiation history→ mostly b/l disease at early age
- **S/S:** insidious onset dull hip pain or referred knee pain and altered gait/limping with no preceding trauma. Minor trauma can sometimes exacerbate the pain
- **High degree of suspicion as knee pain (referred pain) and not hip pain is the common presentation with this condition**
- **PE:** pt holds affected leg in passive external rotation and loss internal rotation, abduction and flexion as well as external rotation of thigh when hip is being flexed
- **Dx:** plain radiograph of hip in AP and frog-leg lateral view→ posteriorly and inferiorly/medially displaced femoral head in relation to femoral neck—both hips should be imaged for comparison and contralateral displacement
- **Rx:** immediate surgical screw fixation at current degree of displacement to avoid avascular necrosis and chondrolysis

- 

LEG CALVE PERTHES DISEASE

- **Etiology:**
  Idiopathic avascular necrosis of femoral head. Can be due to thrombophilia in some patients
  Commonly affects boys 4-10 years. Peak incidence is at 5 and 7 years
- **S/S:**
  Mild, chronic hip or knee pain of insidious onset as well as antalgic gait (shorter time weight bearing on affected side due to pain)
- **PE:**
  As the disease progresses→ abduction and internal rotation markedly ↓. Proximal thigh atrophy may also be present
- **Dx:**
  Requires high index of suspicion as initial x-rays may be negative leading to initial diagnosis of transient synovitis which may occur after viral infection but resolve in 1-4 wks
  Persistent symptoms→ repeat imaging as it can take months for concerning changes to appear on xray



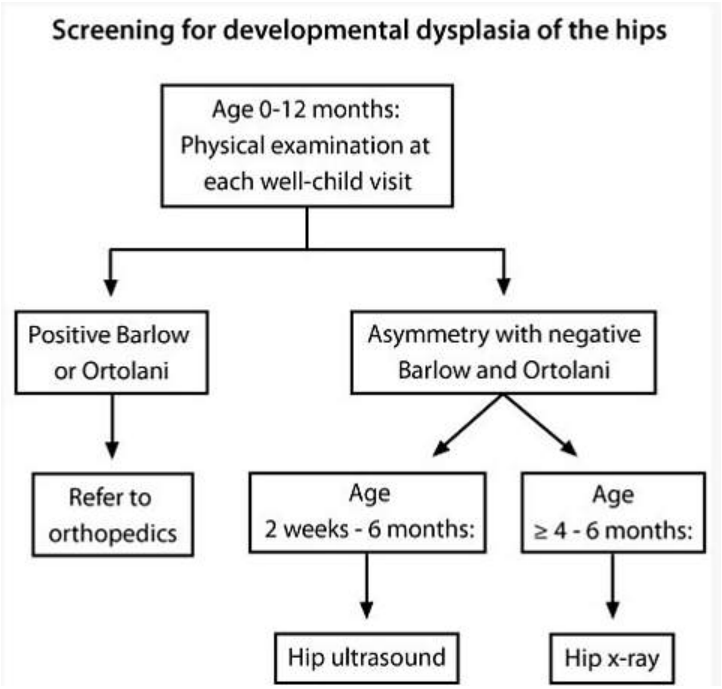
MRI and bone scans can show subtle femoral head necrosis weeks to months earlier than x-ray→ early diagnosis

- **Treatment:**
  In general, these patients are managed conservatively with observation and bracing, the surgery may be indicated in cases where the femoral head is not well contained within the acetabulum. Pt should refrain from weight-bearing exercises

HIP DYSPLASIA

- Abnormal development in utero
- Obvious at birth or may be noticed later when limp is noted
- Leg length discrepancy
- Overtime it can progress to degenerative joint disease
- X-ray: poorly formed femoral head

DEVELOPMENTAL DYSPLASIA OF HIP

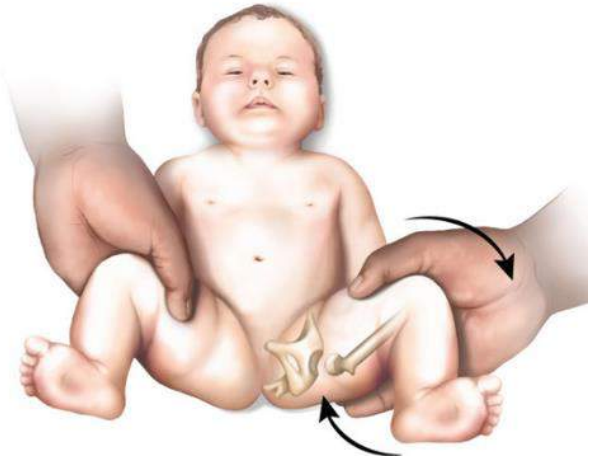


- **Developmental dysplasia of the hip**—dislocation of femoral head from the acetabulum.
- Early diagnosis is critical as treatment initiation before the age six months protends favorable prognosis. Delayed diagnosis is one of the most common reasons for malpractice suits against pediatricians due to **potential complications** such as limp (Trendelenburg gait), scoliosis, arthritis, and avascular necrosis.
- Risk factors: breech presentation, female sex, white ethnicity, and family history of developmental dysplasia of the hip increase the risk, most patients approximately 75% have no risk factors. Therefore, all infants must have serial hip examinations from birth until they are walking (~1year)
- **Barlow and Ortolani maneuvers** should be performed to assess joint stability. This consists of placing the infant supine with each hip flexed to 90 degrees followed by abduction to feel for dislocatability and adduction to feel for reducibility of an unstable joint. A **palpable clunk** with

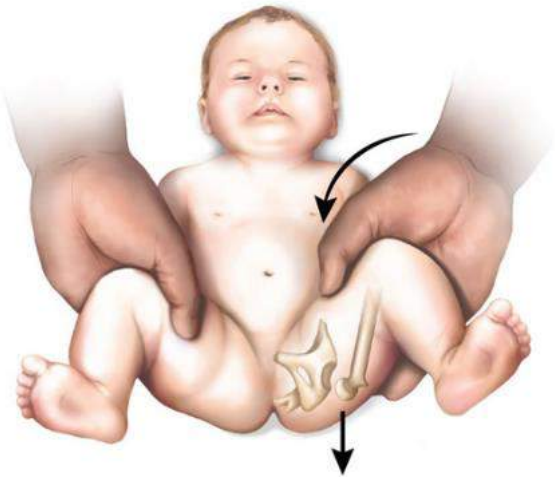
either maneuver is alarming sign of hip dislocation and should prompt referral to an orthopedic surgeon. Equivocal signs such as a soft click, leg length discrepancy, or asymmetric inguinal skin fold suggest possible hip laxity.

- Hip laxity that is present at birth usually resolves by age 2 weeks. Therefore, imaging is not recommended until >/=2 weeks. Infants age 2 weeks-6 months with abnormal examination should undergo ultrasonography. Developmental dysplasia of hip is bilateral in approximately 20% of patients and thus, both sides should be imaged. X-ray is not helpful until Age 4 to 6 months because the femoral head and acetabulum are not yet ossified. After ossification, x-ray is better at showing acetabular development and positioning.

Barlow & Ortolani maneuvers

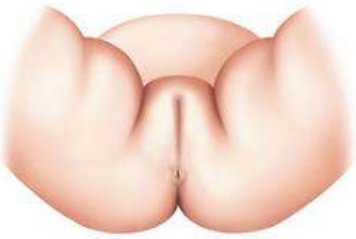


Ortolani Maneuver:
Abduction with anterior lifting of the hip

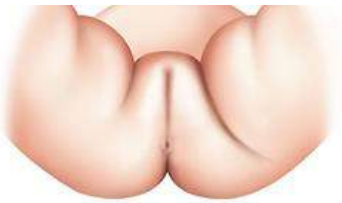


Barlow Maneuver:
Adduction with posterior pressure on the hip

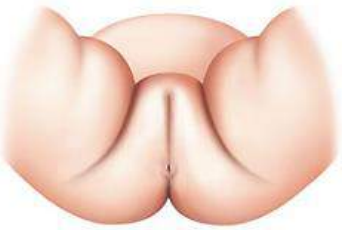
Developmental dysplasia of the hip - asymmetric inguinal folds



(A) Normal inguinal folds do not extend beyond the anal aperture



(B) The inguinal fold on the left extends beyond the anal aperture, suggesting possible developmental dysplasia of the left hip



(C) The inguinal folds on both sides extend beyond the anal aperture, suggesting bilateral developmental dysplasia of the hip

- A positive Barlow and ortolani test or abnormal Imaging results→ prompt referral for treatment. The Pavlik harness is a splint that holds the hip in flexion and adduction while preventing extension and abduction, which can exacerbate dislocation. It is the treatment of choice age less than six months as most hip joints are able to remain in a stable position. After age 6 months, however, the harness is far less successful and reduction under anaesthesia is required. CT and MRI can be helpful in perioperative assessment of affected hip but unnecessary for initial screening.

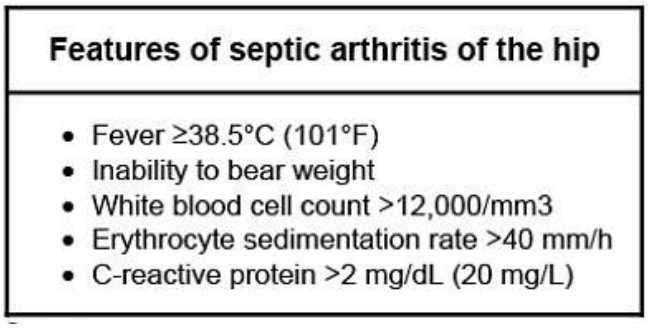
The Pavlik Harness

FEMORAL NECK STRESS FRACTURE

- In athletes and runners
- Gradual ↑ in hip pain esp with activity
- Pain in passive ROM, esp external and internal rotation

TRANSIENT SYNOVITIS

- Most common cause of hip pain in children, typically occurring in boys age 3 to 10 years.
- Cause unknown but usually follows viral infection or mild trauma.
- Synovial inflammation→ pain, decreased ROM and limping
- **Examination**: the affected hip is typically flexed, slightly abducted and externally rotated. This position maximizes the joint space, and thereby providing some pain relief. Able to bear weight
- Perform labs to differentiate from septic arthritis and assess severity of information. In contrast to septic arthritis, children with transient synovitis rarely have fever or significant laboratory abnormalities



- Ill- appearing, febrile child with >3 or 4 of the findings shown in the table→ immediate arthrocentesis and IV antibiotics.
- Obtain plain radiographs to exclude bony lesions, fractures, and Legg Calve Perthes disease→ AP and frog-leg lateral view of both hips should be obtained to compare both sides for subtle changes
- No additional work-up unless symptoms are persistent or worsening
- Rx: rest and NSAIDS except aspirin→ follow-up after 1 wk
- Usually recover within 1-4 wks without complications→ persist or worsen→ reconsider LCP→ perform MRI

PAUCI-ARTHRITIS

- Pauci-arthritis or pauci-articular onset juvenile idiopathic arthritis is the most common subgroup of juvenile idiopathic arthritis.
- Serum antinuclear antibodies are usually the only abnormality.
- Although pauciarthritis can present with a morning limp, its typically occurs in a female toddlers and really involves the hip.

RICKETS

Vitamin D deficiency rickets	
Risk factors	• **Increased skin pigmentation** • **Exclusive breastfeeding** • Inadequate sun exposure • Maternal vitamin D deficiency

Clinical manifestations	• Craniotabes ("ping-pong ball" skull)
	• Delayed fontanel closure
	• Enlarged
	  • Skull (frontal bossing)
	  • Costochondral joints (**"rachitic rosary"**)
	  • Long-bone joints (wrist widening)
	• **Genu varum**

X-ray features	• Osteopenia • Metaphyseal cupping & fraying • Epiphyseal widening
Serum laboratory findings	• Calcium: Normal to ↓ • Phosphorous: Normal to ↓ • Alkaline phosphatase: ↑↑ • Parathyroid hormone: ↑ • 25-OH vitamin D: ↓

- Although breast feeding is the gold standard nutrition <1year but exclusive breast feeding or homemade nutrition are inadequate in vitamin D if child is not taking fortified baby food or formula→ given vitamin D 400 IU daily to prevent rickets
- Rx of rickets: vitamin D repletion with 1000-2000 IU daily

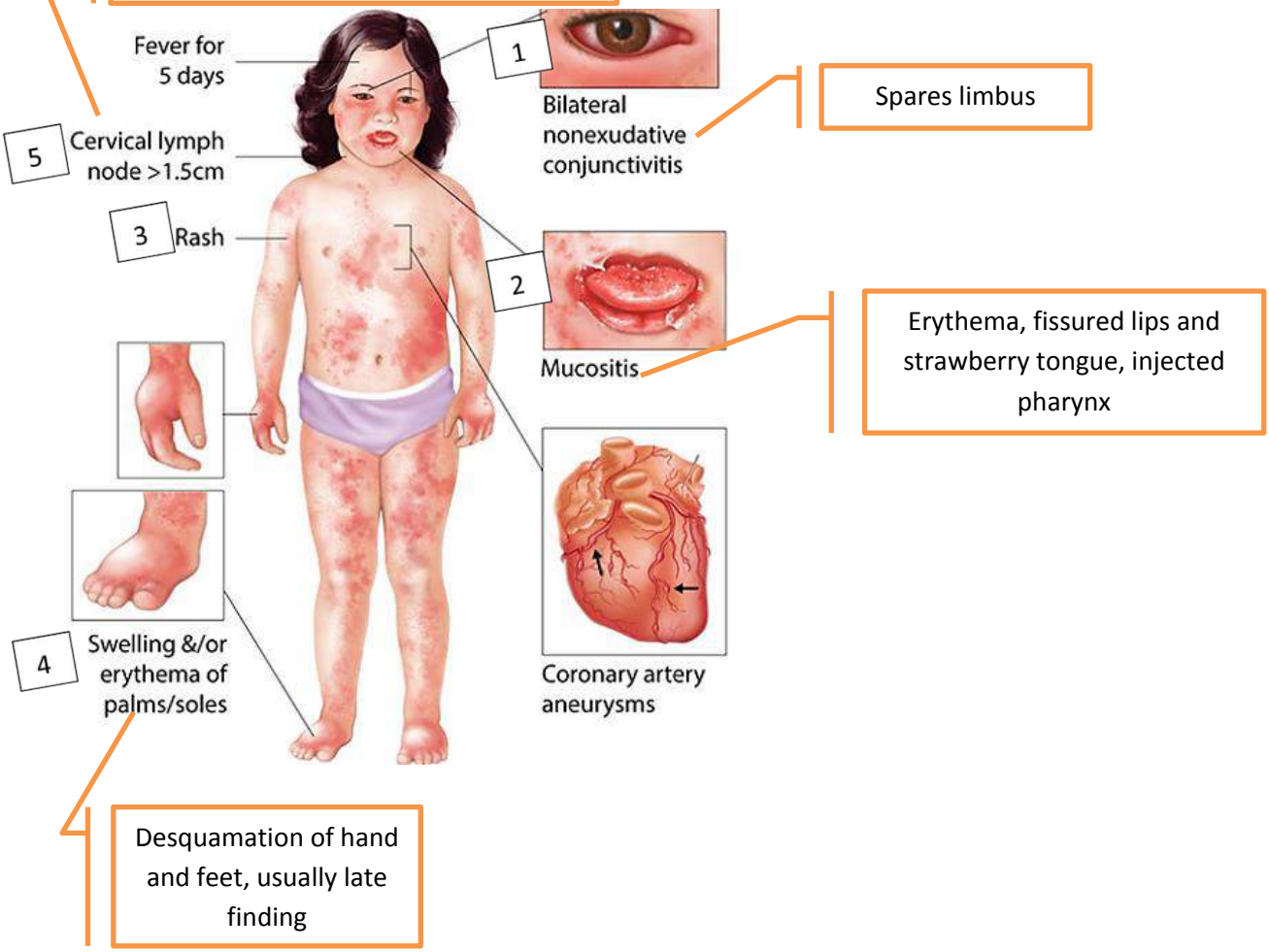
OSTEOGENESIS IMPERFECTA

- Most commonly inherited from autosomal dominant mutation of COL1A1
- Varying spectrum of severity: mild (type I), moderate (type III-IX) to fatal perinatal (type II)
- Suspect in anyone with blue sclera
- Other manifestations depend on severity of disorder: recurrent fractures, easy bruisability, hypotonia and hearing loss—normal intelligence
- Dentinogenesis imperfecta→ in many pts→ blue-gray to yellow brown discolored dentin shining through translucent and weak enamel—both primary and permanent teeth are affected

KAWASAKI DISEASE

- Acute vasculitis of small and medium sized vessels
- Peak age 18-24 months and almost all cases <5years and rarely in adults—greatest among East Asian ethnicity

- Persistent release of proinflammatory cytokines→ prolonged high fever—minimally responsive to antipyretics, irritability and systemic inflammation
- Diagnosis on clinical grounds. Fever for >/= 5 days and any 4 of 5 of the following:
-



- **Pts with atypical presentation→** support with following labs:
  - Elevated CRP and ESR
  - Leukocytosis with neutrophilia (as opposed to lymphocytosis in viral infections)
  - Reactive thrombocytosis
  - Sterile pyuria on urine analysis
- **D/D:**
  - **Scarlet fever:** similar presentation including fever, rash, strawberry tongue and cervical LAD, but **ocular manifestations uncommon, pharyngitis** more common and **sand paper rash that spares palms and soles**
  - **Staphylococcal scalded skin syndrome:** more common in **newborns**→ fever, rash, irritability→ diffuse erythema typically begins around mouth and spreads rapidly throughout body→ **flaccid blisters 1-2 days later in flexural areas and +ve Nikolsky's sign**
  - **Hand, foot and mouth disease:** fever, vesicles in oral mucosa and tongue, small, tender and cutaneous lesions on palms and soles. Caused by Coxsackie virus. **Self-limited in 2-3 days**
- **Rx:**

Aspirin plus IV immunoglobulin—preferably started within 10 days of symptom onset to prevent complications. Systemic inflammation resolves in 12 days if untreated but can lead to CV complications. Echo performed at the time of diagnosis and repeated 6-8 wks later to look for changes that may require close monitoring and prolonged therapy

- **Complications:**
  Coronary artery aneurysm
  Myocardial ischemia and infarction

ACQUIRED TORTICOLLIS

- Torticollis—also known as wryneck→ neck twisting due to asymmetric muscle activity
- **Most common causes:** upper respiratory infections, minor trauma, cervical lymphadenitis
- **More serious causes:** retropharyngeal abscess and atlantoaxial subluxation
- Cervical spine radiographs should be obtained in children presenting with torticollis to ensure no spine fracture or dislocation, which requires extreme caution

ATLANTOAXIAL INSTABILITY IN DOWN SYNDROME PATIENTS

- 10-15% cases of Down syndrome—1-2% symptomatic
- Excessive laxity in posterior transverse ligament→ ↑ mobility between atlas (C1) and axis (C2)
- **Sx:** progressive over several weeks and result from compression of spinal cord→ behavioral symptoms, torticollis, urinary incontinence and vertebrobasilar symptoms like vertigo, dizziness and diplopia
- **PE:** UMN symptoms like leg spasticity, upgoing plantar, hyperreflexia and clonus usually present. Down syndrome pts are normally hypotonic – may remain hypotonic or may have ↑ tone due to UMN lesion signs
- **Dx:** suspected on physical exam and diagnosed with lateral radiographs of cervical spine in flexion, extension and in neutral position. Open mouth radiographs—helpful in visualizing odontoid
- **Rx:** surgical fusion of 1st and 2nd cervical vertebrae

SPONDYLOLISTHESIS

- Chronic back pain is common in adults and usually benign in nature
- But chronic back pain in children needs careful search of the cause as back pain in children is usually due to organic causes
- Spondylolisthesis is a developmental disorder characterized by a forward slip of vertebrae usually L5 over S1.
- It is usually presents in preadolescent children with chronic back pain and neurologic dysfunction in combination with palpable "step off" at lumbosacral area (step off is palpable if condition is severe)

LYTIC BONE LESIONS IN CHILDREN

- **D/D:**

- Infectious (Brodie abscess from osteomyelitis),
- Endocrine(hyperparathyroid osteitis fibrosa cystica),
- Neoplastic (Ewing sarcoma, Langerhans cell histiocytosis, metastases) and

- Idiopathic (benign bone cyst, aneurysmal bone cyst) etiologies.
- **Lytic bone lesion + hypercalcemia D/D:**
- Hyperparathyroid state (parathyroid adenoma is the most common cause of primary hyperparathyroidism—occurs in pts >50 yo)
- Lytic bone neoplasm

LANGERHANS CELL HISTIOCYTOSIS

- Also known as Langerhans cell granulomatosis, histiocytosis X
- Cause solitary, lytic, long bone lesions
- Eosinophilic granuloma—the least severe form of histiocytosis X—generally in children and young adults—solitary bone lesion
- May be painful, have overlying tender swelling and cause pathologic fractures
- May be locally destructive, typically resolve spontaneously and therefore regarded as benign and treated conservatively

POINTERS

- Most common cause of osteomyelitis in children is hematogenous seeding by staph aureus. It tends episodes it tends to affect metaphysis and spares epiphysis

Contents

RHEUMATOLOGY/ORTHOPEDICS & SPORTS-SURGERY

STRESS FRACTURE

Stress fracture	
Risk factors	• Repetitive activities (eg, running, gymnastics) • Abrupt increase in physical activity • Inadequate calcium & vitamin D intake • Decreased caloric intake • Female athlete triad: low caloric intake, hypomenorrhea/amenorrhea, low bone density
Clinical presentation	• Insidious onset of localized pain • Point tenderness at fracture site • X-ray can be negative in the first 6 weeks
Management	• Reduced weight-bearing for 4-6 weeks • Referral to orthopedic surgeon for fracture at high risk for malunion (eg, anterior tibial cortex, fifth metatarsal)

Local swelling may also be present

i.e. rest

- Bone responds to mechanical stress by remodeling but abrupt ↑ in intensity, duration or frequency of physical activity (without adequate rest)→repeated tension or compressive stress to bone→ microfractures that eventually coalesce within cortical bone.
- **Categorized as**: activity related (eg. excessive training and improper footwear), biomechanical (eg. weak calf muscles, high-arched feet etc) or metabolic (eg. demineralized bone from hormonal or nutritional diseases). Sudden increase in repeated tension or compression without adequate rest→ eventually breaks the bone.
- **Tibia**—major weight-bearing bone in the leg→ patients usually develop **medial tibial stress syndrome** (i.e. "shin splints" with no tibial tenderness on palpation)→ further activity→ complete or incomplete fracture, resulting in pain to palpation of tibia. Classically occur in anterior part of middle third of tibia in jumping sports and posteromedial of distal third of tibia in runners
- **Metatarsal stress fracture (non-displaced hairline fracture)**: typically occur in athletes and military recruits—due to sudden and drastic ↑ in activity—2nd metatarsal most commonly involved as subjected to significant extremes of loading during gait—slow onset foot pain- initially with activity but later during rest too—point tenderness over affected metatarsal—bone scans and MRI are done if plain films don't demonstrate fracture
- **Fractures of 2nd, 3rd and 4th metatarsals**: managed conservatively as surrounding metatarsals act as splints and nonunion is uncommon—rest and pain control are most important—hard sole shoe and light activity may be resumed immediately—plaster casting used for pts with more persistent pain following more conservative treatment
- **Fracture of 5th metatarsal**: surgical intervention reserved for fracture of 5th metatarsal, such as Jones fracture, or for displaced fracture not amenable to closed reduction
- **Diagnosis:** made **clinically** on examination with pain at a specific area, ↑ with jumping or running, associated with local swelling and point tenderness to palpation.

- **X-rays** frequently normal but can reveal periosteal reaction in the site of fracture. **MRI or bone scans**→ best tests.
- **Treatment:** rest and healing of stress fracture

HIP FRACTURE

- Can be intracapsular (femoral head or neck) or extracapsular (eg intertrochanteric or subtrochanteric)
- Intracpsular is at higher risk of avascular necrosis and
- Extracapsular is at greater need of implants like nails, rods
- Surgical repair should be done as soon as feasible to reduce pain, minimize complications and reduce length of hospital stay
- Surgery can be delayed up to 72 hours to address unstable comorbid conditions but longer delay is associated with more complications
- Surgical traction has been advocated in those who require delayed surgical repair but it does not relieve pain or improve surgical outcome

CLAVICULAR FRACTURE

- One of the most commonly injured bones
- Mostly injured in middle third
- Classically during athletic events and mostly after a fall on outstretched hand or a direct blow to shoulder
- **S/S:** pain and immobility of affected arm→contralateral hand is classically used to support weight of affected arm→shoulder on affected side is displaced inferiorly and posteriorly
- Careful neurovascular exam should be performed due to close proximity to subclavian artery (perform angiogram) and brachial plexus (motor exam of arm and hand usually sufficient—may rarely perform nerve conduction study)
- **Rx: Fracture of middle-third** (most common)→ usually treated non-operatively with brace, ice and rest→early range of motion and strengthening recommended to prevent loss of motion at shoulder in non-operative cases
  Fracture of distal third of clavicle→ open reduction and internal fixation to prevent nonunion

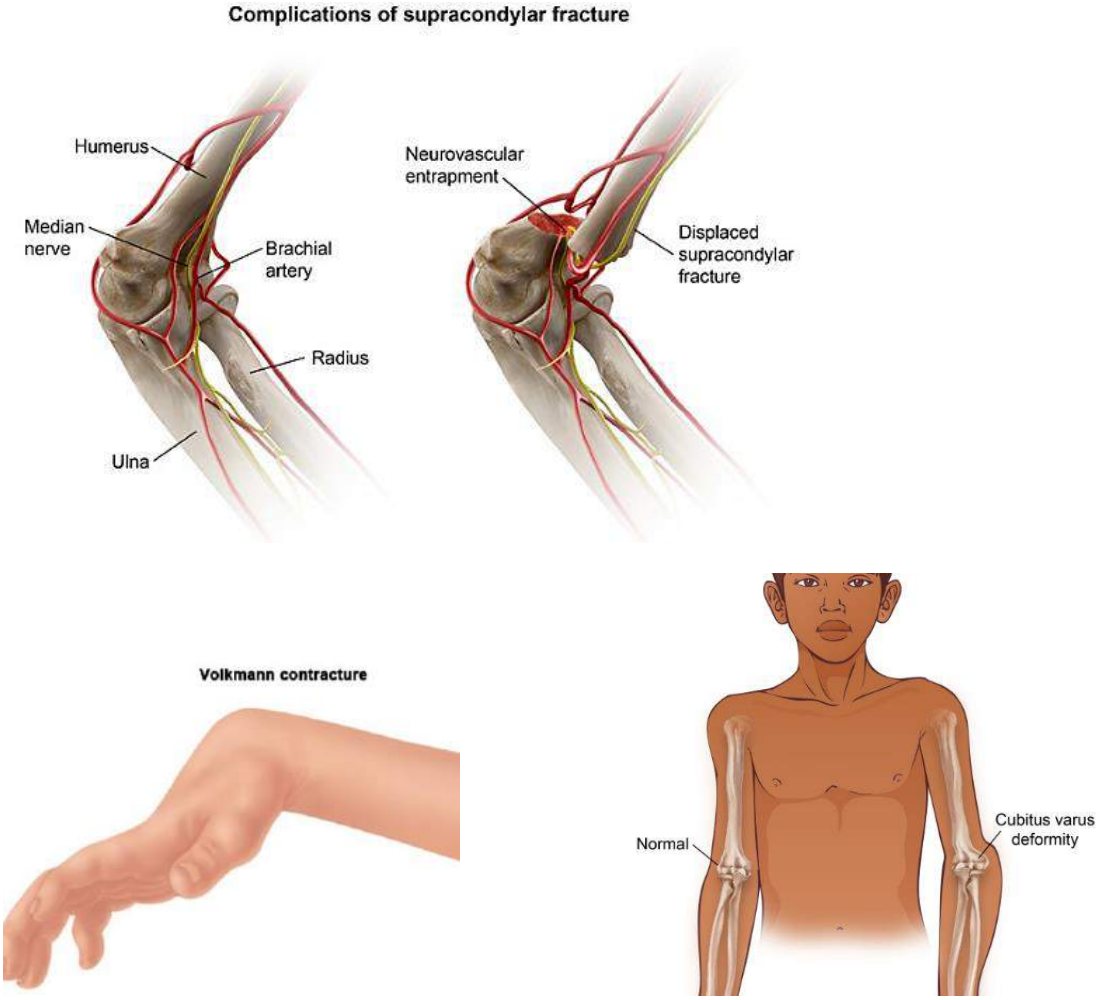
SUPRACONDYLAR FRACTURE OF HUMERUS

Supracondylar fracture of the humerus	
Mechanism	Fall on an outstretched hand most common
Complications	• Brachial artery injury • Median nerve injury • Cubitus varus deformity • Compartment syndrome/Volkmann ischemic contracture

1st two are most common complications. Impingement of brachial artery results in a loss of brachial and radial artery pulses. Distal perfusion should always be assessed on examination. Motor and sensory functions should also be assessed due to the risk of median nerve injury

- Most common fractures in pediatric population.

- Common because supracondylar area is thin and weak due to physiological remodeling in childhood
- Compartment syndrome Mosaic application also supracondylar fracture of humerus. Ischemia and infarction from compartment syndrome can lead to Volkmann contracture
- Limb length discrepancy is a common complication of proximal humerus and distal forearm fractures. However, the distal physis (growth plate) of the humerus contributes minimally to longitudinal growth due to limited remodeling. As a result, patients with supracondylar fracture of humerus are at increased risk of cubitus varus deformity



- **Rx:**
  Treatment consists of analgesia and immobilization. Displaced fractures→ orthopedic consultation. Neurovascular injury often resolves after orthopedic alignment and immobilization. Treated promptly → good prognosis

SCAPHOID FRACTURE

- Most commonly fractured carpal bone—usually across waist of scaphoid bone—proximal fracture fragment vulnerable to avascular necrosis due to tenuous blood supply
- After a fall on outstretched arm with a dorsiflexed wrist >95*
- **S/S:** pain at wrist joint. Tenderness at anatomic snuff box-most sensitive. Minimally decreased ROM (unless dislocated), decreased grip strength and possible swelling

- **Dx:** Scaphoid views (plain xray)- full pronation and ulnar deviation to better expose scaphoid are necessary to avoid missing fracture. Initial x-ray may be normal or show radiolucent line in non-displaced fracture (i.e. displacement <2mm and no angulation)
- **Rx:** wrist immobilization with thumb spica cast in all non-displaced suspected or proven fractures for 6-10 wks to avoid non-union and repeat x-ray in 7-10 days or perform immediate advanced imaging like CT scan or MRI if patient cannot tolerate immobilization or immediate diagnosis is needed to distinguish fracture and ligament rupture
  Fracture displacement→ open reduction and internal fixation

MINOR LIGAMENT SPRAIN

- RICE treatment→ i.e. rest, ice, compression and elevation

COMPARTMENT SYNDROME

- Due to ↑ pressure in compartment due to edema and/or bleeding. Common in forearm and calf but can occur in any compartment

Clinical features of compartment syndrome	
Common	• Pain out of proportion to injury • **Pain ↑ on passive stretch** • Rapidly increasing & tense swelling • **Paresthesia (early)**
Uncommon	• ↓ sensation • Motor weakness (within hours) • Paralysis (late) • ↓ distal pulses (uncommon)

- 5P's→ pain, pallor, paresthesia, pulselessness and pressure
- **Predisposing factors:** direct trauma, prolonged compression of extremity and recent revascularization after acute limb ischemia
- Considerable variation in signs and symptoms and high index of suspicion is needed to make diagnosis
- **Dx**: confirmed by **measuring compartment pressures** in affected extremity. But in high-risk pts (eg limb revascularization), can be diagnosed clinically by Sx of CS (pain, swelling and paresthesia)
- **Time to fasciotomy—**most critical prognostic indicator and should be performed early. Supportive measures taken to maintain perfusion pressures by keeping the limb at level of torso (not higher or lower)

Contents

HEMATOLOGY & ONCOLOGY-IM

PHYSIOLOGY

RETICULOCYTES

- Have slightly bluish tint and stain with methylene blue

PATHOLOGIC RBC FORMS

HOWELL JOLLY BODIES

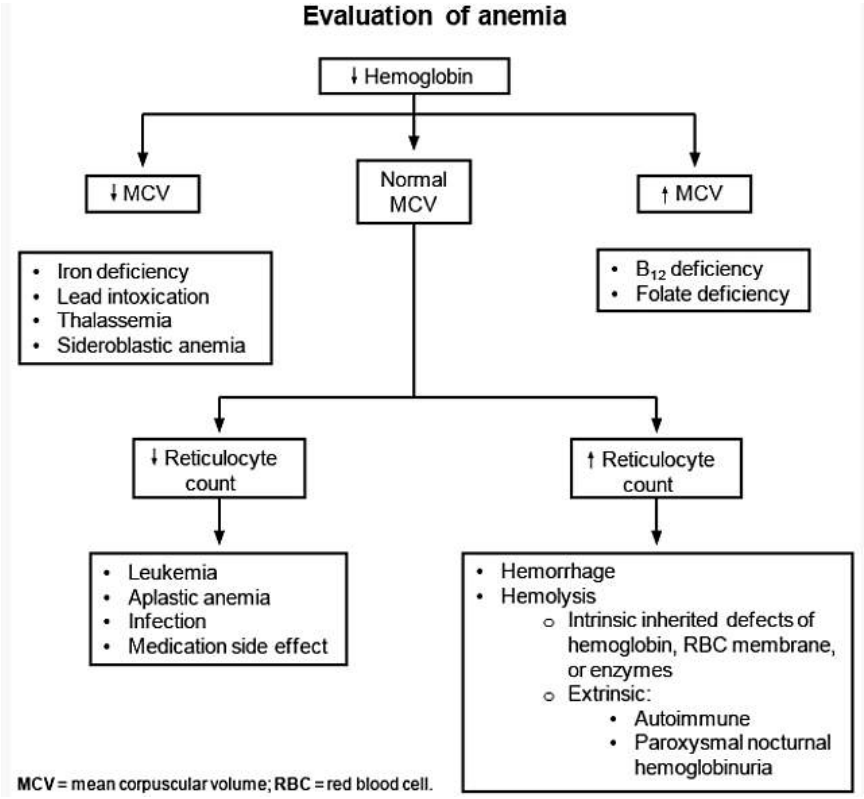
- Nuclear remnants in RBCs—typically removed by spleen
- Indicate splenectomy, functional hypofuntioning of spleen due to autosplenectomy, infiltrative disorders of spleen, or splenic congestion
- **Peripheral blood smear:** Appear as single, round, blue inclusions on **Wright stain**

HEINZ BODIES

- In G6PD def. → Hb oxidized→ forms insoluble precipitants i.e. Heinz bodies
- **Peripheral blood smear:** appear in RBCs after staining with dyes such as crystal violet

ANEMIA

EVALUATION OF ANEMIA



MICROCYTIC HYPOCHROMIC ANEMIA

- Most common→ iron deficiency anemia
- The differential diagnosis should include:

- Iron deficiency- decreased intake or increased blood loss—chronic GI bleeding is the most common cause in adult male and post-menopausal woman. Look for occult blood in stool
- Defective utilization of storage iron - anemia of chronic disease
- Reduced globin production - thalassemia and other hemoglobinopathies—do not respond to iron supplementation—**β thalassemia minor** presents with modest anemia, Hct ranges from 28-40%, and MCV between 55-75fL—common in Mediterranean descent
- Reduced heme synthesis - lead poisoning, sideroblastic anemia

Microcytic/hypochromic anemias	Findings in Iron Studies
1. Iron-deficiency anemia	Typically depressed serum iron level, increased total iron binding capacity (TIBC), and decreased serum ferritin level
2. Thalassemias	Normal to high serum iron and ferritin levels
3. Anemia of chronic disease	Below normal TIBC; Normal or increased serum ferritin level
4. Sideroblastic anemia	Normal to high serum iron and ferritin values

Iron studies in microcytic anemia					
Cause	**MCV**	**Iron**	**TIBC**	**Ferritin**	**Transferrin saturation (Iron/TIBC)**
Iron deficiency	↓	↓	↑	↓	↓
Thalassemia	↓↓	↑	↓	↑	↑↑
Anemia of chronic disease (inflammation)	Normal/↓	↓	↓	Normal/↑	Normal/↓

MCV = mean corpuscular volume; **TIBC** = total iron binding capacity.

Parameter	Iron deficiency anemia	α-thalassemia minor	β-thalassemia minor
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBCs	↓	Normal	Normal
Peripheral smear	Microcytosis, hypochromia	Target cells	Target cells
Serum iron studies	↓ Iron & ferritin ↑ TIBC	Normal/ ↑ iron & ferritin (RBC turnover)	Normal/ ↑ iron & ferritin (RBC turnover)
Response to iron supplementation	↑ Hemoglobin	No improvement	No improvement
Hemoglobin electrophoresis	Normal	Normal	↑ Hemoglobin A2

MCV = mean corpuscular volume; **RBC** = red blood cell; **RDW** = red cell distribution width; **TIBC** = total iron-binding capacity.

IRON DEFICIENCY ANEMIA

- **↑ RDW** is the earlier lab finding in iron def. anemia—occurs in nutritional deficiencies as nutrient levels available for RBC synthesis vary throughout the day, resulting in cells of varying sizes. RDW >20% suggest iron def. anemia. Normal in thalassemia i.e. 12-14%

THALASSEMIA

- β-thalassemia is more common in Mediterranean descent and α is more common in Southeast Asia
- Majority of α and β thalassemia minor cases are asymptomatic (often incidental finding); have varying degrees of anemia, microcytosis, target cells and teardrop cells on peripheral smear; MCV <75fL; normal RDW as all cells are same size and width
- Thalassemia minor is often confused with iron deficiency anemia:
  - Both thalassemia traits have microcytosis out of proportion to the degree of anemia, Hb> 10 g/dl, and disproportionately normal or high RBC count. This typically results in **Mentzer index (MCV/RBC) < 13.** Hematocrit is usually >30% in pts with thalassemia minor.
  - Iron def. anemia has low RBC count, and rarely becomes microcytic until Hb <10g/dl or hematocrit <30%. **Mentzer index >13**

LEAD POISONING IN ADULTS

Lead poisoning in adults	
Risk factors	Occupational exposure (eg, lead paint, batteries, ammunition, construction)
Clinical features	• Gastrointestinal (abdominal pain, constipation, anorexia) • Neurologic (cognitive deficits, peripheral neuropathy) • Hematologic (anemia)
Laboratory findings	• Anemia • Elevated venous lead level • Elevated serum zinc protoporphyrin level • Basophilic stippling on peripheral smear

Plumbing, mining, painting, paper hanging, auto repair

Signs of acute poisoning

Signs of chronic lead poisoning: non-specific symptoms (eg fatigue, irritability, insomnia), HTN, motor and sensory deficits, nephropathy

X-ray fluorescence to measure bone lead conc.

- Lead is readily absorbed via respiratory (in adults) or gastrointestinal (in children) tracts
- 99% bound to RBCs and disrupt Hb synthesis at high levels (>80mcg/dl)→ microcytic anemia
- **Rx:** via chelation therapy

ACQUIRED SIDEROBLASTIC ANEMIA

- Due to pyridoxine dependent impairment of early steps of protoporphyrin synthesis
- Isoniazid is a known cause of pyridoxine deficiency→ give pyridoxine supplementation
- Two groups of RBC population: hypochromic and normochromic ("dimorphic RBC population")
- Iron studies: ↑ serum iron and ↓TIBC→ differentiate iron def. from sideroblastic anemia
- Bone marrow sampling: confirm diagnosis by showing "ringed sideroblasts" (a specific Dx in this type of pts)
- Pappenheimer bodies: iron containing inclusion bodies found in peripheral RBCs—result from phagosomes that engulf excessive amount of iron—typically seen in sideroblastic anemia

MACROCYTIC ANEMIA

Common causes of macrocytic anemia (MCV >100 fL)

- Folate deficiency
- Vitamin B12 deficiency
- Myelodysplastic syndromes
- Acute myeloid leukemias
- Drug-induced (eg, hydroxyurea, zidovudine, chemotherapy agents)
- Liver disease
- Alcohol abuse
- Hypothyroidism

-Megaloblastic anemia →due to impaired DNA synthesis→ MCV>110fL, low reticulocyte count, macroovalocyte RBCs, hypersegmented neutrophils (mean lobe count >5), anisocytosis and poikilocytosis.

Non-megaloblastic—normal, increased or decreased reticulocyte count

- Peripheral blood smear and reticulocyte count are the best next step in management→ if ↑MCV→ folate and B12 levels→ if low→ further tests to elucidate cause.
- MCV >110fL favor megaloblastic anemia
- **Vitamin B12:** total body stores: 2-5 mg. Minimum daily requirement: 6-9 µg/day. Dietary source: only animal products (meat and dairy). Deficiency: 4-5 years of pure vegan diet to cause deficiency.

FOLATE DEFICIENCY

- Occurs within 4-5 months of dietary deficiency.
- Alcoholic abuse→ impair enterohepatic cycle and folic acid absorption→ develop folic acid def. → can develop megaloblastic anemia in 5-10 wks of alcohol abuse.
- Some medicines like phenytoin, primidone and phenobarbital impair folic acid absorption→ folate def. → folic acid supplementation can effectively prevent this condition
- Trimethoprim and methotrexate→ inhibit dihydrofolate recutase→ megaloblastic anemia
- Basophilic stippling: ribosomal precipitates that form varying size of blue granules in RBC cytoplasm, non-specific sign→ lead poisoning, alcohol abuse, thalassemias

PERNICIOUS ANEMIA:

- Most imp cause B12 deficiency→ neurologic deficits and achlorhydria—most common cause of B12 deficiency in pts of northern European descent. There can be presence of other autoimmune diseases like autoimmune thyroid problems and vitiligo.
- Pernicious anemia causes B12 def. by two ways:
  1. By the presence of anti-IF antibodies
  2. Pts develop chronic atrophic gastritis→ ↓ production of IF by gastric parietal cells. Atrophic gastritis ↑ the risk of intestinal type gastric CA and gastric carcinoid tumors by 2-3 times over general population→ monitor with periodic stool testing for presence of blood in stool
- Dx confirmation: presence of anti-IF antibodies
- Pernicious anemia and myelodysplastic syndromes (more common in elderly) present with pancytopenia and macrocytosis (↑MCV)—differentiated by careful examination of peripheral smear and bone marrow for dysplastic cells
- Homocysteine ↑ in folate and B12 def. Homocysteine and methylmelonic acid ↑ in B12 def.

NORMOCHROMIC NORMOCYTIC ANEMIAS

Causes of hemolysis	
Intravascular hemolysis	• Microangiopathic hemolytic anemia (eg, disseminated intravascular coagulation) • Transfusion reactions • Infections (eg, clostridial sepsis) • Paroxysmal nocturnal hemoglobinuria • Intravenous Rho(D) immune globulin infusion
Extravascular hemolysis	• Intrinsic RBC enzyme deficiencies (eg, G6PD) • Hemoglobinopathies (eg, sickle cell, thalassemia) • Membrane defects (eg, hereditary spherocytosis) • Hypersplenism, intravenous immunoglobulin infusion • Warm- or cold-agglutinin autoimmune hemolytic anemia (most cases) • Infections (eg, *Bartonella*, malaria)

Hb released from lysed RBCs→bind haptoglobin→haptoglobin-Hb complex cleared by liver→haptoglobin ↓to undetectable levels. RBC hemolysis→ ↑LDH and indirect bilirubin

Largely in reticuloendothelial system (LN and spleen). Normal to slightly low haptoglobin, slightly ↑ LDH, and ↑ indirect bilirubin

Coombs test is performed to confirm the diagnosis—even if negative and suspicion is high→ perform micro-Coombs test to confirm diagnosis. Warm (IgG)—Cold (IgM)—some intravascular hemolysis can occur esp. in IgM mediated

INTRINSIC HEMOLYTIC ANEMIA

HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis	
Epidemiology	• Autosomal dominant inheritance (~75%) • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• **↑ Mean corpuscular hemoglobin concentration** • **Spherocytes** on peripheral smear • Negative Coombs test • ↑ Osmotic fragility on **acidified glycerol lysis test** • Abnormal **eosin-5-maleimide binding test**
Treatment	• Folic acid supplementation • Blood transfusions • Splenectomy
Complications	• Pigment gallstones • Aplastic crises from parvovirus B19 infection

Can be autosomal recessive or due to spontaneous mutation→ defect is most common in ankyrin gene→abnormal spectrin protein

(due to membrane loss and RBC dehydration), ↑ reticulocytosis, ↑ RDW, normal or low MCV

Calcium bilirubinate→ can lead to cholecystitis→ perform cholecystectomy

- Most common hereditary hemolytic anemia in northern European population
- Hemolysis→ hyperbilirubinemia manifests as: Dark urine (cola colored), jaundice and pigment gall stones (calcium bilirubinate)
- Reticulocyte count is normally high in hemolytic anemia, but if it presents in neonates, they are unable to produce appropriate erythropoiesis in response to anemia→ severe anemia and need of transfusion

- Traditional NaCl osmotic fragility test has poor sensitivity. Acidified glycerol lysis test along with Eosin-5-maleimide binding test (flow cytometry) is the gold standard of diagnosis now
- In case of cholecystitis, remove gall bladder. Splenectomy also improves gall stones
- **Complications of splenectomy:** Immediate: hemorrhage, post-op infection, injury to nearby organs. Long-term: sepsis with encapsulated bacteria esp. S. pneumoniae. Risk of penumococcal sepsis is present 30 years and more after splenectomy→ prevention: anti-pneumococcal (conjugate vaccine), Hemophilus, and meningococcal vaccines several weeks before surgery, and daily oral penicillin prophylaxis for 3-5 years post-splenectomy or until adulthood (for pediatric pts)→ penicillin prophylaxis may be given lifetime or antibiotics made available at home for immediate treatment of any significant fever

GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia following oxidative stress (infection, sulfa drugs, fava beans) • Asian, African, or Middle Eastern descent (X-linked, often men)
Manifestations	• Pallor & fatigue • Dark urine • Jaundice • Abdominal/back pain
Laboratory findings	• Hemolysis (low hemoglobin, increased indirect bilirubin, increased lactate dehydrogenase, decreased haptoglobin) • Bite cells with Heinz bodies (denatured hemoglobin precipitates) on peripheral smear • Negative Coombs test • G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Supportive care

- G6PD activity may be used as a screening test but levels are usually normal during the episode as G6PD deficient RBCs are hemolysed early in the episode and reticulocytes with normal G6PD are abnormally high→ better to retest after 3 months of episode

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Usually presents in 4th decade of life with following clinical presentations
- an acquired genetic defect that results in lack of the glycosylphosphatidylinositol anchor, which connects proteins, including CD55 and CD59, to the cell surface→ absence of CD55 and CD59 from cell surface→ activation of complement membrane attack complex →hemolysis

Clinical features of paroxysmal nocturnal hemoglobinuria	
Clinical manifestations	• Hemolysis → fatigue • Cytopenias (impaired hematopoiesis) • Venous thrombosis (intraabdominal, cerebral veins)
Workup	• Complete blood count (**hypoplastic/aplastic anemia**, thrombocytopenia, leukopenia) • Elevated lactate dehydrogenase & low haptoglobin (hemolysis) • Indirect hyperbilirubinemia • Urinalysis (**hemoglobinuria**) • Flow cytometry (**absence of CD55 & CD59**)
Treatment	• Iron & folate supplementation • **Eculizumab** (monoclonal antibody that inhibits complement activation)

Both intravascular and extravascular hemolysis

- Patients with hemolytic anemia have a tendency for venous thromboembolism but PNH patients are at particular risk, esp. intra-abdominal and cerebral vein

SICKLE CELL ANEMIA

Sickle cell anemia	
Pathophysiology	Autosomal recessive inheritance of sickle β globin mutation in African & Hispanic populations
Clinical features	• Hemolytic anemia • Dactylitis • Acute vasoocclusive pain crises
Laboratory findings	• ↓ Hematocrit, ↑ reticulocytes, ↑ serum low-density lipoprotein, ↑ unconjugated bilirubin • Peripheral smear: Sickled red cells, Howell-Jolly bodies
Management	**Maintenance** • Vaccination • Penicillin (until age 5) • Folic acid supplementation • Hydroxyurea (for patients with recurrent vasoocclusive events) **Acute pain crises** • Hydration • Analgesia • +/- Transfusion

Earliest manifestation of vaso-occlusion in sickle cell anemia (6months to 2 years)→ warrant complete workup for previously asymptomatic SCD—Patho: vascular necrosis of metacarpals and metatarsals—osteolytic lesions on x-ray

Polychromasia on peripheral blood smear

Nuclear remnants usually removed by spleen but ↓ spleen function→ Howell- Jolly bodies

Daily in all pts to correct underlying folate def.

- Chronic extravascular and intravascular hemolysis

- **Hydroxyurea** works by stimulating erythropoiesis is primitive erythroid precursors→↑HbF→↓HbS. Primary dose-limiting S/E is myelosuppression (neutropenia, thrombocytopenia, anemia) but is otherwise safe
- **Exchange transfusion** is used to prevent stroke and also one of the primary treatments of stroke in pt with SCD→ does not reverse, rather prevent further stroke by ↓ing no. of sickled RBCs in blood

Sickle cell trait

- Painless microscopic or gross hematuria is the most common renal finding in pts with sickle cell trait.
- **Hyposthenuria**:
  - Found in sickle cell disease and also common but less severe in patients with sickle cell trait
  - RBC sickling in vasa recta of inner medulla→ impairment of countercurrent exchange and free water reabsorption→ impairment in kidney's ability to concentrate urine→ nocturia and polyuria
- Less commonly, UTIs may occur esp. in pregnancy

Sickle cell trait	
Clinical features	• Usually no symptoms of sickle cell anemia • More prevalent in African, Middle-Eastern & Mediterranean countries; African American & Hispanic individuals • No change in overall life expectancy
Diagnosis	• Normal hemoglobin, reticulocyte count, RBC indices & morphology • Hemoglobin electrophoresis shows both Hb A & Hb S, with the amount of Hb A greater than Hb S
Complications	• **Renal:** Hematuria, urinary tract infection, renal medullary carcinoma • **Thrombosis:** Splenic infarction (especially at higher altitudes), venous thromboembolism, priapism

Hb A = hemoglobin A; **Hb S** = hemoglobin S; **RBC** = red blood cells.

- Renal papillary necrosis can occur→ massive hematuria but episodes usually mild and resolve spontaneously. U/A: normal appearing RBCs
- Distal renal tubular acidosis can occur due to tubular damage

Acute Severe Anemia in SCD

Acute severe anemia in sickle cell disease		
Cause	**Reticulocytes**	**Key features**
Aplastic crisis	↓ (<1%)	• Transient arrest of erythropoiesis • Secondary to infection (eg, parvovirus B19)
Splenic sequestration crisis	↑	• Splenic vasoocclusion → rapidly enlarging spleen • Occurs in children prior to autosplenectomy

Aplastic Crisis:

- No splenomegaly
- Anemia typically severe—Hb <6g/dl
- Pallor, weakness, fatigue + functional systolic murmur due to hyperdynamic blood flow
- WBC and platelets usually normal
- Usually before age 15 as parvo outbeaks common in school-aged children
- Blood transfusion—mainstay of treatment

Splenic sequestration crisis:

- Occurs periodically, beginning as early as infancy
- Acute anemia, manifests as ↑ing fatigue and hypotension in severe cases
- Low to absent haptoglobin on labs

Autoinfarction of Spleen

- Pts with SCD have infarcted spleens by first 18 to 36 months of life→ Howell-Jolly bodies on peripheral blood smear
- Hence, pts are at ↑ed risk of sepsis from S. pneumoniae, H. influenza, N. meningitides
- Vaccination has ↓ed incidence of bacteremia. Despite vaccination, S. pneumoniae by far remains the most common cause of bacteremia in SCD pts, usually from **non-vaccine serotypes.**
- Pts with SCD can be prevented from invasive infections by encapsulated organisms through vaccinations e.g. conjugate S. pneumoniae vaccine. Twice daily prophylactic penicillin till they reach 5 years

Avascular necrosis

- Upto 50% pts with SCD develop by adulthood
- Commonly affected sites: humeral and femoral head
- Pathogenesis: Sickling, microinfarctions and bone hyperplasia
- S/S: restricted ROM, significant pain, no erythema or tenderness to palpation, difficulty bearing weight
- Rx: pain management and limitation of weight bearing, with surgical intervention if conservative fails (e.g. joint reconstruction)

Electrophoresis

Hemoglobin electrophoresis patterns			
Diagnosis	**Hemoglobin A**	**Hemoglobin S**	**Hemoglobin F**
Normal	~99%	0%	<1%
Sickle cell disease	0%	85-95%	5-15%
Sickle cell trait	50-60%	35-45%	<2%

EXTRINSIC HEMOLYTIC ANEMIA

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia		
	Warm agglutinin AIHA	**Cold agglutinin AIHA**
Etiology	• Drugs (eg, penicillin) • Viral infections • Autoimmune (eg, SLE) • Immunodeficiency states • Lymphoproliferative (eg, CLL)	• Infections (eg, *Mycoplasma pneumoniae* infection & infectious mononucleosis) • Lymphoproliferative diseases
Clinical presentation	• Asymptomatic to life-threatening anemia • Direct Coombs' positive with anti-**IgG**, anti-C3, or both	• Symptoms of anemia • Livedo reticularis & acral cyanosis with cold exposure that disappear with warming • Direct Coombs' positive with anti-C3 or anti-**IgM**, but usually not IgG
Treatment	• Corticosteroids • Splenectomy for refractory disease	• Avoidance of cold temperatures • Rituximab +/- fludarabine
Complications	• Venous thromboembolism • Lymphoproliferative disorders	• Ischemia & peripheral gangrene • Lymphoproliferative disorders

High dose to ↓ autoantibodies

WARM AGGLUTININ AIHA

- Splenomegaly due to erythrocyte entrapment and reticulocytosis usually present
- Blood smear: spherocytes, microspherocytes, elliptocytes and ↑ no. of polychromatophilic cells (eg reticulocytes)

NON-HEMOLYTIC NORMOCHROMIC NORMOCYTIC ANEMIAS

CHRONIC KIDNEY DISEASE OR END STAGE RENAL DISEASE

- CKD→↓ erythropoietin production→ normochromic, normocytic, hypoproliferative anemia→ give erythropoietin supplementation (DOC)→ new RBCs→ iron utilized→ rapid depletion of body's iron stores additionally because of chronic illness→ microcytic hypochromic anemia (iron deficiency anemia).
- Because of possibility of developing subsequent iron def. anemia→ iron stores should be evaluated prior to erythropoietin supplementation—treatment of choice in pt with iron def. anemia undergoing dialysis→IV iron prep like iron dextran and then recombinant erythropoietin
- All patients with chronic renal failure and **hematocrit < 30% (or hemoglobin <10 g/dl**) are candidates for recombinant erythropoietin therapy after iron deficiency has been ruled out
- Erythropoietin is also indicated in hemodialysis patients who have symptoms attributed in part to anemia
- Some of the most common side effects of erythropoietin therapy are:

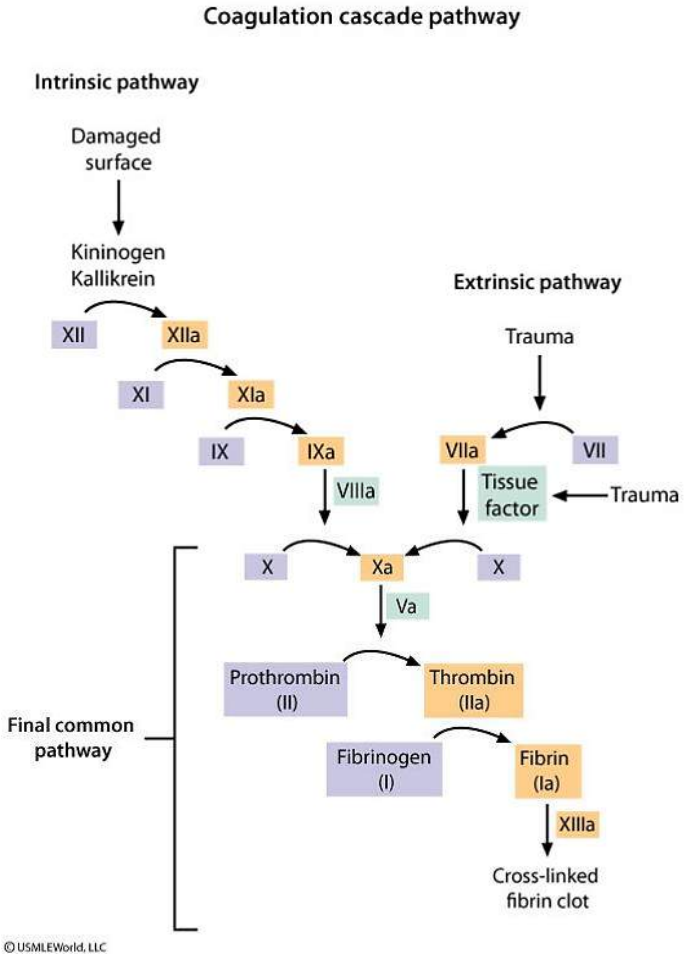
1. **Worsening of hypertension**: Approximately 30% of patients—20-50% of patients receiving IV erythropoietin will have more than a 10 mmHg rise in diastolic BP. Less common with SC route as compared to IV route. Even hypertensive encephalopathy can occur when there is a rapid rise in BP. MOA is unclear. Rx: fluid removal (by dialysis) and use of anti-hypertensive drugs (beta blockers and vasodilators are preferred). Prevention: slowly raise the hematocrit, with a goal hematocrit of 30-35%.
2. **Headaches:** 15% patients
3. **Flu-like syndrome:** 5% of patients. Responsive to anti-inflammatory drugs, and is less commonly seen with SC erythropoietin administration.
4. **Red cell aplasia:** Rare, but potential side effect

BLEEDING DISORDERS

<table>
<tr><th colspan="4">Bleeding disorders</th></tr>
<tr><th>Type</th><th>Symptoms</th><th>Examples</th><th>Laboratory results</th></tr>
<tr><td>Clotting defect</td><td>• Hemarthrosis
• Deep tissue hematomas</td><td>• Hemophilia A
• Hemophilia B</td><td>↑Activated partial thromboplastin time</td></tr>
<tr><td>Platelet aggregation defect</td><td rowspan="2">• Easy or prolonged mucosal bleeding
• Ecchymoses
• Petechiae</td><td>• von Willebrand disease
• Bernard-Soulier syndrome</td><td>Abnormal platelet function testing</td></tr>
<tr><td>Thrombocytopenia</td><td>• Idiopathic thrombocytopenic purpura
• Leukemia</td><td>↓Platelet count</td></tr>
</table>

COAGULATION DISORDERS

COAGULATION PATHWAY



HEMOPHILIAS

Hemophilia A & B	
Inheritance	• X-linked recessive

Clinical features	• Delayed/prolonged bleeding after mild trauma or procedure
	  ○ Hemarthrosis, hemophilic arthropathy
	  ○ Intramuscular hematomas
	  ○ Gastrointestinal or genitourinary tract bleeding

Laboratory findings	• Prolonged activated partial thromboplastin time • Normal platelet count, bleeding time, prothrombin time • Decreased or absent factor VIII (hemophilia A) or factor IX (hemophilia B) activity
Treatment	• Administration of factor VIII or factor IX • Desmopressin for mild hemophilia A

Female carriers can be mildly symptomatic

Can occur with minor trauma or without trauma—begin during toddlerhood when child is active and ambulatory

Recombinant or purified product

- Hematuria (cola colored urine)—common but renal impairment does not occur
- Can affect almost every organ system and result in long-term complication
- **HEMOPHILIC ARTHROPATHY:**
  - Late complication in both hemophilias
  - Caused by **iron/hemosiderin deposition**→ synovitis and fibrosis within joint (and not exactly caused by microtrauma)—other mechanisms may be involved
  - **S/S:** chronic worsening joint pain and swelling, can result in contracture and limited ROM
  - More common in pts with recurrent hemarthroses
  - May be visible on plain x-ray—MRI is helpful in making earlier diagnosis and characterization of degree of joint damage
  - Cannot be entirely prevented but early prophylactic treatment with factor concentrates→ significantly ↓ risk of developing arthropathy

VITAMIN K DEFICIENCY

Vitamin K deficiency	

Risk factors	• Inadequate dietary intake (eg, malnutrition)
	• Disorders of fat malabsorption
	  ○ Cystic fibrosis
	  ○ Biliary atresia
	• Disorders of intestinal inflammation
	  ○ Celiac disease
	  ○ Inflammatory bowel disease
	• Decreased production by bacterial flora (eg, frequent antibiotic use)

Clinical features	• Easy bruising • Mucosal bleeding • Gastrointestinal bleeding
Laboratory findings	• ↑ PT & INR • Normal aPTT (unless severe deficiency)

aPTT = activated partial thromboplastin time; PT = prothrombin time.

Exocrine pancreatic insufficiency→impaired fats and fat-soluble vitamin absorption→ pancreatic enzyme replacement and fat soluble vitamin supplementation

- Fat soluble vitamin (A,D,E,K)
- Important role in coagulation→ acts as cofactor in enzymatic carboxylation of glutamic acid residues on prothrombin complex proteins
- **Deficiency:** hepatocellular disease→ loss of storage sites— liver normally stores a 30-day supply of vitamin K, acutely ill person with underlying liver disease (eg alcoholic) can become vitamin K depleted in 7-10 days. NPO state and broad-spectrum antibiotics also contribute to quick depletion
- Leads to ↓ coagulation factors 2, 7, 9, 10 and protein C and S
- **Initially increases PT, followed by prolongation of PTT (**in newborns who do not receive vitamin K injection: severe def. ↑PT and PTT, mild def. ↑PT and normal PTT—diagnosed by reversal of symptoms with vitamin K administration)
- **Rx:** administer vitamin K→ rapidly replenishes the stores in 8-10 hours. Fresh frozen plasma→used for management of acute hemorrhage in interim

PLATELET DISORDERS

THROMBOCYTOPENIA

Common causes of thrombocytopenia	
Decreased platelet production	• Viral infections (eg, Epstein-Barr virus, hepatitis C, HIV) • Chemotherapy • Myelodysplasia (especially for age >60) • Alcohol use • Congenital (eg, Fanconi syndrome) • Vitamin B12 or folate deficiency
Increased platelet destruction	• Systemic lupus erythematosus • Medications (eg, heparin) • Idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome • Antiphospholipid syndrome
Other	• Dilutional due to massive red blood cell transfusion • Splenic sequestration

IMMUNE THROMBOCYTOPENIA

- Can occur at any age—most commonly affected age group: 2-5 years

Immune thrombocytopenia		
Clinical presentation	• Antecedent viral infection • Asymptomatic petechiae & ecchymosis most common • Mucocutaneous bleeding (eg, epistaxis, hematuria, gastrointestinal bleeding)	
Laboratory findings	• Isolated thrombocytopenia <100,000/µL • Peripheral smear with megakaryocytes and no other abnormalities	

Treatment	Children	• Skin manifestations only: Observe
		• Bleeding
		  ◦ IVIg
		  OR
		  ◦ Glucocorticoids

	Adults	• Platelets ≥30,000/µL without bleeding: Observe
		• Platelets <30,000/µL OR bleeding:
		  ◦ IVIg
		  OR
		  ◦ Glucocorticoids

Normal Hct and leukocyte count

Usually spontaneous recovery within 6 months—hence, treat only if bleeding +ve regardless of platelet count

- Autoimmune disorder→ ↑platelet destruction (in spleen) and inhibition of megakaryocyte platelet production due to IgG autoantibodies against platelet membrane glycoproteins

- Common cause of isolated thrombocytopenia—diagnosis of exclusion. Megakaryocytes are seen on peripheral blood smear
- Other than history, PE, CBC and examination of blood smear, only other recommended tests in pts with presumptive Idiopathic Thrombocytopenic Purpura are HIV and HCV if risk factors exist as 5-10% patients with chronic HIV may present with isolated thrombocytopenia before any other symptoms develop. But before this it is also important to rule out pseudothrombocytopenia due to platelet clumping by EDTA, abciximab administration or inadequate anticoagulation of blood sample. Bone marrow biopsy may be needed in pts with negative tests and unexplained thrombocytopenia
- Treatment of underlying causes can alter the course of 2° ITP—splenectomy is the last resort for catastrophic bleeding or chronic ITP that is refractory to IVIg or corticosteroids
- Idiopathic thrombocytopenic purpura and immune TP are same or different????

THROMBOTIC THROMBOCYTOPENIC PURPURA

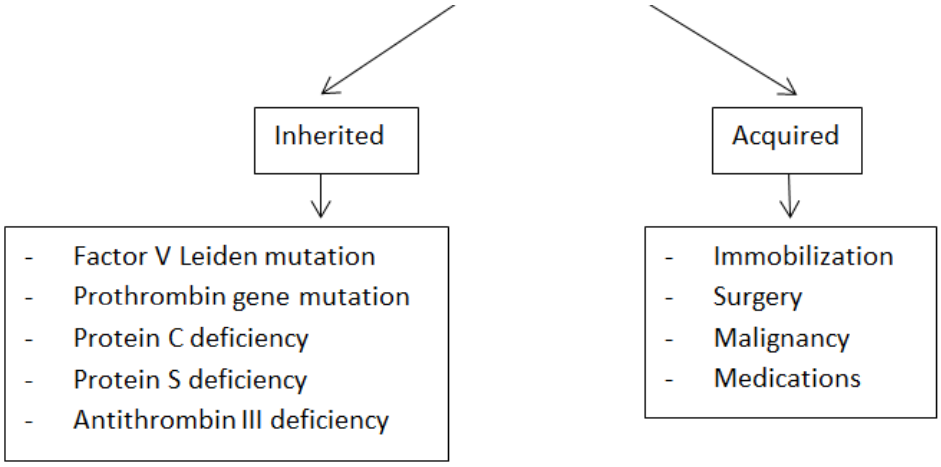
Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ **ADAMTS13** activity leading to **large vWF multimers** & resulting in diffuse **microvascular platelet-rich thrombi** • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic **anemia** (↑ LDH, ↓ haptoglobin) with **schistocytes** • **Thrombocytopenia** (↑ bleeding time, normal PT/PTT) Sometimes with • Renal failure • Neurologic manifestations • Fever
Management	• Plasma exchange

LDH = lactate dehydrogenase; **PT** = prothrombin time; **PTT** = partial thromboplastin time; **vWF** = von Willebrand factor.

(PEX)—removes pt's plasma and replaces it with donor plasma→ removes autoantibodies and replenishes ADAMTS13

- Life-threatening condition→ without emergent PEX→ mortality rate is 90%
- ↓ADAMTS13→ long chains of vWF accumulate on endothelial wall→trap platelets→ generate thrombi in areas of high shearing force (eg arterioles, capillaries)
- HIV is a risk factor for this but most cases are either idiopathic or 2° to drug toxicity.
- Peripheral blood smear is done to check the presence of schistocytes as present in almost all cases and absence suggest some other diagnosis
- Diagnosis is based mainly on clinical and laboratory findings. Combo of thrombocytopenia and hemolytic anemia in the absence of alternative cause is enough to make diagnosis and start treatment with plasma exchange

THROMBOPHILIA/DEEP VENOUS THROMBOSIS



Hereditary thrombophilias*	
Factor V Leiden	• Most common in those of white ethnicity • Activated protein C resistance
Prothrombin mutation	• 2nd most common in those of white ethnicity • ↑Prothrombin levels
Antithrombin deficiency	• Inherited form is rare • Acquired: DIC, cirrhosis, nephrotic syndrome
Protein C or S deficiency	• ↓Inactivation of factors Va & VIIIa • Warfarin-induced skin necrosis (protein C only)

*Typically autosomal dominant with variable penetrance;
DIC = disseminated intravascular coagulation.

If possible, discontinue vitamin K antagonist like warfarin prior to evaluating protein S levels

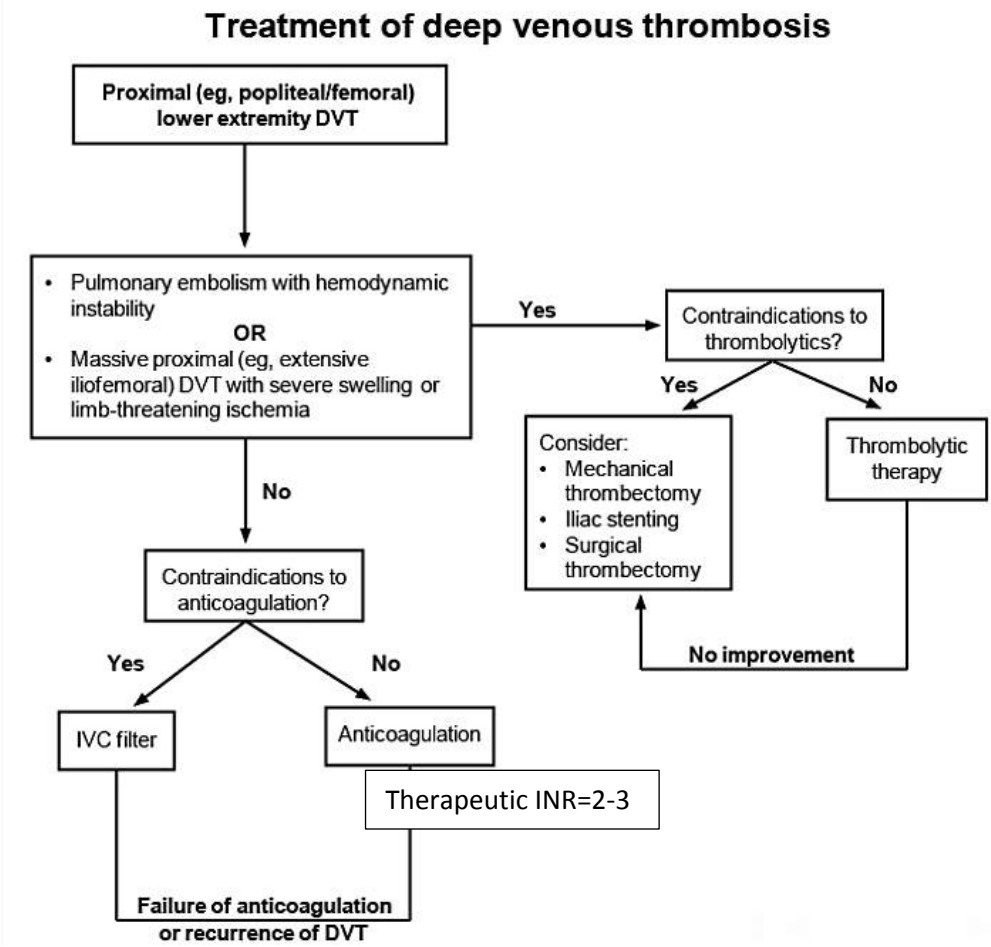
WORKUP FOR CAUSE

- Careful history and PE
- Testing is recommended in young (age <45) patients with a first-time unprovoked DVT/PE, patients with recurrent DVT/PE, and patients with unusual sites of thrombi (eg, cerebral, mesentery, portal veins)
- Lab studies including CBC, comprehensive metabolic panel, coagulation studies (aPTT, PT/INR), ESR, hemoccult stool testing and CXR→ further testing based on above results
- Absence of clear provoking factor (eg recent procedure, immobilization), in pts with 1st episode of VTE→ refer for **age-appropriate cancer screening** (eg colonoscopy, mammography) and CXR in most pts with 1st episode of unprovoked VTE
- Concerns for occult malignancy (eg due to suggestive Sx like weight loss or pain) or recurrent or multiple site VTE→ extensive cancer screening (eg CT chest, abdomen, pelvis)

FACTOR V LEIDEN MUTATION

- Most have AD point mutation in gene for factor V that makes gene unable to respond to activated protein C, an innate anticoagulant
- This mutation leads to:
  - Slowed degradation of activated factor V (Va)→ continued thrombi formation
  - Slow degradation of activated factor VIII (VIIIa) as factor Va acts as a cofactor to degrade VIIIa

TREATMENT OF DVT



HEMODYNAMICALLY STABLE PATIENT:

- Anticoagulants that can be used: warfarin with heparin initially or direct factor Xa inhibitors

Comparison of rivaroxaban & warfarin		
	Rivaroxaban	**Warfarin**
Mechanism of action	Direct factor Xa inhibitor	Vitamin K antagonist
Therapeutic effect	2–4 hours	5–7 days
Acute DVT treatment	Single agent	Overlap with heparin for ~5 days
Need for monitoring	None	Prothrombin time/INR
Antidote if hemorrhage	None	Fresh frozen plasma, vitamin K

CONTRAINDICATIONS TO ANTICOAGULATION

- Significant active bleeding /massive GI bleeding

- Recent surgery but can be started in hemodynamically stable patient as early as 48-72 hours after surgery
- Acute hemorrhagic stroke

INDICATIONS FOR RIVAROXABAN

- Acute DVT or PE
- Recurrent or refractory DVT
- If pt does not want daily injection (heparin) or has difficulty with dietary restriction and frequent INR monitoring (warfarin)
- It has same efficacy as low molecular weight heparin and warfarin

IVC FILTERS:

- **Indications:** contraindications to anticoagulation and recurrent or extending thromboembolism while pt is fully anticoagulated (i.e. INR between 2-3)
- Placed via a transvenous approach
- Preferably place retrievable filter that can be removed when no longer needed
- **Short-term complications:** bleeding, infection and thrombus at puncture site
- **Long-term complications:** filter migration or erosion into surrounding structures and recurrent thrombus (including one that extends into IVC and surrounds the filter)
  - ➔ **Trousseau's Syndrome:** hypercoagulable state→ superficial venous thrombosis at unusual sites (eg arm, chest area)→ associated with pancreatic (most common), lung, prostate, stomach and colon cancers and acute leukemias→ perform CT scan of abdomen to rule out prostate cancer and then go for further tests

MANAGEMENT OF PROVOKED DVT AFTER SURGERY

- Provoked DVT due to recent surgery is likely to be treated for 3 months
- Warfarin and IV unfractionated heparin (start on same day)—preferred long term anticoagulant for pts with end stage renal disease (low molecular weight heparin and rivaroaxaban are CI in ESRD). Heparin is continued for initial 4-5 days till the therapeutic INR (goal 2-3) is reached

THRESHOLD FOR RBC TRANSFUSION

Red blood cell transfusion thresholds	
Hemoglobin (g/dL)	**Recommendation**
<7	• Generally indicated
7-8	• Cardiac surgery • Oncology patients in treatment • Heart failure
8-10	• Symptomatic anemia • Ongoing bleeding • Acute coronary syndrome • Noncardiac surgery
>10	• Not generally indicated

BLOOD TRANSUFION REACTIONS

Immunologic blood transfusion reactions	
Transfusion reaction	**Clinical features & etiology**
Febrile nonhemolytic (most common reaction)	• Fever & chills • Within 1-6 hours of transfusion • Caused by cytokine accumulation during blood storage
Acute hemolytic Medical emergency	• Fever, flank pain, hemoglobinuria, renal failure & disseminated intravascular coagulation • Within 1 hour of transfusion • Positive direct Coombs test, pink plasma • Caused by ABO incompatibility
Delayed hemolytic	• Mild fever & hemolytic anemia • Within 2-10 days after transfusion • Positive direct Coombs test, positive new antibody screen • Caused by anamnestic antibody response
Anaphylactic	• Rapid onset of shock, angioedema/urticaria & respiratory distress • Within a few seconds to minutes of transfusion • Caused by recipient anti-IgA antibodies
Urticarial/allergic	• Urticaria, flushing, angioedema & pruritus • Within 2-3 hours of transfusion • Caused by recipient IgE antibodies & mast cell activation
Transfusion-related acute lung injury	• Respiratory distress & signs of noncardiogenic pulmonary edema • Within 6 hours of transfusion • Caused by donor anti-leukocyte antibodies
Primary hypotension reaction	• Transient hypotension often in patients taking angiotensin- converting enzyme inhibitors • Within minutes of transfusion • Caused by bradykinin in blood products (normally degraded by angiotensin-converting enzyme)
Bacterial sepsis	• Fever, chills, septic shock & DIC • Within minutes to hours of transfusion

Due to immune complex deposition—oliguric RF

Plasma free Hb ≥25mg/dl—repeat type and cross match show mismatch

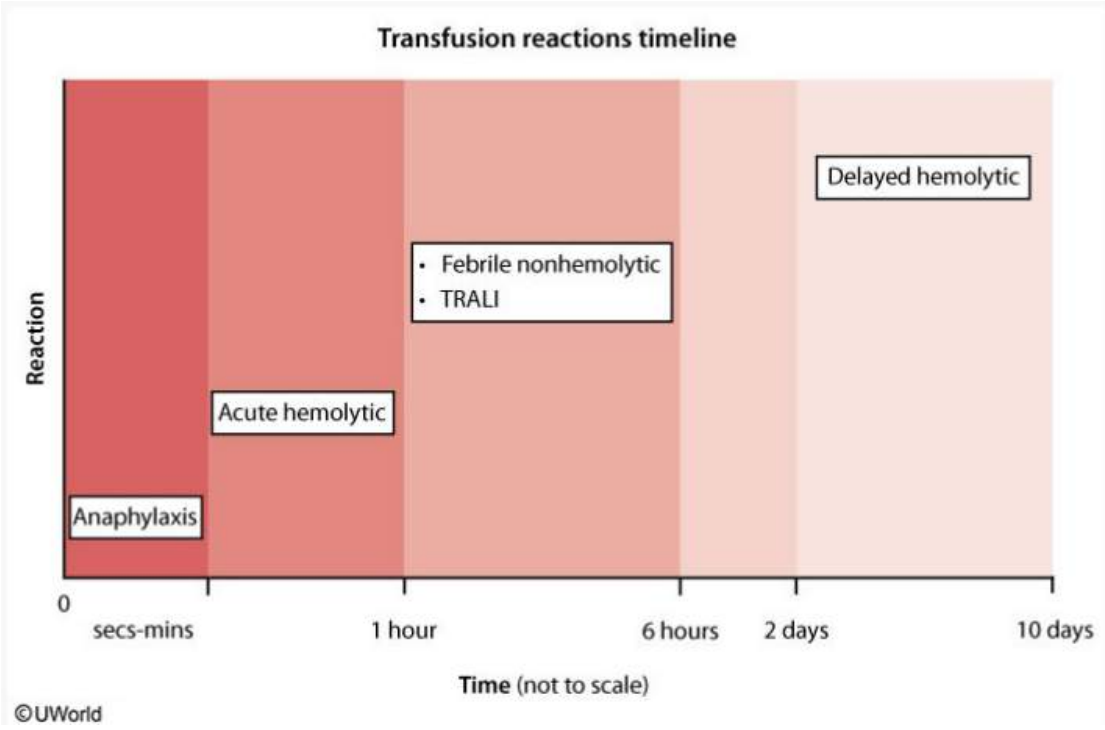
Possibly due to clerical error

IgG antibodies

CXR: B/L interstitial infiltrates

Blood transfusion reactions associated with hypotension

- Adverse reaction to blood transfusion occur despite multiple tests and inspections of blood



FEBRILE NON-HEMOLYTIC

- Blood stored→ leukocytes release cytokines→ transfused→ fever, chills and malaise
- **Prevention:** use leukoreduced blood products
- **Treatment:** stop transfusion to exclude other serious reactions, administer antipyretics (avoid aspirin in thrombocytopenic patients) and use leukoreduced blood in future

ACUTE HEMOLYTIC REACTION

- S/S: discomfort at infusion site
- **Management:** immediate cessation of transfusion while maintaining IV access for fluids (normal saline) and supportive care

DELAYED HEMOLYTIC REACTION

- Due to anamnestic antibody response to red blood cell antigen to which person was previously sensitized
- Ab's are undetectable prior to transfusion but reappears rapidly following transfusion
- Low grade hemolysis
- No treatment usually required

ANAPHYLACTIC REACTION

- S/S: hypotension, difficulty breathing→ LOC, shock and respiratory failure
- **Management:**
  - Stop transfusion immediately
  - Give IM epinephrine
  - Circulatory and respiratory support with vasopressors and mechanical ventilation
  - Histamine blockers and glucocorticoids should also be administered
  - Future transfusions: IgA deficient plasma and washed red cell products

INDICATIONS FOR SPECIALIZED RBC TREATMENTS

Indications for specialized RBC treatments	
Irradiated	• Bone marrow transplant (BMT) recipients • Acquired or congenital cellular immunodeficiency. • Blood components donated by first or second degree relatives
Leukoreduced	• Chronically transfused patients • CMV seronegative at-risk patients (e.g., AIDS, transplant patients) • Potential transplant recipients • Previous febrile nonhemolytic transfusion reaction
Washed	• IgA deficiency • Complement-dependent autoimmune hemolytic anemia • Continued allergic reactions (e.g., hives) with red cell transfusion despite antihistamine treatment

Washed to remove as much plasma as possible as it contains proteins including IgA and can cause allergic reaction

LEUKOREDUCED

- Reduce the no. of transfused leukocytes through filtering, or other methods like saline washing, freezing and deglycerolizing or buffy coat removal
- It also reduces the risk of HLA alloimmunization and transmission of CMV

CALCIUM GLUCONATE INFUSION

- Used to avoid or treat severe hypocalcemia following massive transfusion—specially occurs in pts who have received equivalent of more than one blood volume of blood transfusion or packed RBCs over 24 hours—occurs because of presence of citrate which chelates calcium and magnesium in plasma—used as anticoagulant in whole blood (for transfusions)→cause paresthesias

WARMING

- When massive blood transfusion is needed→ to prevent hypothermia

CO POISONING

Features of carbon monoxide (CO) poisoning	
Symptoms	Mild-moderate intoxication: • **Headache** (most common), confusion • Malaise, dizziness, nausea Severe intoxication: • Seizure, syncope, coma • Myocardial ischemia, arrhythmias
Causes	• **Smoke inhalation** (most common) • Defective heating systems • Use of fuel-burning appliances or motor vehicles in poorly ventilated areas
Diagnosis	• **Carboxyhemoglobin level** • Check ECG in all patients • Measure cardiac enzymes in the elderly & in those with cardiac risk factors or signs of ischemia
Treatment	• **100% oxygen** (non-rebreathing face mask)

- Non-smokers have low levels (<3%) of carboxyhemoglobin (due to normal enzymatic reactions). Cigarette smokers can have as high as 10% → a little exposure to CO→ symptomatic CO poisoning
- CO→ shifts oxygen dissociation curve to left→ inability of Hb to unload oxygen at tissue level→ kidney produces EPO→ secondary polycythemia
- **Dx:** pulse oximetry cannot differentiate oxyHb from carboxyHb. Diagnosis is made on ABGs with cooximetry

FROSTBITE

Frostbite	
Clinical findings	• Superficial pallor & anesthesia • Blistering, eschar formation • Deep tissue necrosis & mummification
Management	• **Rapid rewarming** in 37-39 C (98.6-102.2 F) water bath • Analgesia & wound care • Thrombolysis in severe, limb-threatening cases

- **Frostbite:** freezing of tissue→ disruption of cell membrane, ischemia, vascular thrombosis and inflammatory changes
- Affected tissues typically have stiff or waxy texture
- Most affected parts: face, ear and distal limbs

- Rewarming should not be done if there is risk of refreezing before definitive care can be provided as it can worsen tissue damage
- Aggressive analgesia should be provided during rewarming as it can lead to severe pain
- Hot air rewarming not recommended
- In the field, rewarming can be accomplished by holding affected limbs against rescuer's abdomen
- CCB not indicated in acute frostbite (used in Raynaud's)

MULTIPLE MYELOMA

Multiple myeloma	
Pathophysiology	• Monoclonal plasma cell proliferation
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia • Monoclonal paraproteinemia
Radiology	• Osteolytic lesions/osteopenia (osteoclast activation)

Leads to fatigue, constipation and depression

Hypogammaglobulinemia

- Bone marrow infiltration by plasma cells
- Hyperviscosity syndromes are rarely present in these patients
- Respiratory (eg streptococcal pneumonia) and UTIs are most common infections in MM
- **Labs:**
  - Protein gap (difference between total protein and albumin >4g/dl): means ↑ed non-albumin proteins in serum→ seen in polyclonal gammopathies(infection, connective tissue diseases) or excess monoclonal proteins (MM, Waldenstrom gammopathy)
  - SPEP- serum protein electrophoresis→ most common screening test for MM→ M-spike (IgG or IgA) (identify whether mono or polyclonal proteins)
  - Bone marrow biopsy, more invasive test→ then confirm the diagnosis **(>10% clonal plasma cells)**→ performed only after gathering more information from peripheral blood smears (Rouleaux formation), serum free light chain analysis, SPEP and urine protein electrophoresis
  - ➔ Bone scans show only osteoblastic activity as in some tumors—hence not useful for diagnosing MM, rather skeletal survey is more important

WALDENSTROM'S MACROGLOBULINEMIA

- Rare, chronic, plasma cell neoplasm
- Characterized by abnormal plasma cells which multiply out-of-control and invade the bone marrow, lymph nodes, and spleen
- Typically, there is also production of excessive amounts of IgM antibody in the blood, which causes hyperviscosity (thickening) of the blood
- The following are the major signs and symptoms of the disease
  1. Increased size of the spleen, liver, and some lymph nodes

2. Tiredness, usually due to anemia (too few red blood cells)
3. Tendency to bleed and bruise easily
4. Night sweats
5. Headache and dizziness
6. Various visual problems like retinal vein engorgement due to hyperviscosity
7. Pain and numbness in the extremities due to a predominantly demyelinating sensorimotor neuropathy.

LEUKEMIAS

LYMPHADENOPATHY

- **Benign LAD:** small <1.0 cm, mobile, rubbery, most often occur in URTIs→ observe→ if grow in size or any symptoms develop→ further evaluation—common in children and young adults
- **Malignant LAD:** >2.0 cm, firm, immobile, in elderly and smokers→ raise suspicion of malignancy and granulomatous disease

LYMPHOID NEOPLASMS

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute Lymphoblastic Leukemia	
Epidemiology	• Most common childhood cancer • Peak age: 2-5 years • Male > female
Clinical features	• Nonspecific systemic symptoms • Bone pain • Lymphadenopathy • Hepatosplenomegaly • Pallor (from anemia) • Petechiae (from thrombocytopenia)
Diagnosis	• Bone marrow biopsy with >25% lymphoblasts
Treatment	• Multi-drug chemotherapy

- Pts with Down syndrome are also at ↑ risk
- Half of patients with ALL may have leukocytes <10,000/µL but >20% have leukocytes >50,000/µL
- 30-50% present with infections and half with LAD and HSM
- Lymphoblasts→ lack peroxidase +ve granules (positive in meyloblasts) but +ve cytoplasmic aggregates of PAS +ve material
- Immunostaining for terminal deoxyribonucleotidyltransferase (Tdt)→ +ve in 95% cases. Only pre-B and pre-T lymphoblasts express Tdt

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia	
Clinical	• **Lymphadenopathy** (cervical, supraclavicular, axillary) • **Hepatosplenomegaly** • Mild thrombocytopenia & anemia • Often asymptomatic
Diagnostic	• **Severe lymphocytosis & smudge cells** • **Flow cytometry** • Lymph node & bone marrow biopsy not generally needed
Prognostic	• Median survival 10 years • Worse prognosis with: o Multiple chain lymphadenopathy o Hepatosplenomegaly o Anemia & thrombocytopenia
Complications	• **Infection** • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter transformation)

Shows clonality of mature B cells

HAIRY CELL LEUKEMIA

- Also known as leukemic reticuloendotheliosis—B-cell derived chronic leukemia→ pancytopenia, 10-20% may have leukocytosis
- Hairy-projections of lymphocytes→ trapped in red pulp of spleen→ splenomegaly
- Bone marrow becomes fibrotic→ dry tap
- TRAP (tartrate resistant acid phosphatase) stain +ve and CD11c marker is relatively specific for HCL
- Relatively benign course as compared to other leukemias
- Rx: cladribine (purine analog, 2-chlorodeoxyadenosine, 2-CdA)—toxic to bone marrow—SE: neurological and kidney damage
  - ➔ Chlorambucil and prednisone—for CLL
  - ➔ CHOP regimen—for non-Hodgkin lymphoma

MYELOPROLIFERATIVE DISORDERS

CHRONIC MYELOGENOUS LEUKEMIA

	Leukemoid reaction	Chronic myeloid leukemia
Leukocyte count	>50,000/mm^3	Elevated (often >100,000/mm^3)
Cause	Severe infection	*BCR-ABL* fusion
LAP score	High	Low
Neutrophil precursors	More mature (metamyelocytes > myelocytes)	Less mature (metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present

LAP = leukocyte alkaline phosphatase.

- Late neutrophil precursors→ metamyelocytes and bands
- Early neutrophil precursors→ promyelocytes and myelocytes
- CML is usually found on routine blood work in asymptomatic patients but may present with fatigue, weight loss, night sweats or abdominal fullness (splenomegaly), thrombophilia and anemia are common

POLYCYTHEMIA VERA (PV)

Polycythemia vera	

Manifestations	• ↑ Blood viscosity
	  ○ **Hypertension**
	  ○ **Erythromelalgia** (burning cyanosis in hands/feet)
	  ○ Transient visual disturbances
	• ↑ RBC turnover (gouty arthritis)
	• **Aquagenic pruritus**
	• Bleeding

Examination	• Facial plethora (ruddy cyanosis) • Splenomegaly
Laboratory findings	• **Elevated hemoglobin** • Leukocytosis & thrombocytosis • **Low erythropoietin** level • **JAK2 mutation** positive
Complications	• **Thrombosis** • Myelofibrosis & acute leukemia
Treatment	• **Phlebotomy** • Hydroxyurea (if ↑ risk of thrombus)

But normal oxygen saturation

Bone marrow suppressive medications

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea	
Pathophysiology	• Relaxation of pharyngeal muscles leads to closure of airway • Loud snoring with periods of apnea
Symptoms	• Daytime somnolence • Non-restorative sleep with frequent awakenings • Morning headaches • Affective & cognitive symptoms
Sequelae	• Systemic hypertension • Pulmonary hypertension & right heart failure

- Chronic hypoxemia→ kidneys produce EP→ polycythemia

ANDROGEN ABUSE

Clinical features of androgen abuse	
Types of androgens	• Exogenous (eg, testosterone replacement therapy) • Synthetic (eg, stanozolol, nandrolone) • Androgen precursors (eg, DHEA)

Side effects/ clinical presentation	• **Reproductive**
	  ○ **Men:** Decreased testicular function & sperm production, gynecomastia
	  ○ **Women:** Acne, hirsutism, voice deepening, menstrual irregularities
	• **Cardiovascular:** Left ventricular hypertrophy, possible ↓HDL & ↑LDL
	• **Psychiatric:** Aggressive behavior (men), mood disturbances
	• **Hematologic:** Polycythemia, possible hypercoagulability

DHEA = dehydroepiandrostenedione.

And hepatotoxicity

↑ in Hct and Hb are dose-dependent

HEREDITARY HEMOCHROMATOSIS

Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk of hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

- Initial diagnosis based on elevated iron studies and confirmed by genetic analysis of HFE mutation
- Serial phlebotomy can significantly ↓ the risk of cirrhosis and HCC

SUPERIOR VENA CAVA SYNDROME

- >60% cases due to lung cancer (esp. small cell lung CA) and NHL. Other causes: fibrosing mediastinitis (eg due to TB or Histoplasmosis) or thrombosis due to indwelling central venous devices.
- When history and PE suggestive→ chest X-ray (identify cause in 80% cases)→ abnormality→ CT chest and histology to determine type of CA and to guide therapy

HEAD AND NECK SQUAMOUS CELL CA

- Hard, u/l, non-tender LN→ always suspicious of cancer and must be evaluated immediately→ biopsy LN→ if squamous cell CA→ panendoscopy (esophagoscopy, bronchoscopy and laryngoscopy—best initial test) to look for primary site→ biopsy when primary tumor is detected (gives histologic diagnosis—imp in determining proper management and prognosis)
- H/o smoking and alcohol use.
- LN enlargement of submandibular or cervical region are highly suspicious of head and neck cancer
- Majority cancers in head and neck area are SCC→ prompt biopsy done to complete evaluation
- Treatment of head and neck cancer depends on stage, grade and histology of tumor. Various treatment options: radical neck dissection, tumor resection, platinum based chemotherapy, radiotherapy and palliative management
- If adenocarcinoma on LN biopsy→ consider breast cancer and perform further tests.

PROSTATE CANCER

- Localized prostate cancer→ radical prostatectomy→ in case of recurrence of PSA later→ salvage radiation therapy can provide long term disease control for localized recurrent disease (salvage treatment is defined as form of treatment given when standard treatment has failed to control the disease)

- Limited disease→ non-steroidal anti-androgen i.e. flutamide along with LHRH agonist prolongs survival. But no demonstrable benefits in pts with orchiectomy. Estramustine, a combination of estrogen and nitrogen mustard→40% response rate in castrated men but not well-tolerated by men with cardiovascular or hematopoietic disorders
- Radiation therapy is the best for management of progressive pain in a patient with prostate cancer and bony metastases after androgen ablation (i.e. orchiectomy)
- If mets are localized to a few sites, focal external beam therapy is most appropriate

(Q.id 3847)

SPINAL CORD COMPRESSION

Spinal cord compression	
Causes	• Spinal injury (eg, motor vehicle accident) • Malignancy (eg, lung, breast, prostate cancers; myeloma) • Infection (eg, epidural abscess)
Signs & symptoms	• Gradually worsening severe local back pain • **Pain worse** in the recumbent position/at **night** • Early signs: Symmetric lower-extremity weakness, hypoactive/absent deep-tendon reflexes • Late signs: Bilateral Babinski reflex, decreased rectal sphincter tone, paraparesis/paraplegia with increased deep-tendon reflexes, sensory loss
Management	• Emergency MRI • Intravenous glucocorticoids • Radiation-oncology & neurosurgery consultations

EPIDURAL SPINAL CORD COMPRESSION

- Suspect epidural spinal cord compression in pt with h/o malignancy
- 60% thoracic and 30% lumbosacral involvement
- Lung, breast, prostate and MM most likely tumors
- Early diagnosis and less neurologic involvement→ better outcome
- Although MRI is imp. But IV glucocorticoid should not be delayed→↓ vasogenic edema caused by obstructed epidural venous plexus, help alleviate pain and may restore neurologic function → perform MRI→ ESCC confirmed→ neurosurgical consultation
- Radionuclide bone scans and skeletal survey (xray of major bones)→ detect bone mets but not thecal sac compression, hence not recommended

TUMOR LYSIS SYNDROME

- Tumors with high cell turnover like poorly differentiated lymphomas (eg Burkitt lymphoma) and leukemias (particularly ALL and rarely AML)→ tumor lysis syndrome
- Metabolic abnormalities associated with TLS:

- ↑phosphate: intracellular electrolyte→ cell break→ phosphate comes out
- ↓ calcium: released phosphate binds calcium and cause hypocalcemia. Also occur due to release of intracellular products by cell breakdown
- ↑ potassium: intracellular electrolyte→ cell lysis→ K+ ↑
- ↑ uric acid: degradation of cellular proteins→ ↑ uric acid. Allopurinol prevent acute urate nephropathy but not tumor lysis syndrome

- Prompt identification and immediate treatment necessary as may lead to fatal arrhythmias, ARF and even sudden death

CANCER RELATED ANOREXIA/CACHEXIA SYNROME (CACS)

- Hypermetabolic state associated with weight loss, anorexia and excessive reduction in skeletal muscle
- Weight loss is multifactorial: due to systemic inflammation and caloric reduction
- Rx: nutritional counseling and supplementation with enteral or parenteral feeding do a little to reverse CACS. Pharmacologic intervention with progesterone analogues (eg megestrol acetate or medroxyprogesterone acetate) or glucocorticoids→ effective at ↑ing appetite, causing weight gain and improving well-being. In pts with longer life expectancy→ progesterone analogues better than corticosteroids due to less S/E
  - ➔ Synthetic cannabinoids are useful in HIV cachexia but not CACS

PAIN MANAGEMENT IN CANCER PATIENTS

Three key principles to the use of pain medications in patients with terminal stages of cancer are as follows:

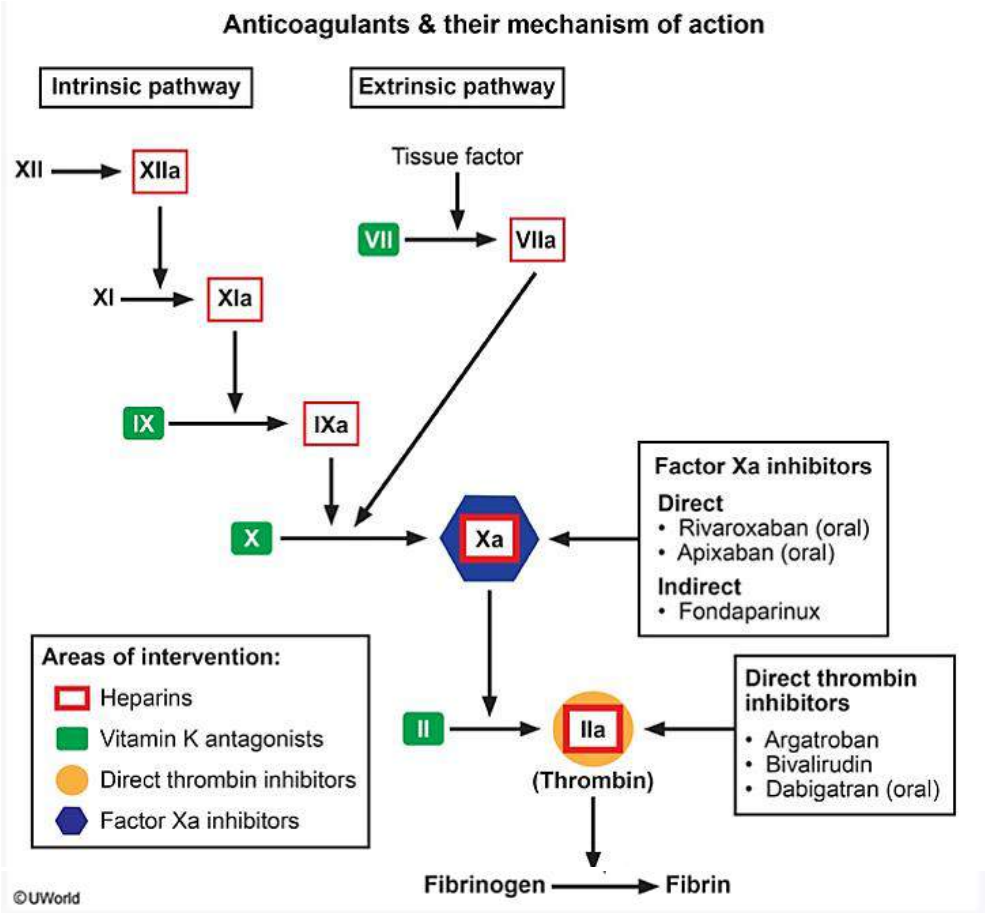
1. Try non-narcotic measures first, unless you are sure (using your clinical judgment) that the patient is in severe pain
2. Do not be afraid to give narcotic analgesics
3. Prescribe adequate amounts of medication

- Initially treat with a dose of short-acting morphine, and then subsequent doses titrated as needed to achieve complete pain control. Once the dose is established, the patient can be switched to long-acting narcotics, and the short-acting morphine is then used as needed for break through pain

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING MANAGEMENT

- In the absence of ↑ lipase levels, rebound and guarding on abdominal examination, presence of bowel movement→ diagnosis of pancreatitis, perforation and abdominal obstruction are less likely
- Dry mucous membranes suggest volume depletion→ IV fluids are the 1st line of management→ next treat N/V
- Serotonin receptor antagonists (eg ondansetron)—best therapy for chemo induced N/V—target 5HT3 receptor—low s/e profile and highly efficacious—acute management and sometimes prophylaxis—sometimes used in combo with corticosteroids
- Dopamine receptor antagonists like metoclopramide and prochlorperazine—2nd or 3rd line for refractory vomiting
  - ➔ GI-specific opioid antagonists such as methylnaltrexone→ reverse opioid induced constipation

ANTICOAGULANTS AND THEIR MOA

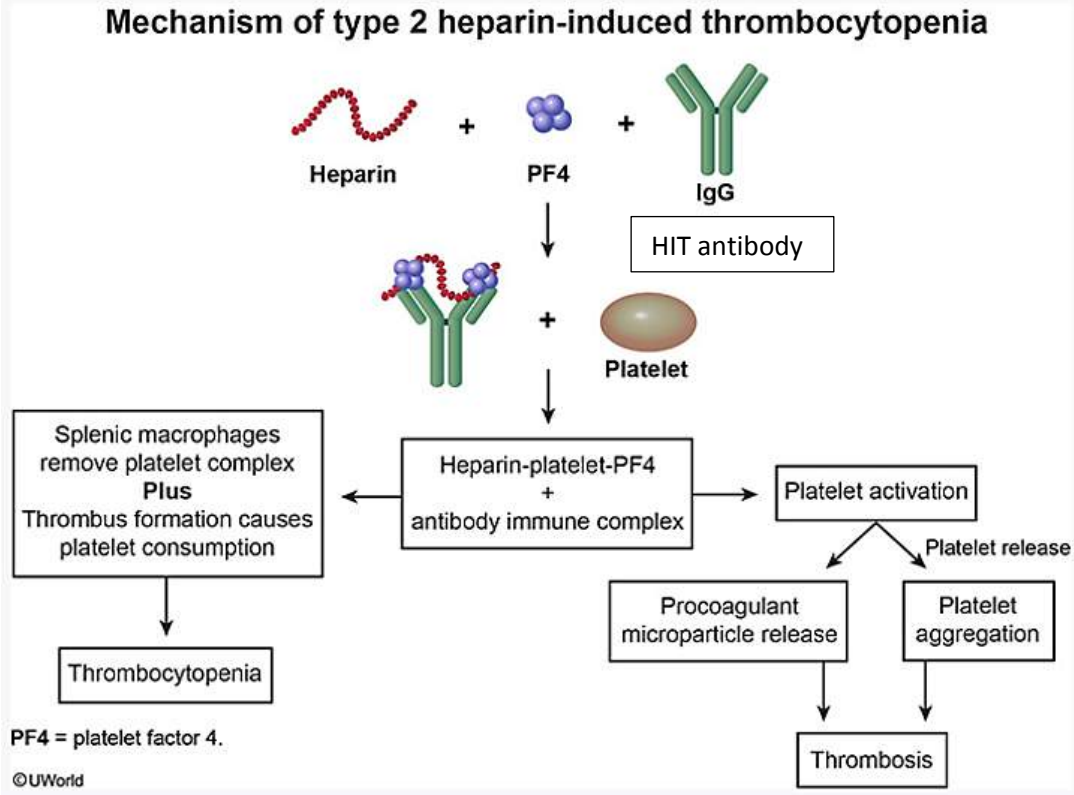


HEPARIN-INDUCED THROMBOCYTOPENIA

TYPE 1 HIT

- Type 1 HIT is marked by nonimmune-mediated platelet aggregation
- It results in mild thrombocytopenia (platelets rarely <100,000/mm'), usually within 2 days of heparin initiation.
- Type 1 HIT does not require intervention and does not cause ill effects; the thrombocytopenia resolves without cessation of heparin

TYPE 2 HIT



Clinical features of type 2 heparin-induced thrombocytopenia	
Clinical signs	Suspected with heparin exposure >5 days **&** any of the following: • Platelet count reduction >50% from baseline • Arterial or venous thrombosis • Necrotic skin lesions at heparin injection sites • Acute systemic (anaphylactoid) reactions after heparin
Diagnostic evaluation	• **Serotonin release assay**: Gold standard confirmatory test • Start treatment in suspected cases prior to confirmatory tests
Therapy	• Stop **ALL** heparin products • Start a direct thrombin inhibitor (eg, argatroban) or fondaparinux (synthetic pentasaccharide)

May manifest earlier in pts previously exposed to heparin

Esp. in those receiving heparin subcutaneously (eg enoxaparin)—classically occurs at abdominal injection site

Or high titer immunoassay of blood

Switch to warfarin once platelet count is >150,000/mm3

- Thrombocytopenia is mild to moderate (mean nadirs of 60,000/mm3) with minimum risk of bleeding. Severe thrombocytopenia (<20,000/mm3) is uncommon
- Thrombosis risk is as high as 50% in untreated HIT. Venous thrombosis: leg, cardiac and skin (at the site of heparin injection) is common. Arterial thrombosis: heart, limbs and CNS
- Heparin induces conformational change to platelet surface protein (platelet factor 4, PF4)→neoantigen formation→ recognition by immune system
- Platelet count usually normalizes 2-7 days after stopping heparin—transfusion not needed unless overt bleeding (uncommon in HIT)

WARFARIN INDUCED SKIN NECROSIS

- Typically occurs within first few days of therapy (usually at large loading doses)
- Esp. occurs in pts with underlying protein C deficiency
- Involve extremities, trunk, breast and penis and marginate over period of hours
- Left untreated→ edematous, purpuric, and ultimately necrotic
- Rx: discontinue warfarin immediately and administer protein C concentrate

DEFINITIONS

ADJUVANT THERAPY

Adjuvant therapy is defined as treatment given in addition to standard therapy. This would be the case if the radiation therapy was given at the same time as the radical prostatectomy.

INDUCTION THERAPY

Induction therapy is an initial dose of treatment to rapidly kill tumor cells and send the patient into remission (<5% tumor burden). A typical example is induction chemotherapy for acute leukemia.

CONSOLIDATION THERAPY

Consolidation therapy is typically given after induction therapy with multidrug regimens to further reduce tumor burden. An example is multidrug therapy after induction therapy for acute leukemia.

MAINTENANCE THERAPY

Maintenance therapy is usually given after induction and consolidation therapies (or initial standard therapy) to kill any residual tumor cells and keep the patient in remission. An example is daily antiandrogen therapy for prostate cancer.

NEOADJUVANT THERAPY

Neoadjuvant therapy is defined as treatment given before the standard therapy for a particular disease. This would be the case in this patient if the radiation therapy was given before the radical prostatectomy was done.

SALVAGE THERAPY

Salvage therapy is defined as treatment for a disease when standard therapy fails, such as radiation therapy for prostate-specific antigen recurrence after radical prostatectomy for prostate cancer.

Contents

ANEMIA

IRON DEFICIENCY ANEMIA

Iron deficiency anemia in children age <2	

Risk factors	• Prematurity
	• Lead exposure
	• Infants who consume:
	  ○ Low-iron formula
	  ○ Cow's milk, soy milk, or goat's milk before age 1 year
	  ○ Exclusive breastfeeding after age 6 months
	• Toddlers who consume:
	  ○ >24 ounces/day of milk =700ml/day
	  ○ <3 servings/day of iron-rich foods (eg, meat, fortified cereal)

Universal screening	• Complete blood count in all children at age 9-12 months
Treatment	• Empiric trial of iron supplementation

Recheck in 4 weeks→if Hb ↑ 1g/dl→continue oral iron therapy for 2-3 months after Hb normalizes to replete iron stores

- Most common nutritional def. in children
- An infant's iron stores are affected by:
  - Mother's iron stores
  - Prenatal and perinatal hemorrhage
  - Gestational age of infant at delivery
- Term infants have sufficient iron stores for 6 months. After 6 months, dietary def. becomes the most imp cause of iron def.
- Often caused by excessive consumption of cow's milk (>24 ounces [700ml] per day). Causes anemia 2° to:
  - Low iron content of iron in milk
  - Poor bioavailability of iron from milk
  - ↑ intestinal blood loss from cow's milk protein-induced colitis
- Children usually asymptomatic—classic symptoms typically absent
- Dx usually made on CBC—peripheral blood smear usually not needed—no further testing in pts with classic presentation

ANEMIA OF PREMATURITY

Anemia of prematurity	
Etiology	• Impaired erythropoietin production • Short red blood cell life span • Iatrogenic blood sampling
Clinical manifestations	• Usually **asymptomatic** • Tachycardia, apnea, poor weight gain
Laboratory findings	• **Low** hemoglobin & hematocrit • **Low** reticulocyte count • Normocytic, normochromic red blood cells
Treatment	• Minimize blood draws • Iron supplementation • Transfusions

RBC transfusion can be given if infant is symptomatic but it can further exacerbate EPO suppression and delay recovery. Supplemental EPO—not effective in preventing need of transfusion

- Affects most pre-term infants and severity and onset depends on degree of prematurity
- Normal: EPO declines after delivery due to ↑ O2 concentration in tissues→ ↓ reticulocyte count→↓RBC (physiological)→ occurs at 2-3 months in term
- Preterm: early onset anemia (40-50days)
- Diagnosis of exclusion: hemolysis, hemoglobinopathies, enzyme defects and infections should be ruled out

APLASTIC ANEMIA

- Aplastic anemia can be acquired or congenital
- Congenital causes more common in children→ Fanconi anemia is the most common congenital cause

ACQUIRED APLASTIC ANEMIA

- Pancytopenia (in contrast aplastic crisis→↓Hb)

Acquired Causes of Aplastic Anemia
Drugs (e.g., NSAIDs, sulfonamides, etc.)
Toxic chemicals (e.g., benzene, glue, etc.)
Idiopathic
Viral infections (e.g., HIV, EBV, etc.)
Immune disorders
Thymoma

Chemotherapy and chloramphenicol

Benzene is an industrial chemical, CCl4, phenylbutazone, insecticides

- Results from injury to bone marrow by ionizing radiation—suspect in any child with pancytopenia and any of the recent above things
- 5-15% pts with thymic tumors have pure red cell aplasia but this finding is common in older women and not in children

FANCONI ANEMIA

- Autosomal recessive or X-linked with clinical findings as below:

Location	Clinical Manifestations of Fanconi Anemia
Bone marrow	Aplastic anemia and progressive bone marrow failure
Appearance	Short stature, microcephaly, abnormal thumbs, and hypogonadism
Skin	Hypopigmented/hyperpigmented areas, café au lait spots, and large freckles
Eyes/ears	Strabismus, low-set ears, and middle ear abnormalities (e.g., hemorrhage, incomplete development, chronic infections, deafness, etc.)

- Other characteristic congenital anomalies such as eye or eyelid changes (microphthalmia), upper limb anomalies (absent thumb), skeletal anomalies, and renal malformations (horeshoe kidneys) may also be present
- Progressive pancytopenia and macrocytosis. Blood counts start to ↓ between 4-12 years of age (average age of diagnosis 8 years) and initial manifestation is usually thrombocytopenia, followed by neutropenia, then anemia. Most children are diagnosed by age 16 years and have predisposition for cancers
- **Pathogenesis:** numerous genes all believed to be involved in DNA repair have been implicated
- **Dx:** chromosomal breaks on genetic analysis along with clinical findings
- **Definitive treatment:** hematopoietic stem cell transplantation

DIAMOND BLACKFAN ANEMIA (DBA)

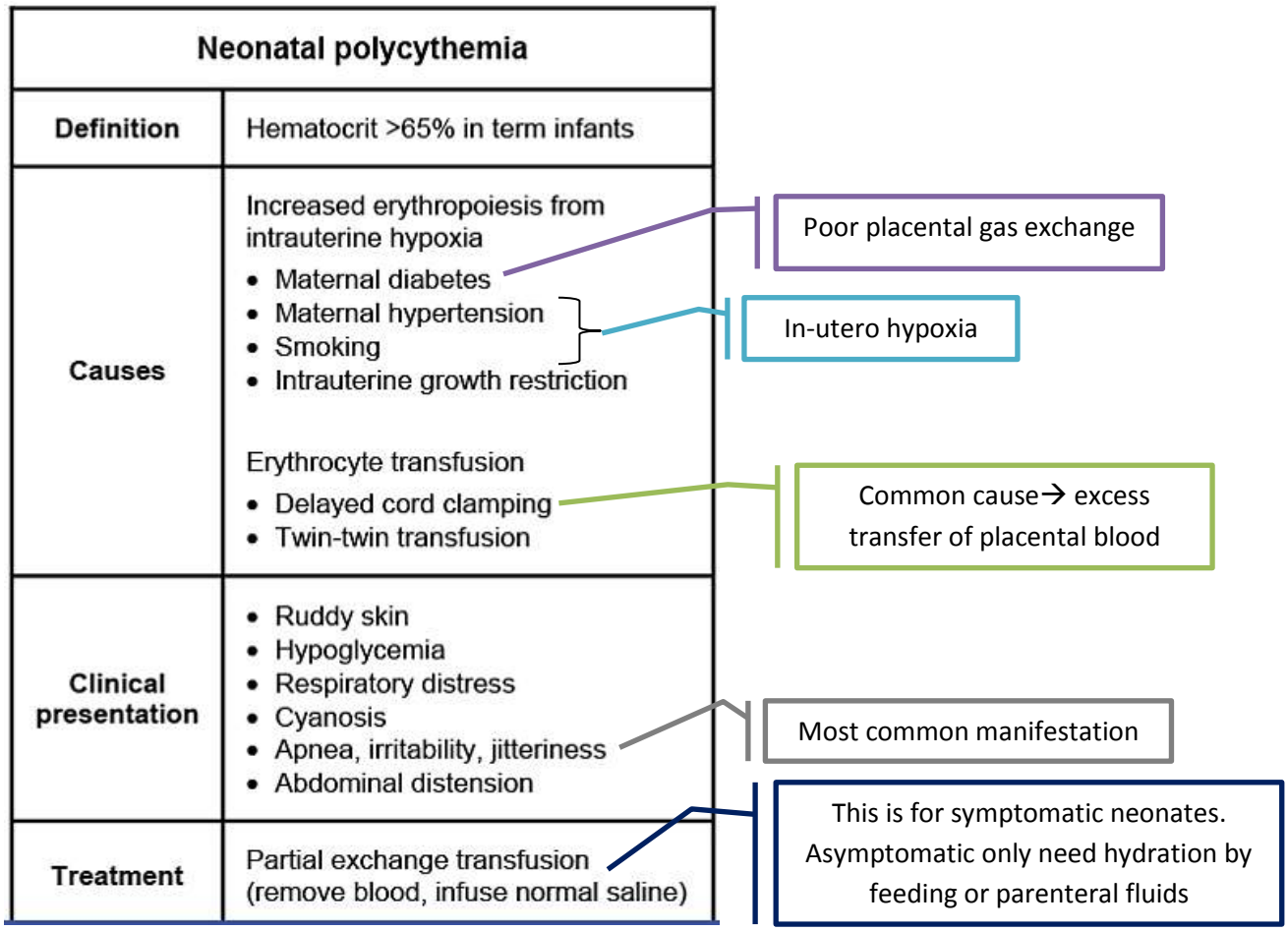
- Also known as congenital pure red cell aplasia
- **S/S:** Present in **1st 3 months of life** with pallor and poor feeding— >90% cases diagnosed in 1st year of life with average within 3 months
- Suspect DBA when: Normocytic or **macrocytic** anemia (but not megaloblastic as neutrophils etc are normal) + **reticulocytopenia + congenital anomalies** (present in >50% cases—like webbed neck, shield chest, cleft lip, triphalangeal thumb) are present
- WBC and platelets are normal
- Majority cases are sporadic—15% may have dominant or recessive inheritance
- **Primary pathology:** intrinsic defect of erythroid progenitor cells→ ↑ apoptosis (programmed cell death)
- **Electrophoresis:** ↑ HbF. Normal chromosomal studies
- **Treatment:** mainly corticosteroids. Non-responsive pts: transfusion

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD (TEC)

- Acquired pure red cell aplasia
- Occur in healthy children between **6months and 5 yo**—most cases are diagnosed after 1st year—no associated congenital anomalies
- Gradual onset with pallor and ↓ activity
- PE: unremarkable except pallor and tachycardia
- Labs: **normocytic normochromic anemia (**without macrocytosis)—Hb ranging from 3-8 g/dl, and extremely low reticulocyte count

NEONATAL POLYCYTHEMIA

Neonatal polycythemia	
Definition	Hematocrit >65% in term infants
Causes	Increased erythropoiesis from intrauterine hypoxia • Maternal diabetes • Maternal hypertension • Smoking • Intrauterine growth restriction Erythrocyte transfusion • Delayed cord clamping • Twin-twin transfusion
Clinical presentation	• Ruddy skin • Hypoglycemia • Respiratory distress • Cyanosis • Apnea, irritability, jitteriness • Abdominal distension
Treatment	Partial exchange transfusion (remove blood, infuse normal saline)



- Most neonates are asymptomatic other than appearing ruddy/plethoric
- As Hct ↑→ ↑ viscosity→ impair blood flow to various organs
- ↑ RBC mass→ ↑ uptake of glucose and calcium by cells→ hypoglycemia and hypocalcemia

IMMUNODEFICIENCIES

WISKOTT ALDRICH SYNDROME (WAS)

Wiskott-Aldrich syndrome	
Etiology	• X-linked recessive defect in WAS protein gene • Impaired cytoskeleton changes during cell signaling in leukocytes, platelets
Clinical features	• Eczema • Microthrombocytopenia (small platelets, low platelet count) • Recurrent infections
Treatment	• Stem cell transplant

C/F can range from petechiae or purpura to severe bleeding like intracranial hemorrhage, hematemesis and hematochezia

Bacterial, viral and fungal

- WAS gene is found in hematopoietic stem cells
- Autoimmune disorders occur in most patients with WAS—eczema being most common, hemolytic anemia, arthritis and vasculitis may also occur
- Dx: clinical but gene testing allows screening of other family members

TUMORS IN CHILDREN

WILM'S TUMOR (NEPHROBLASTOMA)

Wilms tumor (nephroblastoma)	

Epidemiology	• Most common renal malignancy in childhood
	• Fourth most common childhood cancer
	• Peak age 2-5 years
	• Usually sporadic
	• Associated syndromes:
	  • WAGR (**W**ilms tumor, **A**niridia, **G**enitourinary anomalies, intellectual disability [mental **R**etardation])
	  • Beckwith-Wiedemann syndrome
	  • Denys-Drash syndrome

Clinical presentation	• Asymptomatic, firm, smooth, abdominal mass that does not cross midline
Treatment	• Tumor excision or nephrectomy • Chemotherapy • +/- Radiation therapy
Prognosis	• 5-year survival rate with treatment: 90%

Usually asymptomatic→ incidentally found by caretaker or physician. Some may develop **abdominal pain, HTN, hematuria or fever**

Esp. if treated early

- Affects **single kidney**. <10% have B/L renal involvement (stage V cancer)
- Commonly metastasizes to lungs→ children rarely present with pulmonary symptoms
- **Management:** 1st step: abdominal USG (to differentiate Wilms from other abdominal masses)→ followed by contrast enhanced CT of abdomen (to evaluate nature and extent of mass) and chest to identify pulmonary mets

NEUROBLASTOMA

- 3rd most common tumor in children after leukemia and brain tumors but most common in 1st year of life
- Arise anywhere in sympathetic chain but most common in adrenal glands
- Abdominal mass that crosses midline with systemic symptoms

PRIMARY BRAIN TUMORS OF CHILDHOOD

- Most common solid tumors in children and second most common tumors in children after leukemias

Manifestations of central nervous system tumors by location	
Supratentorial	↑ ICP*, seizures , weakness and sensory changes
Posterior fossa	↑ ICP*, ataxia, clumsiness (cerebellar dysfunction)
Brainstem	Ataxia, clumsiness, cranial nerve palsies
Spinal cord	Back pain, weakness, abnormal gait

*Morning headache, vomiting, papilledema, macrocephaly.
ICP = intracranial pressure.

PILOCYTIC (LOW GRADE) ASTROCYTOMA

- Most common brain tumor in children
- Sx depend on tumor location but ↑ ICP irrespective of location as the tumor size ↑. Mostly cause Sx due to local pressure and do not undergo malignant transformation

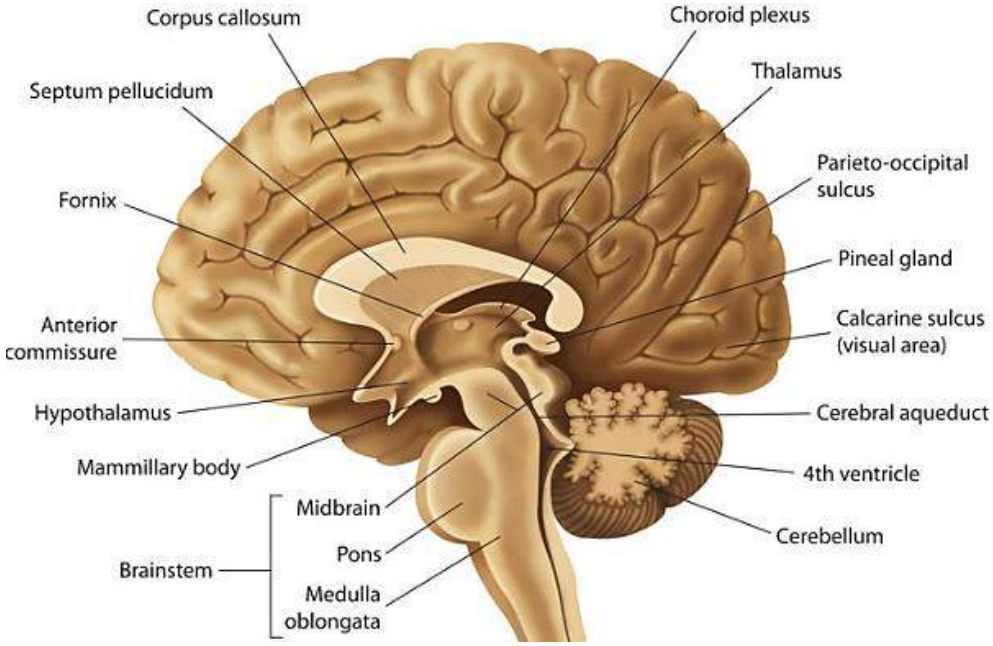
PINEAL GLAND TUMOR/PINEALOMA

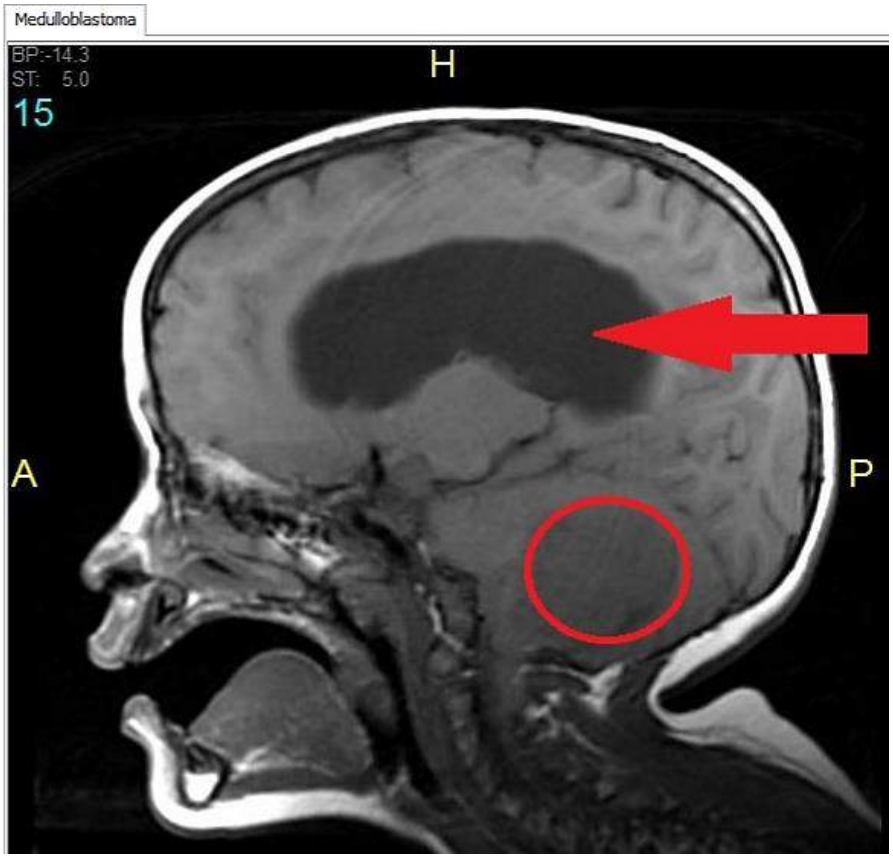
- Pineal gland—located in quadrigeminal cistern→ produce melatonin
- Rare tumors and germ cell tumors account for majority of them
- Serious complications result from mass effect

Clinical features of pineal gland masses	
Parinaud syndrome (dorsal midbrain syndrome)	• Limited upward gaze • Upper eyelid retraction (Collier sign) • Pupils non-reactive to light, reactive to accommodation →known as **light-near dissociation**
Obstructive hydrocephalus	• Papilledema • Headache, vomiting • Ataxia

Result from pressure on pretectal region of midbrain near superior colliculus and CN-III→ upward gaze limited and preference for downward gaze

By blocking aqueduct of Sylvius


Corpus callosum
Choroid plexus
Septum pellucidum
Thalamus
Fornix
Parieto-occipital sulcus
Pineal gland
Anterior commissure
Calcarine sulcus (visual area)
Hypothalamus
Cerebral aqueduct
Mammillary body
4th ventricle
Midbrain
Cerebellum
Brainstem
Pons
Medulla oblongata


Medulloblastoma
BP:-14.3
ST: 5.0
15
H
A
P

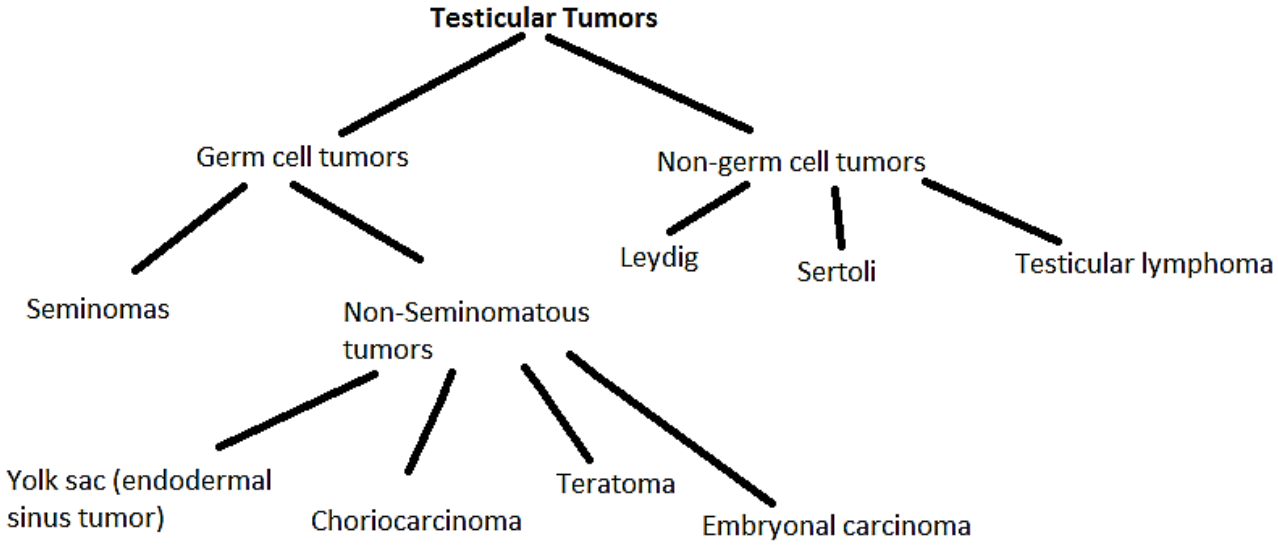
Contents

ANTERIOR MEDIASTINAL MASS

D/D:

- 4 T's
  - Teratoma—including other germ cell tumors
  - Thymoma
  - Thyroid neoplasm
  - Terrible lymphoma

TESTICULAR TUMOR



SEMINOMA VS NON-SEMINOMA

- Serum hormone levels helpful in distinguishing these two
- **Seminoma:** Serum β-hCG levels ↑ in 1/3 pts and AFP levels essentially normal
- **Non-Seminomas:** most have ↑ AFP and a considerable amount have ↑ β-hCG—may be present in the form of mixed germ cell tumor

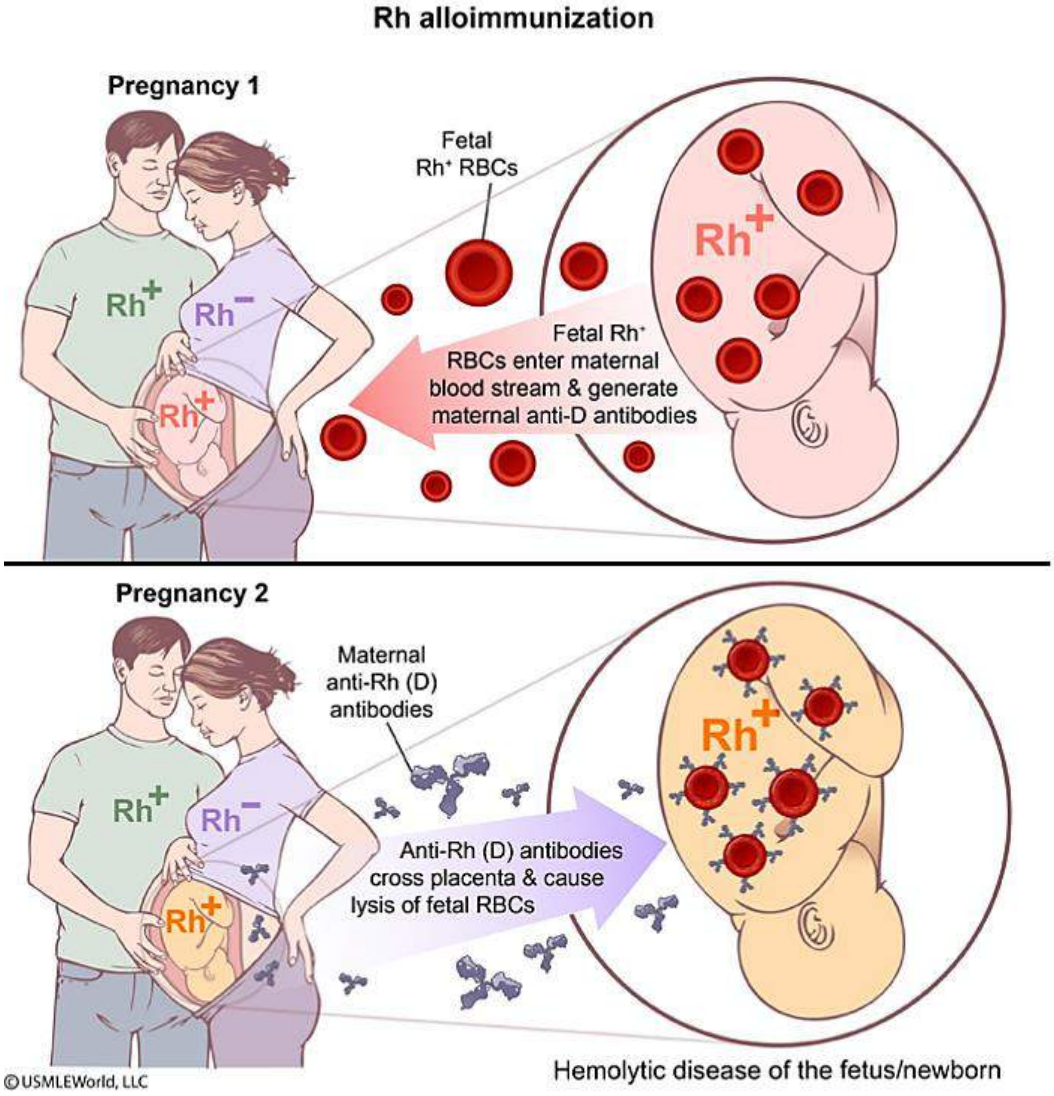
TERATOMA

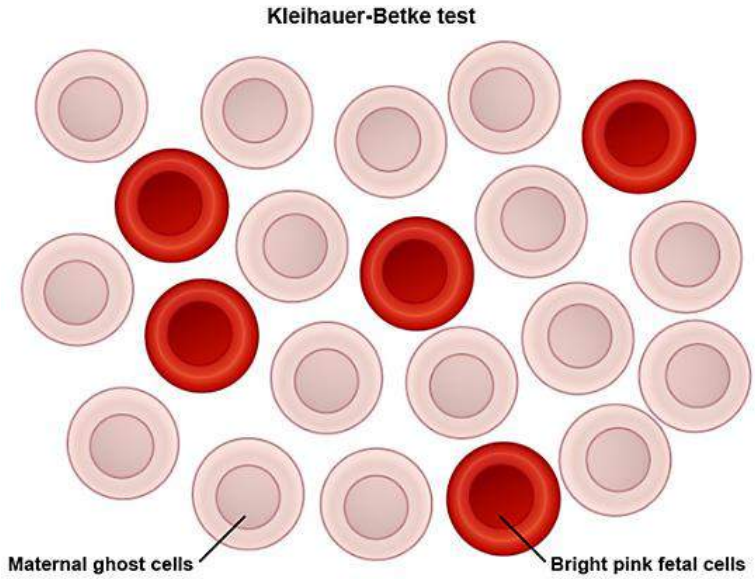
- Can be distinguished from other germ cell tumors by the presence of fat or calcium, esp. if in the form of tooth

Contents

Rh ALLOIMMUNIZATION

- Alloimmunization (i.e sensitization eg anti-D antibody titer of 1:32) occurs when the mother is Rh negative and has an Rh-positive fetus.
- To prevent the maternal immune system from developing anti-D antibodies, anti-D immune globulin is **first administered at 28 weeks gestation and repeated within 72 hours of delivery**.
- A standard dose of 300µg at 28 weeks gestation can usually prevent alloimmunization as the risk of alloimmunization is very low before this time. If pt. develops placental abruption undergo amniocentesis, chorionic villus sampling, and external cephalic version earlier in pregnancy, then KB test should be done to determine dose of anti-D immune globulin.
- ~50% of Rh-negative women will **need a higher dose after delivery**, **placental abruption, or procedures**.
- **The Kleihauer-Betke (KB) test** is commonly used to determine the dose





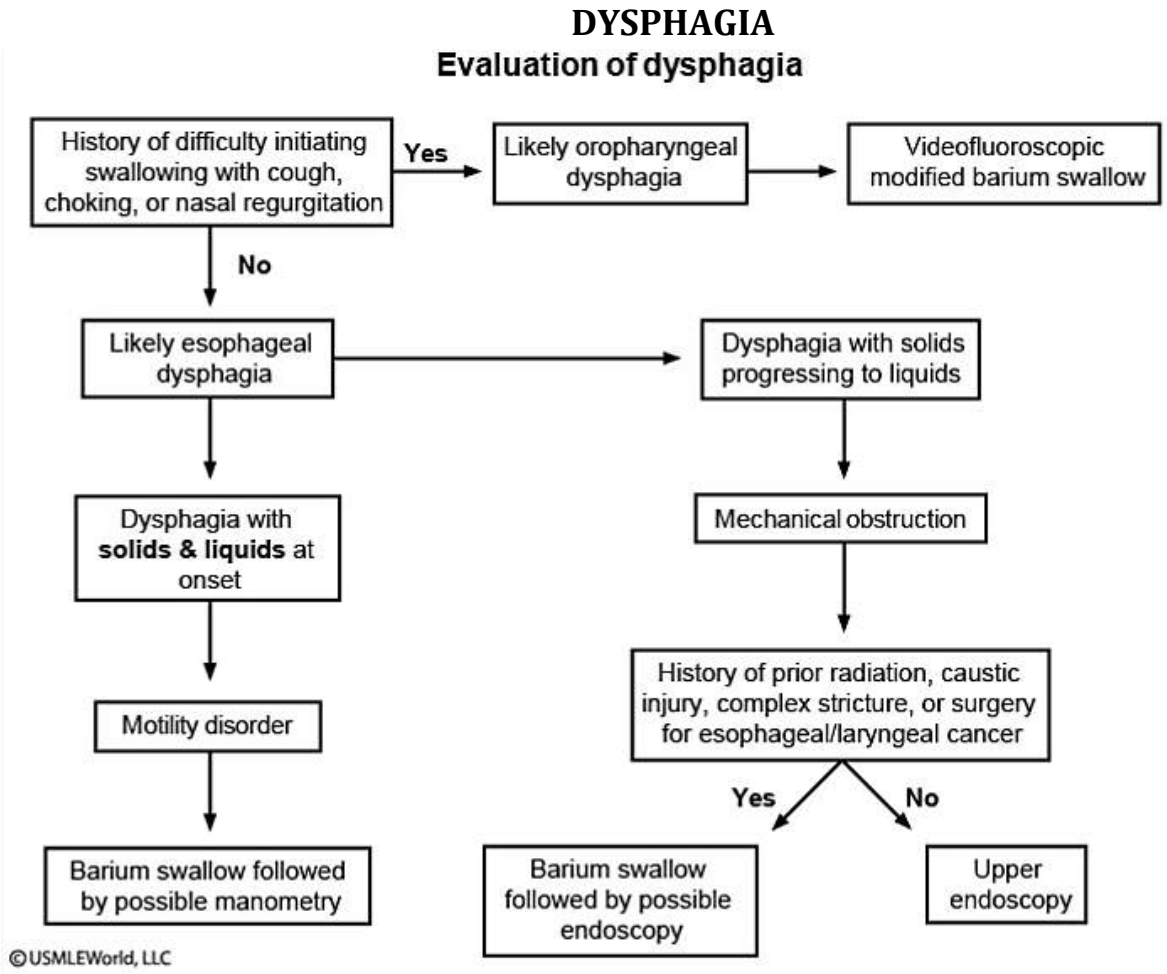
1. RBCs from maternal circulation fixed to a slide
2. Slide exposed to acidic pH solution
3. Maternal Hgb (A) lyses and fetal Hgb (F) remains
4. Lab technician reports % of fetal cells
5. Anti-D immune globulin dose is calculated using % of remaining fetal cells

Leaving ghost cells

ABO ALLOIMMUNIZATION

- O+ mother and father AB+→ less severe hemolytic disease of newborn as compared to Rh incompatibility as varying titers of IgG antibodies are formed and IgM antibodies are also formed. Titers can be high in certain populations like Africans and African Americans leading to severe disease otherwise less severe disease (maybe asymptomatic or with mild anemia or jaundice in newborn) can be usually treated with phototherapy alone
- Only IgG can cross placenta

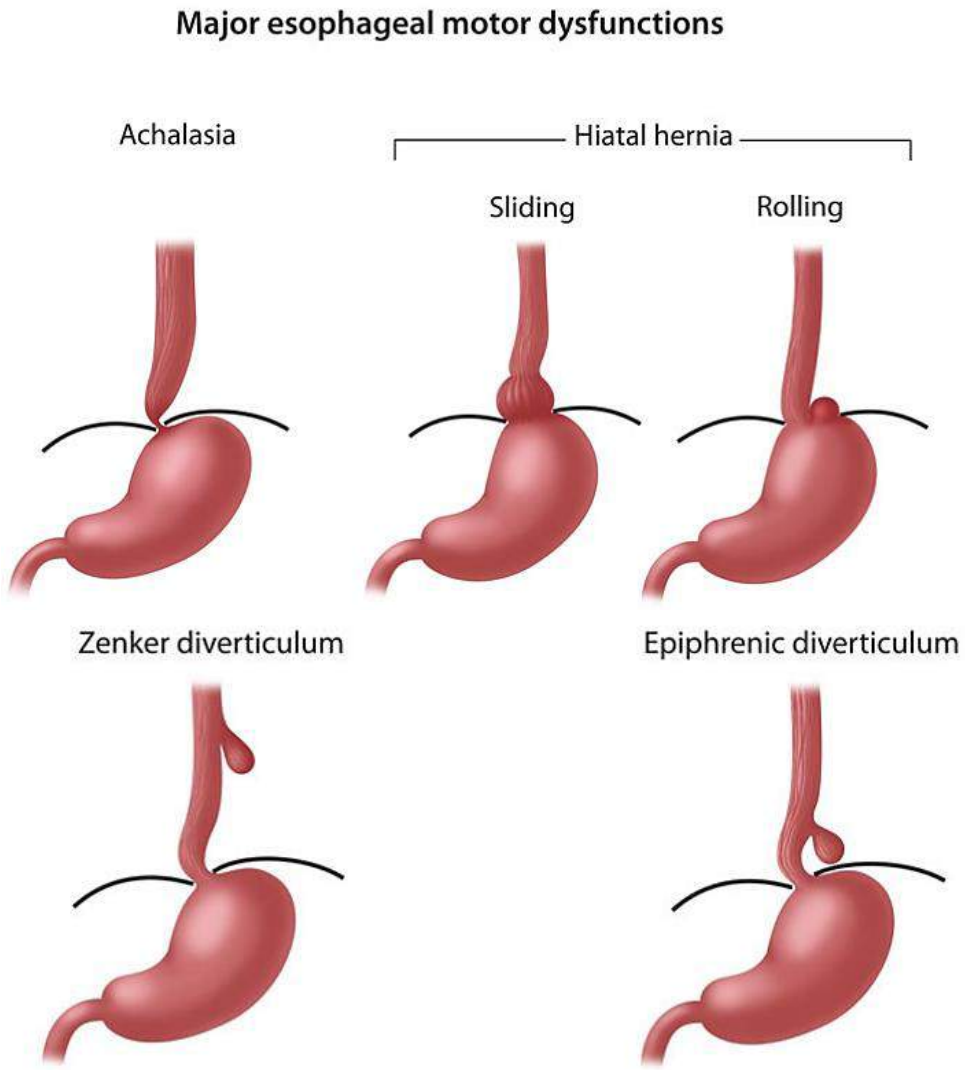
Contents



OROPHARYNGEAL DYSPHAGIA

- Inability to properly transfer food from mouth to pharynx (food stuck in throat—not esophagus)
- Etiologies: stroke, advanced dementia, oropharyngeal malignancy or neuromuscular disorder like myasthenia gravis
- Complications: aspiration pneumonia and weight loss
- Videofluoroscopic modified barium swallow study—preferred initially to evaluate swallowing mechanics, degree of dysfunction and severity of aspiration

ESOPHAGEAL MOTILITY DISORDERS



ACHALASIA AND PSEUDOACHALASIA

- Both present with dysphagia to solids and liquids with smooth tapering of lower esophagus

ACHALASIA:

- Loss of peristalsis in distal esophagus with lack of lower esophageal sphincter relaxation
- Sx for >5 yrs before receiving diagnosis and mild weight loss
- Endoscopy: In achalasia, this evaluation usually shows normal-appearing esophageal mucosa and a dilated esophagus with possible residual material; in addition, it is generally possible to easily pass the endoscope through the lower esophageal sphincter (unlike in malignancy)
- Rx: laparoscopic myotomy and pneumatic balloon dilation→ treatment of choice in pts with low risk of surgery. Pts with high risk of surgery→ botulinum toxin injection, nitrates and calcium channel blockers (but exclude malignancy 1st)

PSEUDOACHALASIA:

- Due to esophageal cancer not due to denervation
- Rapid symptom onset (<6mo), significant weight loss, alcohol and tobacco history, age >60
- Perform→ **Endoscopic evaluation** to exclude malignancy→ later CT for staging and CT can also be performed if endoscopy is unrevealing and there is high suspicion of malignancy

DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm	
Pathophysiology	• Uncoordinated, simultaneous contractions of esophageal body
Symptoms	• Intermittent **chest pain** • **Dysphagia** for solids & liquids
Diagnosis	• Esophagram: **"Corkscrew"** pattern • Manometry: Intermittent peristalsis, multiple **simultaneous contractions**
Treatment	• Calcium channel blockers • Alternate: Nitrates, tricyclics

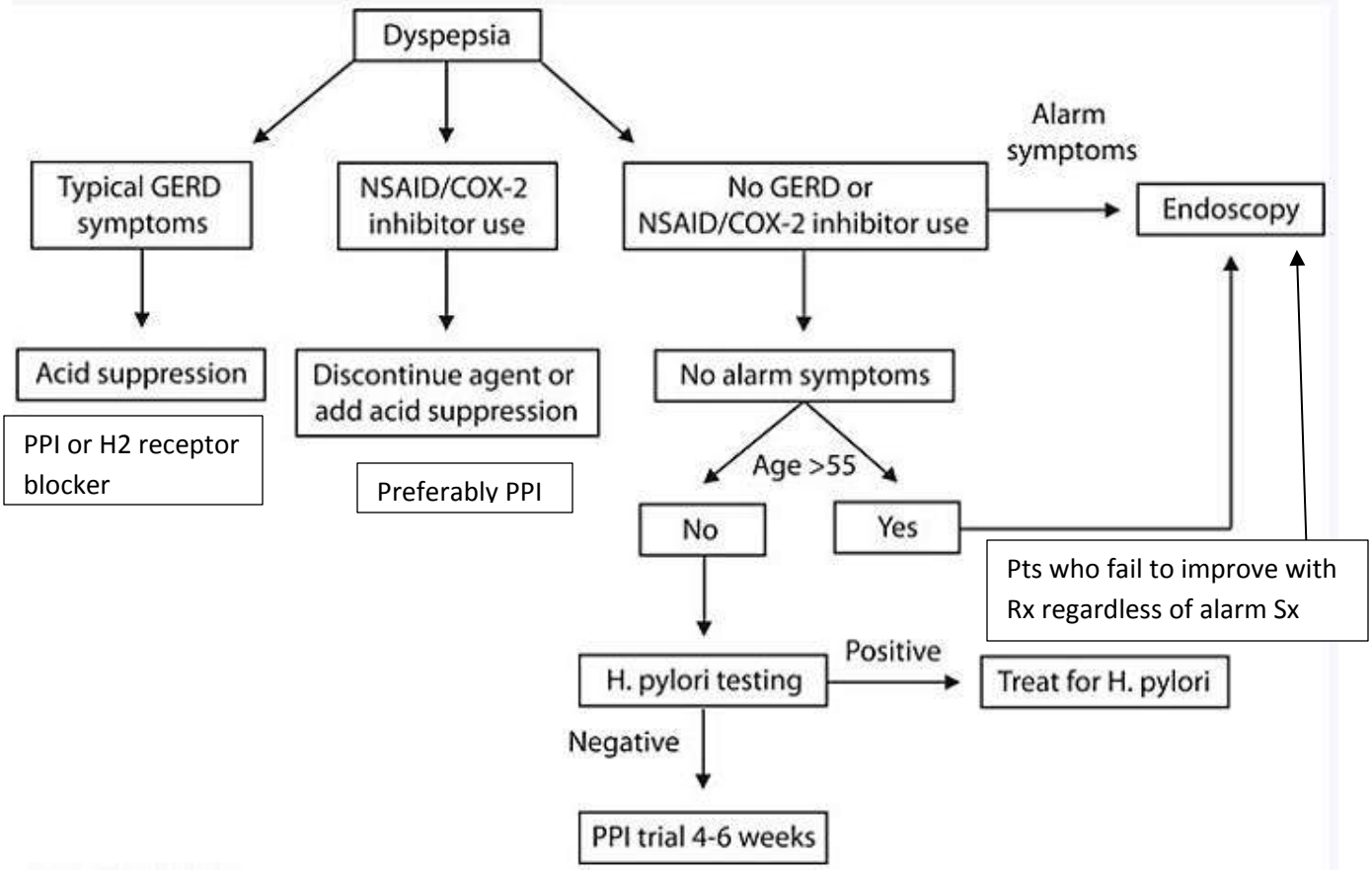
- Due to impaired inhibitory innervation in esophagus
- Often seen in association with emotional factors and functional GI disorders
- Sx resemble achalasia (impaired relaxation of LES) and nutcracker esophagus (excessive tone at LES)
- Endoscopy—usually normal

DYSPEPSIA

CAUSES:

- GERD, nonsteroidal anti-inflammatory drugs, gastric or esophageal cancer, functional dyspepsia, and symptomatic *Helicobacter pylori* infection (with or without peptic ulcer)

MANAGEMENT



- Indications for H. pylori testing: pt with ↑ risk of H. pylori such as those living in regions with high prevalence or house-hold exposure, may elect for **"test and treat"** strategy. Breath test and stool antigen tests are done and not serology

GERD

EVALUATION AND TREATMENT

- Typical GERD without alarm symptoms (dysphagia, odynophagia, weight loss, anemia, GI bleeding, recurrent vomiting)→ trial of daily PPI→ refractory→ change PPI or ↑ use of PPI twice daily→ persistent→ endoscopy or esophageal pH monitoring
- Typical GERD with alarm symptoms (dysphagia, odynophagia, weight loss, anemia, GI bleeding, recurrent vomiting) or men >50 with chronic (>5 years) symptoms or cancer risk factors (eg tobacco use)→ Endoscopy before trial→ esophagitis due to autoimmune or Barrett's esophagus→ treat accordingly—not esophagitis→ further evaluation (e.g manometry)

COMPLICATIONS

- Barrett's esophagus, erosive esophagitis and esophageal (peptic) strictures
- **Benign strictures**

■ Affect 5-15% of pts with GERD. Other causes of esophageal strictures: radiation, systemic sclerosis and caustic ingestions

■ Progressive dysphagia to solids without anorexia and weight loss

■ Leads to improvement in heart burn

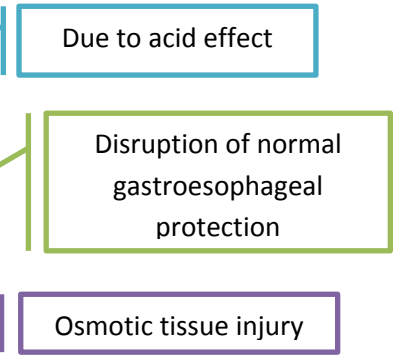
- Symmetric circumferential narrowing on barium swallow
- In any case of stricture in case of Barrett's esophagus, biopsy is necessary to rule out adenocarcinoma. This is done via endoscopy which may be diagnostic and therapeutic (dilation is done if malignancy is not found)

GLOBUS SENSATION (HYSTERICUS)

Globus sensation is a functional disorder of the esophagus characterized by the sensation of a foreign body in the throat. It is often worse when swallowing saliva and is frequently associated with anxiety. Pain, dysphagia, dysphonia, or systemic symptoms are not typical for globus and suggest another condition

PILL ESOPHAGITIS

Medication-induced esophagitis	
Drug class	**Drug**
Antibiotics	Tetracyclines
Anti-inflammatory agents	Aspirin & many nonsteroidal anti-inflammatory drugs
Bisphosphonates	Alendronate, risedronate
Others	Potassium chloride, iron



- Sx: sudden onset odynophagia and retrosternal pain→ difficulty swallowing
- Common in mid-esophagus due to its compression by aortic arch or enlarged left atrium
- Dx: clinically but can be confirmed on endoscopy→ discrete ulcers with normal- appearing surrounding mucosa
- Rx: stop offending med to prevent future injury

ESOPHAGEAL RUPTURE

Clinical features of esophageal perforation	
Etiology	• Spontaneous rupture (Boerhaave syndrome) • Instrumentation (eg, endoscopy) • Esophagitis (infectious/pills/caustic) • Esophageal ulcer
Clinical presentation	• Chest & abdominal pain, systemic findings (eg, fever) • Subcutaneous emphysema in the neck • Hamman sign (crunching sound on chest auscultation)
Diagnosis	• **CXR or CT**: Wide mediastinum, pneumomediastinum, pneumothorax, air around paraspinal muscles, pleural effusion **(late)** • **CT**: Esophageal wall thickening, mediastinal air fluid level • **Water soluble contrast esophagogram**: Leak at perforation site
Management	• Antibiotics & supportive care for all patients • Surgical repair for significant leakage with systemic inflammatory response

SECONDARY TO ENDOSCOPY

- Most common cause of esophageal rupture esp. if performed with other interventions like dilation of stricture
- Life threatening and requires emergent evaluation
- Water-soluble contrast is preferred (less inflammatory to tissues)→ non-diagnostic→ barium study (higher sensitivity)
- Rx: if perforation is confirmed→ primary closure of esophagus and drainage of mediastinum—urgently to prevent development of mediastinitis

CHARACTERISTICS OF GASTROESOPHAGEAL MURAL INJURY

Characteristics of gastroesophageal mural injury

	Mallory-Weiss tear	Boerhaave syndrome
Etiology	• Upper gastrointestinal **mucosal tear** • Caused by forceful retching (↑pressure) Or blunt abdominal trauma • Submucosal arterial or venule plexus bleeding	• Esophageal **transmural** tear • Caused by forceful retching (↑pressure) • **Esophageal air/fluid leakage** into nearby areas (eg, pleura)
Clinical presentation	• Vomiting, retching • Hematemesis • Epigastric pain	• Vomiting, retching, chest & upper abdominal pain Rapid progression • Odynophagia, fever, dyspnea & septic shock can ensue • Subcutaneous emphysema may be seen
Laboratory/ imaging	**Risk factors**: hiatal hernia and alcoholism • EGD confirms diagnosis Longitudinal laceration on endoscopy—mucosal tear in stomach or esophagus	• **CT or contrast esophagography with Gastrografin** confirms diagnosis • Chest x-ray: Pneumomediastinum & pleural effusions • Pleural fluid analysis: **Exudative, low pH, very high amylase** (>2,500 IU/L)
Treatment	• Most tears heal spontaneously • Endoscopic therapy for continual bleed	• Surgery: For thoracic perforations • Conservative measures (eg, antibiotics): For cervical perforations

EGD = esophagogastroduodenoscopy.

PE: can be non-specific but usually shows fever, tachypnea, tachycardia, cyanosis

U/L usually left—with or without pneumothorax—Mediastinal widening can be seen as air and fluid accumulate in mediastinum→ inflammation (mediastinitis)

Amylase—due to saliva in esophageal content—may also contain food particles

With electrocoagulation or local injection of epinephrine

ESOPHAGEAL CARCINOMA

Esophageal cancer	

Subtypes	• **Adenocarcinoma**
	  ○ Distal esophagus, arises from **Barrett esophagus**
	• **Squamous cell carcinoma**
	  ○ Anywhere in the esophagus

Risk factors	• Acid reflux, obesity (adenocarcinoma) • Smoking, alcohol, caustic injury (squamous cell)
Symptoms	• Chest pain • Weight loss • Dysphagia (solids)
Diagnosis	• Endoscopy with biopsy • CT (PET/CT) for staging

PET = positron emission tomography.

Adenocarcinoma: smoking, high dietary calorie or fat intake, medications that promote GERD
SCC: dietary deficiency of beta carotene, vitamin B-1, zinc, selenium, environmental viral infection, toxin producing fungi, hot food and beverages, pickled vegetables and food rich in N-nitroso compounds etc

For definitive diagnosis—esp. start with this in pts > 55 yrs or with alarm Sx like weight loss, gross or occult bleeding, and early satiety

- Young, low-risk pts may first go for barium esophagogram
- Rx: surgery for definitive cure in pts with limited disease

UPPER GI BLEEDING

- Hematemesis, melena, anemia, BUN/creatinine ratio >20 (BUN ↑ because of ↑ intestinal hemoglobin breakdown and ↑ urea absorption in proximal renal tubule due to associated hypovolemia). BUN ↑ in upper GI bleeding and not lower GI bleeding
- Management: supportive management includes supplemental oxygen, bowel rest and IV fluid infusion via large-bore catheters, IV PPI for acid suppression (also reduce rebleeding and need for transfusion and help stabilize clot UGIB- H2 receptor blockers have no such benefit)
- Packed RBC transfusion→ ↑ oxygen carrying capacity

RECOMMENDATIONS/THRESHOLD FOR PACKED RBC TRANSFUSION

Red blood cell transfusion thresholds	
Hemoglobin (g/dL)	**Recommendation**
<7	• Generally indicated
7-8	• Cardiac surgery • Oncology patients in treatment • Heart failure
8-10	• Symptomatic anemia • Ongoing bleeding and hypovolemia • Acute coronary syndrome • Noncardiac surgery
>10	• Not generally indicated

Higher threshold for this due to initial Hb concentration not fully reflecting blood loss—also Hb concentration may drop significantly as blood volume is replaced by crystalloid solutions and mobilization of interstitial fluids

RECOMMENDATIONS FOR INFUSION OF FRESH FROZEN PLASMA

- Contains all clotting factors and plasma proteins from one unit of blood
- Indicated for severe coagulopathy (eg, liver disease, DIC) with active bleeding
- Generally not indicated to correct minimally abnormal INR (<1.6)

RECOMMENDATIONS FOR PLATELET TRANSFUSION

- Given for platelet count <10,000/mm3— because of ↑ risk of spontaneous hemorrhage
- Given for platelet count <50,000/mm3 wit active bleeding

RECOMMENDATIONS FOR WHOLE BLOOD TRANFSUION

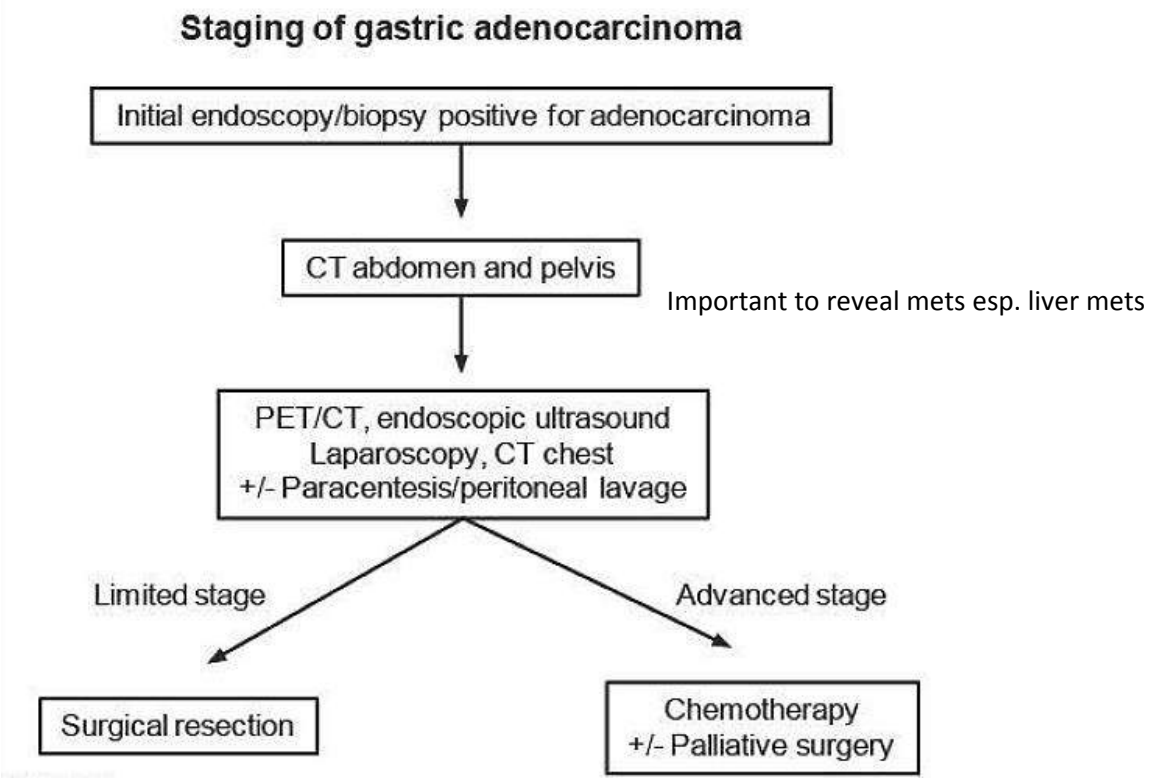
- i.e. PRBC with plasma
- in severe hemorrhage (eg massive trauma) requiring massive transfusion to assist in volume expansion

ACUTE EROSIVE GASTRITIS

- Severe hemorrhagic erosive lesions
- Etiology: exposure of gastric mucosa to injurious agents or substantial ↓ in blood flow
- Aspirin→ causes ↓ in protective PG and direct mucosal injury (alcohol also causes direct mucosal injury and so aggravates aspirin effect)
- Mucosal injury→↓ protective barrier (i.e. ↓ bicarb and mucins and ↓ epithelium integrity)→ allow acid and luminal subs (proteases and bile acids) to penetrate to lamina propria→ further injury to vasculature and subsequent hemorrhage→ hematemesis and abdominal pain

GASTRIC CARCINOMA

GASTRIC ADENOCARCINOMA



- Laparotomy is eventually required for curative or palliative management in most patients, but initial CT imaging is needed to plan the appropriate next steps in evaluation.
- H.pylori is important cause of adenocarcinoma and eradication is recommended before cancer removal to avoid future adenoCA development. Treatment leads to remission in some MALToma cases but not adenoCA

MUCOSA ASSOCIATED LYMPHOID TISSUE LYMPHOMA (MALT LYMPHOMA)

- Low grade MALToma have high association with H.pylori
- Treatment of H. pylori with antibiotics may regress MALToma and is mainstay of gastric MALToma without mets→ no regression→ chemotherapy with CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone) or CHOP + Bleomycyin
- Role of radiotherapy is controversial and currently being used as adjunctive therapy

GASTRIC OUTLET OBSTRUCTION

- Post-prandial pain and vomiting with early satiety
- **Causes:** gastric malignancy, peptic ulcer disease, Crohn disease, strictures (with pyloric stenosis) 2* to caustic acid ingestion—usually develop after 6-12 wks of ingestion after resolution of acute injury and gastric bezoars
- **Maneuver to diagnose gastric outlet obstruction: ABDOMINAL SUCCUSSION SPLASH:** steth placed over upper abdomen and rock back and forth at hip→ retained gastric material >3hours will generate splash indicating presence of gas and fluid in hollow viscous—test has modest sensitivity and specificity but indicate need for more definitive evaluation

- **Initial management:** nasogastric suctioning to decompress stomach, IV hydration and endoscopy for definitive diagnosis
- **Rx:** surgery usually in case of stricture

MALABSORPTION SYNDROMES

CAUSES OF STEATORRHEA

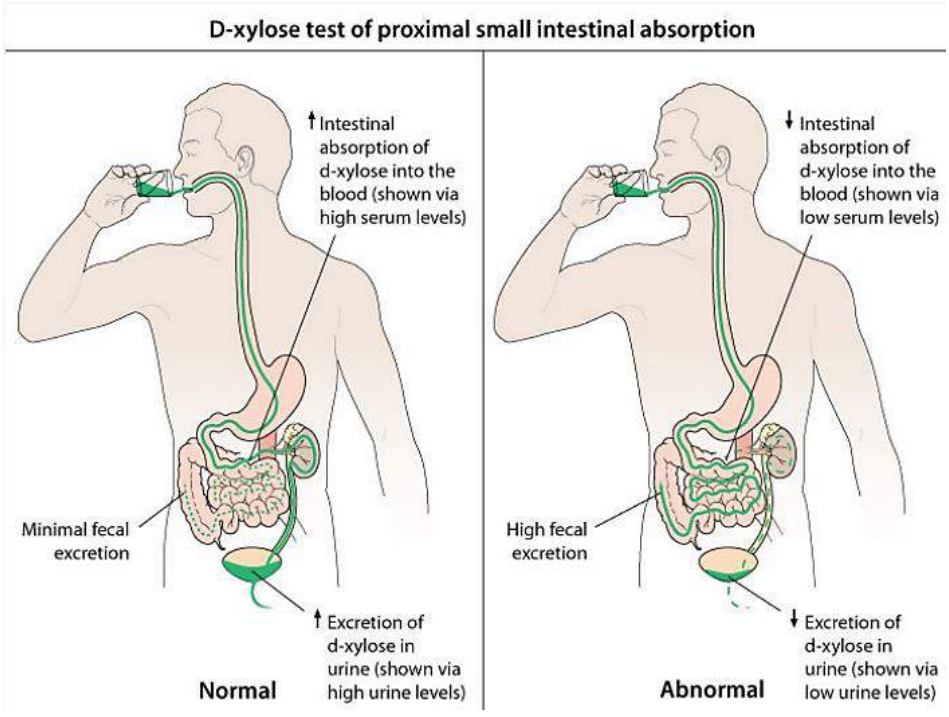
Common causes of steatorrhea	
Pancreatic insufficiency	• Chronic pancreatitis due to alcohol abuse, cystic fibrosis, or autoimmune/hereditary pancreatitis • Pancreatic cancer
Bile salt-related	• Small-bowel Crohn's disease • Bacterial overgrowth • Primary biliary cirrhosis • Primary sclerosing cholangitis • Surgical resection of ileum (at least 60-100 cm)
Impaired intestinal surface epithelium	• Celiac disease • AIDS enteropathy • Giardiasis
Other rare causes	• Whipple disease • Zollinger-Ellison syndrome • Medication-induced

CELIAC DISEASE

Features of malabsorption in celiac disease	
Nutrient	**Symptoms**
General	Bulky, foul-smelling, floating stools
Fat & protein	Loss of muscle mass, loss of subcutaneous fat, fatigue
Iron	Pallor (anemia), fatigue
Calcium & vitamin D	Bone pain (osteomalacia), fracture (osteoporosis)
Vitamin K	Easy bruising
Vitamin A	Hyperkeratosis

- Can also lead to deficiency of vit B12, folic acid and zinc
- Dx: strongly correlated with positive IgA-anti-tissue transglutaminase Ab and IgA anti-endomysial Ab—but many pts with biopsy confirmed celiac have negative IgA antibodies screen due to concurrent selective IgA deficiency which is common in celiac disease.
- If IgA serology is negative and suspicion is high→ measure total IgA or IgG based serologic testing should be done

D-XYLOSE ABSORPTION TEST



- D- xylose—monosaccharide—absorbed directly in proximal small intestine without degradation by pancreatic or brush border enzymes
- **Positive test:** in proximal small intestinal mucosal disease—most common celiac disease
- **False positive:** delayed gastric emptying or impaired glomerular filtration. Small intestinal bacterial overgrowth→ fermentation of d-xylose before absorption—course of antibiotic (rifamixin) will improve d-xylose absorption
- **Negative test:** normal in pancreatic enzyme deficiency, Crohn disease (due to involvement of distal small intestine), lactose intolerance

PANCREATIC INSUFFICIENCY

- Long term alcohol abuse→ chronic pancreatitis→ progressive inflammation→ permanent structural damage→ loss of exocrine and endocrine function→ loss of 90% function→ fat and protein malabsorption→ postprandial epigastric pain (15-30min after meal)—intermittent initially and later becomes persistent
- Dx: pancreatic function test to document pancreatic exocrine insufficiency
- Fecal fat tests (eg, Sudan stain on spot stool specimen or 72-hour collection) confirm steatorrhea and can be used to monitor response to pancreatic enzyme replacement therapy

TROPICAL SPRUE

- Stay in tropical area (eg Peurto Rico) for >1 mo
- Malabsorption→ esp. vit B12 and folate def., glossitis, chelosis, protuberant abdomen, pedal edema, anemia
- Small intestinal biopsy→ blunting of villi, infiltration of chronic inflammatory cells, including plasma cells, lymphocytes and eosinophils
- Careful stool and serologic testing may still be required to exclude infection with *Entamoeba histolytica, Giardia Iamblia, Strongyloides stercoralis, Cryptosporidium parvum,* and *Isospora belli*

LACTOSE INTOLERANCE

- Characterized by a positive hydrogen breath test, positive stool test for reducing substances (not positive urine test for reducing subs—urine test is positive in glucosuria, galactosuria etc), low stool pH (due to fermentation products) and increased stool osmotic gap (due to unmetabolized lactose and organic acids—measured by: 290-[2(stool Na+stool K)]—osmotic gap ↑es >50mOsm/kg in all forms of osmotic diarrhea). There is no steatorrhea.

SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth	
Etiology	• Anatomical abnormalities (eg, strictures, surgery) • Motility disorders (eg, diabetes mellitus, scleroderma) • Other causes (eg, end-stage renal disease, AIDS, cirrhosis, advanced age) Acid suppression, chronic pancreatitis
Signs/ symptoms	• Abdominal pain, diarrhea, bloating, excess flatulence, malabsorption, weight loss, anemia, & nutritional deficiencies
Diagnosis	• Endoscopy (gold standard) with jejunal aspirate showing > 10^5 organisms/mL • Glucose breath hydrogen testing Normal level <10^4 organisms/mL
Common organisms	• Streptococci, *Bacteroides*, *Escherichia*, *Lactobacillus*
Treatment	• 7-10-day course of antibiotics (eg, rifaximin, amoxicillin-clavulanate) • Avoid antimotility agents (eg, narcotics) • Dietary changes (eg, high-fat, low-carbohydrate) • Trial of promotility agents (eg, metoclopramide)

- SIBO is due to ↑ in native and non-native bacteria that cause ↑ fermentation, inflammation and malabsorption
- The proximal small intestine normally contains relatively minimal bacterial colonization due to gastric acidity and peristalsis. Other protective mechanisms against SIBO include bacterial degradation by proteolytic digestive enzymes, trapping of bacteria by intestinal mucus, and an intact ileocecal valve preventing retrograde bacterial movement from the colon.
- Hydrogen breath test using lactulose, show an early peak in hydrogen levels due to rapid lactulose metabolism in the small bowel (normally broken down in the colon)

ZINC DEFICIENCY

- Essential mineral
- Source: animal protein, whole grains, beans and nuts
- Digested in: jejunum
- Risk factors for deficiency: TPN formulations that lack zinc, IBD pts are at risk because of impaired absorption
- Sx: alopecia, abnormal taste, bullous, pustulous lesions surrounding body orifices, and/or extremities and impaired wound healing. In children, it can lead to growth retardation

SELENIUM DEFICIENCY

- Selenium deficiency, like zinc deficiency, may result from chronic TPN.
- It may also result from malabsorption or malnutrition (food sources include nuts, meat, and fish).
- The most important feature of deficiency is cardiomyopathy.

COLLAGENOUS COLITIS

- Collagenous colitis is an uncommon disorder producing chronic watery diarrhea. The colon is frequently involved, but colonoscopy shows normal mucosa. Biopsy shows mucosal subepithelial collagen deposition

IRRITABLE BOWEL SYNDROME

Clinical features of irritable bowel syndrome	
Rome diagnostic criteria	**Recurrent abdominal pain/discomfort ≥3 days/month for the past 3 months & ≥2 of the following:** • Symptom improvement with bowel movement • Change in frequency of stool • Change in form of stool
Warning signs/ symptoms	**Signs/symptoms suggesting etiologies other than IBS** • Rectal bleeding • Nocturnal (awakens from or prevents sleep) or worsening abdominal pain • Weight loss • Abnormal laboratory findings (eg, anemia & electrolyte disorders)

- Common in young women—most common GI Dx in North America
- Can also present with non-specific symptoms of GERD, dysphagia, early satiety and chest pain
- Earlier Dx of exclusion—now: based on ROME III criteria, no alarm symptoms or FH of IBD or colorectal CA→ need no further workup

INFLAMMATORY BOWEL DISEASE

- IBD has bimodal distribution—most present in 20s-30s with second peak around 60s
- Neutrophilic cryptitis is seen in both conditions

CROHN DISEASE	ULCERATIVE COLITIS
Non-caseating granulomas (pathognomonic-60% cases)- granulomas also found in GI TB, sarcoidosis and Yersinia infection	No granulomas
Transmural involvement, skip lesions, cobblestone appearance of colon, creepy fatty appearance of mesentery, fistulas, fissures and perianal disease. String sign due to bowel wall thickening	Crypt abscesses and ulcer (characteristic), mucosal and submucosal involvement only. Lead pipe appearance. Pseudopolyps (inflammatory polyps due to chronic disease—may be present in CD)
Abdominal pain and bloody diarrhea (more common in	Abdominal pain and bloody diarrhea

UC but can occur if disease involves colon)—usually one of the two patterns: fibrostenotic obstructing pattern or penetrating fistulous pattern	
May involve any part from mouth to anus but usually limited to terminal ileum—may cause solitary colitis in 15-20% patients—rectum generally spared	Limited to colon and rectum always involved—sometimes may involve terminal ileum (baskwash ileitis)

ULCERATIVE COLITIS

Ulcerative colitis	
Symptoms	• Bloody diarrhea • Weight loss, fever
Endoscopic findings	• Erythema, friable mucosa • Pseudopolyps • Involvement of rectosigmoid • Continuous colonic involvement (no skip lesions)
Biopsy	• Mucosal & submucosal inflammation • Crypt abscesses
Complications	• Toxic megacolon • Primary sclerosing cholangitis • Colorectal cancer • Erythema nodosum, pyoderma gangrenosum • Spondyloarthritis

- Risk of melanoma and other non-melanomatous skin cancers ↑ in IBD due to immunosuppressive meds

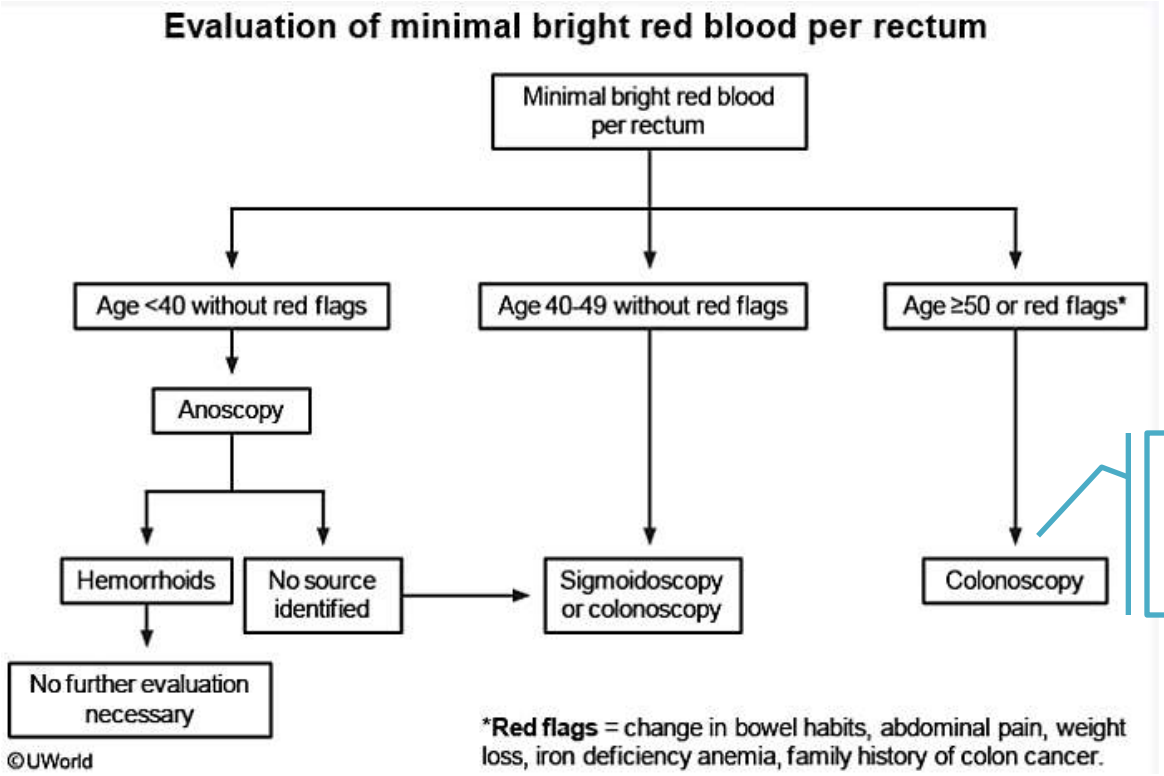
TOXIC MEGACOLON

Toxic megacolon	
Risk factors	• IBD • *Clostridium difficile* infection
Diagnosis	• Systemic toxicity (eg, fever, tachycardia, hypotension) • Bloody diarrhea • Abdominal distension/peritonitis • Marked colonic distension on imaging
Management	• Bowel rest, NG suction, antibiotics • +/– Corticosteroids if IBD-associated • Surgery if unresponsive to medical management

IBD = inflammatory bowel disease; NG = nasogastric.

- UC: usually limited to colonic mucosa—at times extend to smooth muscle layer→ paralysis of muscles→ colonic dilation
- Usually in early disease (usually <3yrs of diagnosis)
- Can be total or segmental colonic dilation
- Other causes: ischemic colitis, volvulus, diverticulitis, infections (eg C. diff, CMV colitis in HIV pts), obstructive colon cancer (less common)
- Sx: severe bloody diarrhea, and systemic findings
- Dx: plain xray (showing dilated right or transverse colon (>6cm), possible multiple air-fluid levels, thick haustral markings that do not extend across entire lumen) and >/= 3 of the following:
  - Fever >38 C, pulse >120/min, WBC > 10,500/µl and anemia. Other findings can be: volume depletion, altered mental status, hypotension, peritonitis and electrolyte imbalance
- Rx: medical emergency→ nasogastric decompression, IV hydration, broad spectrum antibiotics, bowel rest. IV corticosteroids preferred for treating IBD-toxic megacolon. Emergency surgery (subtotal colectomy with end-ileostomy—treatment of choice) if colitis not resolved. >50% cases will respond to conservative management
- Opioids are CI due to antimotility effect that can promote perforation. Discontinue other antimotility drugs like loperamide and anticholinergic agents

MINIMAL BRIGHT RED BLOOD PER RECTUM (BRBPR)



- Usually due to hemorrhoids or rectal fissures. But can be due to serious causes like proctitis, rectal ulcers, colorectal polyps, cancer
- Evaluation depends on pt's presentation and risk factors
- Anoscopy is also useful in older pts to visualize a palpable abnormality found on PE

FACTITIOUS DIARRHEA

- Due to laxative abuse
- Frequent, watery and nocturnal diarrhea
- Characteristic biopsy findings: dark brown discoloration of colon with lymph nodes shining through as pale patches (melanosis coli)—esp. in those using/abusing anthraquinone containing laxatives (e.g. bisacodyl)—generally develop in 4 months of laxative ingestion and disappear in same time of discontinuation
- Alternative way of diagnosis: histological evidence of pigment in macrophages of lamina propria

DIVERTICULA OF GI TRACT

DIVERTICULOSIS

- Association with chronic constipation
- Constipation (↓ fiber intake and ↑ fat diet)→↑intraluminal pressure→diverticula—conversely, altered motility in diverticular disease→ constipation—most common in sigmoid colon but bleeding diverticula are usually on right side—bleeding is usually painless—usually resolve spontaneously, minority require endoscopic or surgical intervention

- ↑ fiber (fruits and vegetables)→ unclear risk of diverticular formation but ↓ risk of acute diverticular complications
- ↑risk of diverticular complications (diverticular hemorrhage and diverticulitis): ↑meat intake, aspirin, NSAID use, obesity and possibly smoking
- Alcohol→↑ diverticula formation but not ↑ risk of diverticular complications

ACUTE DIVERTICULITIS

Clinical features of acute diverticulitis	
Clinical presentation	• Abdominal pain (usually lower left quadrant) • Fever, nausea & vomiting • Ileus (peritoneal irritation) Leukocytosis
Diagnosis	• Abdominal CT (oral & intravenous contrast)
Management	• Bowel rest • Antibiotics (eg, ciprofloxacin, metronidazole)
Complications	• Abscess, obstruction, fistula, perforation

- Inflammation due to microperforation of diverticulum
- Characterized as uncomplicated (75%) and complicated (25%)

Uncomplicated:

- Uncomplicated diverticulitis in stable pts can be managed in outpatient setting by bowel rest, oral antibiotics and observation
- Elderly, immunosuppressed, high fever or significant leukocytosis, or have significant comorbidities→ hospitalization and IV antibiotics

Complicated:

- Associated with abscess, perforation, obstruction or fistula formation
- **Abscess:**
  - Fluid collection <3 cm→ IV antibiotics and observation→ surgery for pts with worsening symptoms
  - fluid collection >3cm→ CT- guided percutaneous drainage→ if Sx not controlled by 5th day→ surgical drainage and debridement
- Sigmoid resection reserved for pts with fistulas, perforation with peritonitis, obstruction or recurrent attacks of diverticulitis

➔ 10-15% pts have urinary frequency, urgency, dysuria due to bladder irritation from sigmoid colon inflammation

➔ CT scan: inflammation in pericolic fat, presence of diverticula, bowel wall thickening, soft tissue masses (eg phlegmons), and pericolic fluid collection suggesting abscess (upright x-ray shows non-specific findings)

➔ Barium enema, sigmoidoscopy and colonoscopy→ CI in acute diverticulitis. Colonoscopy→ performed after resolution of acute diverticulitis to rule out CRC

ZENKER DIVERTICULUM

Zenker diverticulum	
Clinical features	• Usually ≥age 60 • More common in males • **Dysphagia** • **Halitosis** • Regurgitation & aspiration • Variable neck mass
Diagnosis	• **Barium esophagram** • Esophageal manometry
Management	• Open/endoscopic **surgery** • Cricopharyngeal myotomy

- Other C/Fs: oropharyngeal dysphagia associated with neck mass, gurgling in throat
- Potential complications: tracheal compression, ulceration with bleeding
- Develop immediately above upper esophageal sphincter with posterior herniation between fibers of cricopharyngeal muscle
- Occurs due to upper esophageal sphincter dysfunction and esophageal dysmotility

COLOVESICAL FISTULA

Clinical features of colovesical fistula	
Etiology	• Diverticular disease (sigmoid most common) • Crohn disease • Malignancy (colon, bladder, pelvic organs)
Clinical presentation	• Pneumaturia (air in urine) • Fecaluria (stool in urine) • Recurrent urinary tract infections (mixed flora)
Diagnosis	• Abdominal CT with oral or rectal (**not intravenous**) contrast • Colonoscopy to exclude colonic malignancy

Usually occurs at end of urination as gas collects at the top of bladder

Shows contrast in bladder with thickened colonic and bladder walls

- Rx: usually surgery after infection resolution

MESENTERIC ISCHEMIA

ACUTE MESENTERIC ISCHEMIA

Acute mesenteric ischemia	
Presentation	• Rapid onset of periumbilical pain (often severe) • Pain **out of proportion** to examination findings • Hematochezia (late complication)
Risk factors	• **Atherosclerosis** (acute on chronic) • Embolic source (thrombus, vegetations) • Hypercoagulable disorders
Laboratory findings	• Leukocytosis • Elevated amylase & phosphate levels • **Metabolic acidosis** (elevated **lactate**)
Diagnosis	• **CT** (preferred) or MR angiography • Mesenteric angiography, if diagnosis unclear

Urge to defecate

A.fib., cardiovascular aneurysm, shock, vasoconstriction, acute thrombosis due to peripheral arterial disease or low cardiac output states

Elevated Hb (hemoconcentration)

Or low bicarb

- Most common in elderly
- May result from cardiac embolus (a. fib), arterial thrombus (atherosclerosis) or other etiology (as in shock or vasoconstriction)
- Periumbilical abdominal pain can be associated with N/V—out of proportion to PE findings→ if prolonged→ more focal abdominal tenderness (due to local inflammation/infarction, perforation or peritonitis) or peritoneal signs (eg guarding, rebound tenderness)
- CT: focal or segmental bowel wall thickening, pneumatosis intestinalis, small bowel dilation, mesenteric stranding and mesenteric thrombi
- **Management:** Patients with evidence of bowel infarction→ undergo immediate operative evaluation; otherwise, diagnosis can be confirmed radiologically by **CT angiography**. Treatment includes open embolectomy with vascular bypass or endovascular thrombolysis. In addition, patients should be started on broad-spectrum antibiotics and, in the absence of active bleeding, anticoagulation to reduce the risk of clot expansion

CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia	
Etiology	• **Atherosclerosis** (smoking, dyslipidemia)
Clinical features	• Crampy, **postprandial, epigastric pain** • **Food aversion** & weight loss
Diagnosis	• Signs of malnutrition, abdominal bruit • **CT angiography** (preferred), Doppler ultrasonography
Management	• Risk reduction (eg, tobacco reduction), nutritional support • Endovascular or open surgical **revascularization**

May also complain of nausea, early satiety and diarrhea. Pain starts within first hour of eating and resolves within next 2 hours

- Abdominal x-ray and CT may show calcified vessels—diagnosis require better calcification

ISCHEMIC COLITIS

Ischemic colitis	
Risk factors	• Age >60 • Chronic renal disease/hemodialysis • Atherosclerotic vascular disease & procedures • Myocardial infarction
Clinical features	• Mild pain & tenderness • Hematochezia, diarrhea • Metabolic (lactic) acidosis
Diagnosis	• **CT scan**: Thickened bowel wall, double halo sign, pneumatosis coli • **Colonoscopy**: Mucosal pallor or cyanosis, petechia, hemorrhage
Management	• Supportive care: Intravenous fluids, bowel rest • Intravenous antibiotics • Colon resection (bowel infarct or clinical deterioration)

Fever, nausea, leukocytosis

CT scan with IV contrast is performed urgently to assess immediate need for surgery→ i.e. extensive bowel damage, perforation, gangrene → if surgery not needed→ colonoscopy to confirm Dx

- **Commonly involved sites:** splenic flexure at watershed line btw territory of superior and inferior mesenteric artery and rectosigmoid junction at watershed btw sigmoid artery and superior rectal artery

RETROPERITONEAL HEMATOMA

- Back pain, hemodynamic instability (anemia, weakness, dizziness), pt on anticoagulation (normal or supratherapeutic INR)→ raise suspicion for retroperitoneal hematoma→ perform abdominal CT→ isodense area in retroperitoneum
- The risk of bleeding while on warfarin therapy is greatest in patients with risk factors such as **diabetes, age > 60, hypertension and alcoholism.**

ANGIODYSPLASIA

- Due to dilated veins and arteriovenous malformation
- ↑ incidence after 60
- Common in right colon but can occur anywhere
- More frequently diagnosed in pts with: advanced renal disease and vW disease due to ↑ bleeding tendency, aortic stenosis also ↑es risk due to acquired vWF deficiency (from disruption of vW multimers as they traverse the turbulent valve space induced by AS—has been reported to remit after valve replacement)
- Dx: endoscopy but may not be diagnosed properly due to poor bowel prep or location behind a haustral fold
- Rx: asymptomatic→ no treatment needed. Anemia or gross or occult bleeding→ endoscopic cautery usually

COLONIC POLYPS

- A polyp is a grossly visible protrusion from the flat mucosal surface of the intestine. Most polyps are benign.

CLASSIFICATION OF POLYPS

1. Hyperplastic polyps:

- Most common non-neoplastic polyps in the colon. Arise from hyperplastic mucosal proliferation. No further work-up needed.

2. Hamartomatous polyps:

- Include juvenile polyp (a non-malignant lesion, generally removed due to the risk of bleeding) and Peutz Jeghers polyp (generally non-malignant).

3. Adenoma:

- Most common type of polyp found in the colon. Present in approximately 30-50 % of elderly people. These polyps are potentially premalignant; however, <1% of such polyps become malignant. Most polyps are asymptomatic; less than 5% of patients have positive occult stool tests.

The probability of an adenomatous polyp progressing into cancer can be judged clinically by the lesion's gross appearance, histology, and size.

1. Adenoma can be **sessile or stalked (pedunculated)**. Cancer is seen more commonly in sessile polyps
2. **Histologically**, adenoma is divided into tubular, tubulovillous, and the villous variety. Villous adenomas, which are most commonly sessile, are most likely (three times more likely than tubular adenoma for malignant transformation) to become malignant among all three varieties. Second on

the list is tubulovillous, followed by tubular adenoma with the least risk of malignant transformation. Therefore, as the villus component increases, the risk of malignancy increases.

3. The likelihood of an adenomatous lesion containing invasive cancer also depends on the size of the polyp. The risk is negligible (<2%) with <1.5 cm polyp, intermediate (2-10%) with 1.5-2.5 cm size polyp, and substantial (10%) with polyps >2.5 cm in size

LYNCH SYNDROME

- Lynch syndrome is also known as hereditary non-polyposis colorectal cancer (HNPCC). To aid its diagnosis, the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer established criteria known as the Amsterdam Criteria I:

1. At least three relatives with colorectal cancer, one of whom must be a first degree relative of the other two
2. Involvement of two or more generations
3. At least one case diagnosed before age 50
4. Familial adenomatous polyposis has been excluded

- HNPCC is also classically divided into two subgroups on clinical grounds

1. Hereditary site specific colon cancer (Lynch syndrome I)
2. Cancer family syndrome or (Lynch syndrome II)

- Lynch syndrome II is distinctly associated with a high risk of extracolonic tumors, the most common of which is endometrial carcinoma, which develops in up to 43% of females in affected families. Also associated with ovarian and skin cancers

COLORECTAL CANCER

SCREENING

Colon cancer screening in high-risk patients	
Family history of adenomatous polyps or CRC • First-degree relative at age <60	• Colonoscopy at age 40 **or** 10 years before the age of diagnosis in the relative (whichever comes first) • Repeat every 3-5 years
Inflammatory bowel disease • Ulcerative colitis • Crohn colitis	• Begin 8 years post diagnosis (12-15 years if disease only in left colon) • Colonoscopy with biopsies every 1-2 years
Familial adenomatous polyposis	• Begin at age 10-12 • Colonoscopy every year
Hereditary nonpolyposis CRC (Lynch syndrome)	• Begin at age 20-25 • Colonoscopy every 1-2 years

CRC = colorectal cancer.

Also repeat after 5 years if 1-2 small adenomatous polyps are found

And rectum

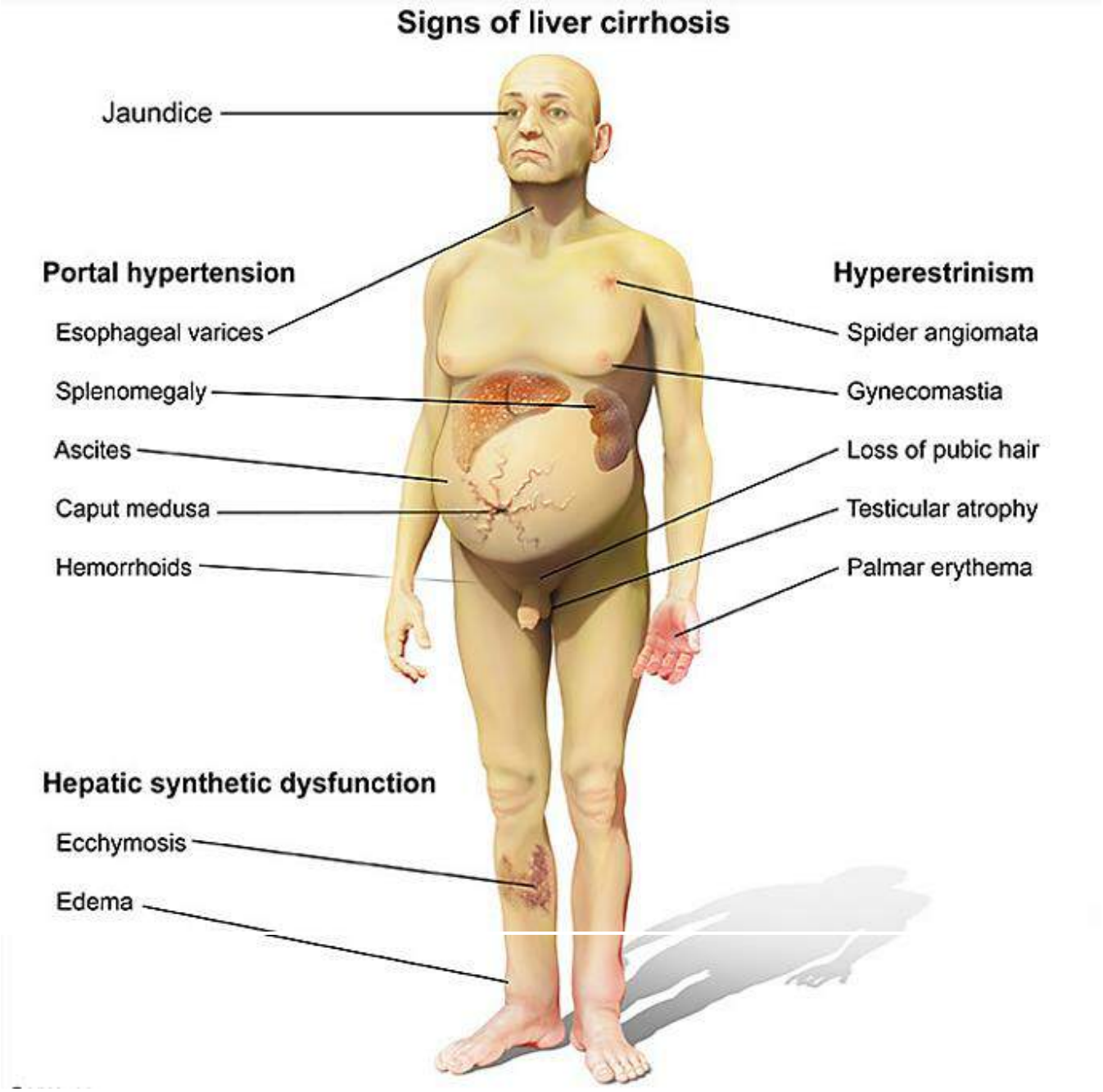
Autosomal dominant—mutation in APC gene—100% risk of cancer if not appropriately treated with proctocolectomy

- Colonic dysplasia→ ↑ risk of adenocarcinoma→ prophylactic colectomy advised
- Normally done in all pts >/= 50 yo.

METHODS OF SCREENING

- Screening can be performed using high-sensitivity fecal occult blood testing (FOBT) annually, flexible sigmoidoscopy every 5 years combined with FOBT every 3 years, or colonoscopy every 10 years.

CIRRHOSIS



COMMON CAUSES OF CIRRHOSIS

Clinical clues for common etiologies of cirrhosis	
More common	• **Chronic hepatitis B or C viral infection:** Intravenous drug use, blood transfusions, multiple sexual contacts • **Alcoholic liver disease:** Excessive alcohol intake • **Nonalcoholic fatty liver disease:** Diabetes, obesity &/or metabolic syndrome • **Hemochromatosis:** Family history of cirrhosis; history of diabetes, "bronze" skin appearance; high transferrin saturation
Less common	• **Autoimmune:** Family history of cirrhosis, history of other coexisting autoimmune disorders (eg, thyroiditis), anti- smooth muscle/liver kidney microsomal type 1 antibodies • **Primary biliary cirrhosis:** More common in women; fatigue, pruritus, elevated alkaline phosphatase; positive antimitochondrial antibody • **Primary sclerosing cholangitis:** Associated with inflammatory bowel disease • **Alpha-1 antitrypsin deficiency:** Coexisting lung involvement, family history of cirrhosis • **Cardiac cirrhosis:** Coexisting right-sided heart failure • **Medications:** eg, Methotrexate, isoniazid • **Wilson disease:** Family history of cirrhosis at young age, Kayser–Fleischer rings in eyes

Alcoholic hepatitis= AST>ALT (ratio >2:1)

NAFLD= ALT>AST (L=lipids)—if AST>ALT in NAFLD→ suggest progression to advanced fibrosis and cirrhosis

- If pt has mildly abnormal LFTs→ obtain drug and alcohol hx, family hx, blood transfusion hx, travel outside US, high risk sexual practices→ if taking drugs or alcohol→ discontinue offending agents→ repeat LFTs→ still ↑ after 6 months→ i.e. chronic → test for Hep B and C, hemochromatosis (iron studies/HFE protein analysis), fatty liver→unremarkable→ search for muscle disorders like polymyositis and thyroid disease
- Drugs that cause ↑ in LFTs: NSAIDs, antibiotics, HMG-CoA reductase inhibitors, antiepileptic drugs, antituberculous drugs, herbal preparations

CLINICAL FEATURES OF CIRRHOSIS

Clinical features of cirrhosis	
Symptoms	• Can be asymptomatic or with nonspecific symptoms (eg, anorexia, weight loss, weakness, fatigue, muscle cramps) • Jaundice & pruritus • Gastrointestinal bleeding (eg, melena, hematemesis) • Encephalopathy (eg, confusion, sleep disturbances) • **Women**: Amenorrhea or irregular menses due to anovulation • **Men**: Hypogonadism (eg, decreased libido, erectile dysfunction, loss of axillary & pubic hair), more common in cirrhosis due to alcohol or hemochromatosis
Physical examination	• **Skin**: Telangiectasias, caput medusae • **Chest**: Gynecomastia (usually bilateral but can be unilateral) • **Abdomen**: Ascites, hepatomegaly, splenomegaly • **Genitourinary**: Testicular atrophy • **Extremities**: Palmar erythema, Muehrcke &/or Terry nails, Dupuytren's contracture, clubbing

- Hypogonadism is due to either primary gonadal injury or hypothalamic pituitary dysfunction
- Liver→ responsible for making serum binding proteins→ liver dysfunction→ ↓ serum binding proteins→↓ **total** T3 and T4 (as most T3 and T4 is in bound form) and **normal free** T3 and T4 and normal TSH
- All cirrhotic pts should undergo surveillance USG every 6 mo to exclude any liver masses irrespective of the cause

ASCITES

CAUSES

Common causes of ascites	
Extraperitoneal causes	• Cirrhosis • Acute liver failure • Alcoholic hepatitis • Budd-Chiari syndrome • Heart failure • Hypoalbuminemia • Malnutrition • Nephrotic syndrome
Peritoneal causes	• Malignancy (ovarian, pancreatic) • Infection (tuberculosis, fungal)

EVALUATION:

- Diagnosis confirmed via clinical, laboratory, and radiologic evaluation
- Abdominal USG— needed to evaluate for complications (e.g. splenomegaly, HCC)
- Paracentesis is recommended in new-onset ascites to determine etiology
- Liver biopsy is required if diagnosis of cirrhosis is unclear or will alter course of management

ASCITES FLUID CHARACTERISTICS

Ascites fluid characteristics	
Color	• **Bloody**: Trauma, malignancy, TB (rarely) • **Milky**: Chylous, pancreatic • **Turbid**: Possible infection • **Straw color**: Likely more benign causes
Neutrophils	• <250/mm^3: No peritonitis • ≥250/mm^3: Peritonitis (secondary or spontaneous bacterial)

Total protein	• ≥2.5 g/dL (high-protein ascites)
	  ○ CHF, constrictive pericarditis, peritoneal carcinomatosis, TB, Budd-Chiari syndrome, fungal (eg, coccidioidomycosis)
	• <2.5 g/dL (low-protein ascites)
	  ○ Cirrhosis, nephrotic syndrome

SAAG	• ≥1.1 g/dL (indicates portal hypertension)
	  ○ Cardiac ascites, cirrhosis, Budd-Chiari syndrome
	• <1.1 g/dL (absence of portal hypertension)
	  ○ TB, peritoneal carcinomatosis, pancreatic ascites, nephrotic syndrome

CHF = congestive heart failure; **SAAG** = serum-to-ascites albumin gradient; TB = tuberculosis.

Leads to ↑ in capillary hydrostatic pressure. ↓ liver synthetic function is indicated by ↓ serum albumin which can cause edema in later stages of liver failure and ↑ PT/INR

↑ capillary permeability

- SAAG= serum albumin – ascites albumin (it is gradient not ratio)

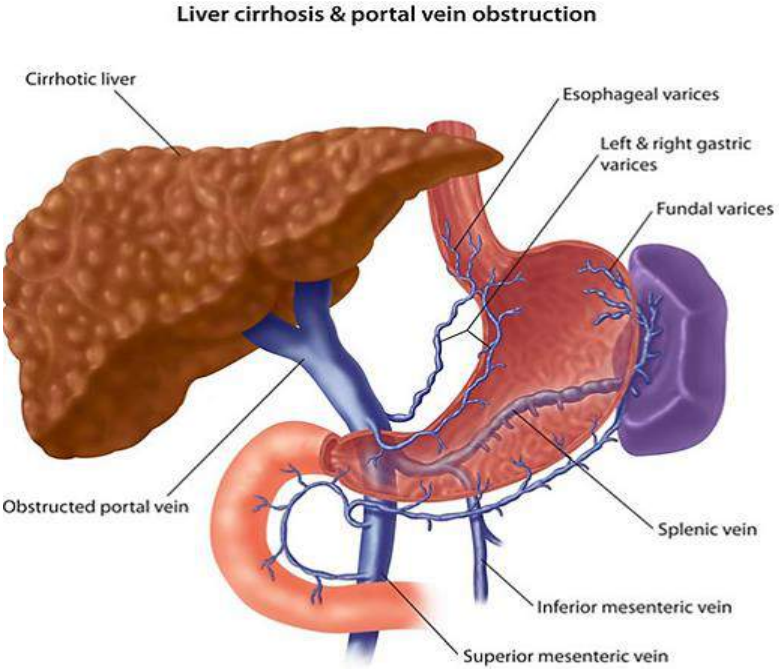
TREATMENT OF ASCITES

1. Start with Na+ and water restriction (2L/day)
2. Diuretic therapy, if needed→ start with spironolactone
3. When maximal dose of spironolactone fails to improve→ add loop diuretic (eg furosemide). Aggressive diuresis (>1 L/day)→ not recommended cox of risk of hepatorenal syndrome
4. Does not respond→ slow tapping of 2-4 L/day of ascitic fluid (with/without albumin infusion) but renal function is regularly monitored→ less aggressive paracentesis in pts with borderline renal function

HEPATIC HYDROTHORAX

- Pleural effusion due to ascites
- Due to defect in diaphragm
- Right sided more common
- Best option for treatment: liver transplant
- Primary treatment: thoracocentesis followed by diuresis and salt restriction→ no response→ TIPS→ TIPS contraindicated→ pleurodesis
- Surgical portosystemic shunts have more morbidity

ESOPHAGEAL VARICES



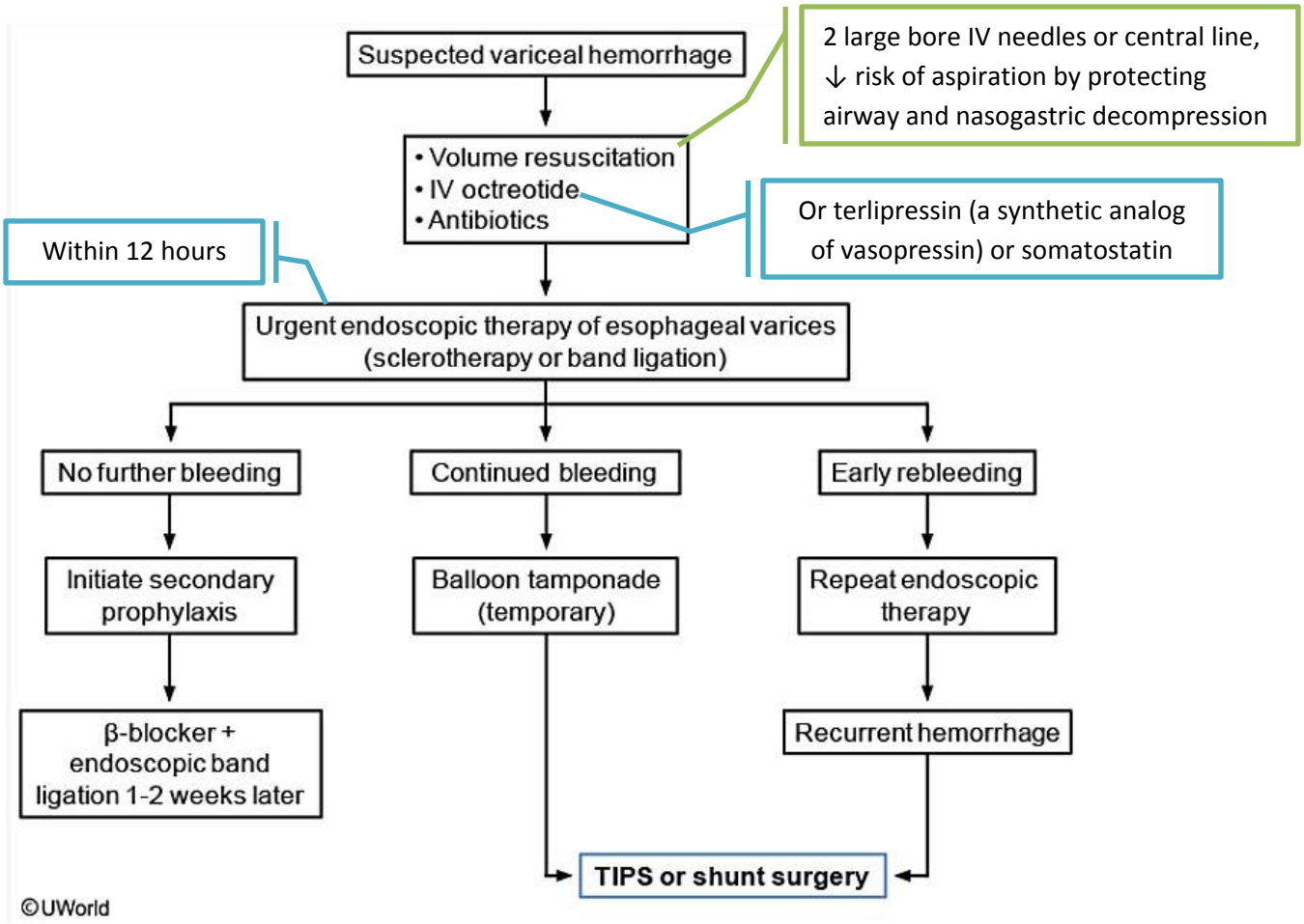
- Variceal hemorrhage develop in 1/3rd pts with esophageal varices and varices occur in almost 50% cirrhotic pts
- All pts with cirrhosis should undergo diagnostic endoscopy to exclude varices, determine risk of variceal hemorrhage and indicate strategies for primary prevention

Prophylaxis

- Small, non-bleeding esophageal varices→ all pts should receive prophylaxis
- 1st line: non-selective β-blockers (eg propranolol, nadolol)→ ↓ risk of progression to large varices and variceal hemorrhage, improve mortality due to bleeding and overall. MOA: ↓adrenergic tone in mesenteric arterioles→ unopposed α-mediated vasoconstriction and ↓portal venous flow
- 2nd line: endoscopic variceal ligation in those with CI to β-blockers

Treatment of variceal bleeding

- Endoscopic sclerotherapy (it has no role in prophylaxis)
- Octreotide— long-acting somatostatin analog→ ↓ glucagon and ↓ release of vasodilator hormones→splanchnic vasoconstriction and ↓ portal blood flow (Rx of active variceal bleeding—no role in prophylaxis)



- Control of bleeding is established in 80% pts→ rebleeding is very common esp. in 6 wks of initial hemorrhage
- Examples of temporary balloon tamponade: Sengstaken- Blackemore, Minnesota, Linton- Nachlas tubes
- Coagulopathy, thrombocytopenia and anemia are common complications and may also need correction
- Blood transfusion will be needed if Hb falls <9g/dl—regularly monitor blood counts
- Fresh frozen plasma for correction of coagulopathy but can cause volume overload
- Platelet transfusion if platelet count <50,000/mm3

HEPATORENAL SYNDROME

- One of the most dangerous complications of end-stage liver disease, occurring in up to 10% of patients with cirrhosis.
- Characterized by decreased GFR in the absence of shock, proteinuria, or other clear cause of renal dysfunction, and a failure to respond to a 1.5 L normal saline bolus and withdrawal of diuretics
- **Pathogenesis:** thought to result from renal vasoconstriction in response to decreased total renal blood flow and vasodilatory substance synthesis. Liver cirrhosis→ portal HTN→ ↑ synthesis of NO from splanchnic circulation→ systemic vasodilation→ ↓ peripheral vascular resistance and BP→ renal hypoperfusion→ activate RAS, sympathetic system and ADH→ Na+ and water retention→ worsen volume overload. Any factor that ↓ glomerular capillary pressure→ acute ↓ in glomerular filtration and precipitate hepatorenal syndrome
- Types:
  - Type 1: rapidly progressive; most patients die within 10 weeks without treatment
  - Type 2: progresses more slowly, with an average survival of 3-6 months.

- The most common causes of death are infection and hemorrhage.
- Rx: no medicine has any proven benefit→ ↑ mortality on dialysis. Liver transplantation is the only intervention with established benefit

Hepatorenal syndrome	
Risk factors	• Advanced cirrhosis with portal hypertension & edema

Precipitating factors	• Reduced renal perfusion
	  ◦ GI bleed, vomiting, sepsis, excessive diuretic use, SBP
	• Reduced glomerular pressure & GFR
	  ◦ NSAID use (constricts afferent arterioles)

Diagnosis	• Renal hypoperfusion
	  ◦ FeNa <1% (or urine Na <10 mEq/L)
	• Absence of tubular injury
	  ◦ No RBC, protein, or granular casts in urine
	• No improvement in renal function with fluids

Treatment	• Address precipitating factors (eg, hypovolemia, anemia, infection) • Splanchnic vasoconstrictors (midodrine, octreotide, norepinephrine) • Liver transplantation

FeNa = fractional excretion of sodium; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **RBC** = red blood cells; **SBP** = spontaneous bacterial peritonitis

Similar to prerenal azotemia and exclude intrinsic renal causes: ↑ serum creatinine (>1.5 mg/dl) and very ↓ urine sodium

ACUTE LIVER FAILURE

- Acute liver failure is defined as acute onset of severe liver injury with encephalopathy and ↓ synthetic function (INR >/= 1.5) in a patient without cirrhosis or underlying known liver disease

Acute liver failure	
Etiology	• Viral hepatitis (eg, HSV; CMV; hepatitis A, B, D & E) • Drug toxicity (eg, acetaminophen overdose, idiosyncratic) • Ischemia (eg, shock liver, Budd-Chiari syndrome) • Autoimmune hepatitis • Wilson disease • Malignant infiltration
Clinical presentation	• Generalized symptoms (eg, fatigue, lethargy, anorexia, nausea) • Right upper quadrant abdominal pain • Pruritus & jaundice due to hyperbilirubinemia • Renal insufficiency • Thrombocytopenia • Hypoglycemia
Diagnostic requirements	• Severe acute liver injury (ALT & AST often >1000 U/L) • Signs of hepatic encephalopathy (eg, confusion, asterixis) • Synthetic liver dysfunction (INR ≥1.5)

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **CMV** = cytomegalovirus; **HSV** = herpes simplex virus.

Most common causes— concurrent use of alcohol ↑ propensity to develop hepatotoxicity from acetaminophen

>10 times normal

- Most important prognostic factor: PT (prothrombin time)
- Patients who improve: have ↓ing transaminases, PT/INR and bilirubin
- Patients who progress: may have **↓ing transaminases**→ indicating ↓ in functional liver tissue and worsening **PT/INR and bilirubin**→ indicate worsening synthetic function

ISCHEMIC HEPATOPATHY

- Rapid and massive ↑ in AST and ALT, with modest ↑ in alkaline phosphatase and total bilirubin (hyperbilirubinemia is more severe in acute viral hepatitis)
- Pts who survive underlying cause (eg septic shock or HF)→ LFTs return to normal within 1-2 wks

DRUG-INDUCED HEPATITIS

- Drugs and toxins typically cause hepatic injury, either through direct toxic effects or through idiosyncratic reactions.
- **Direct toxic effects**: dose-dependent, short latent periods. Some examples of direct toxins include carbon tetrachloride, acetaminophen, tetracycline, and substances found in the Amanita phalloides mushroom.
- **Idiosyncratic reactions**: not dose-dependent and have variable latent periods. Some examples of pharmacological agents that cause idiosyncratic reactions include isoniazid, chlorpromazine, halothane, and antiretroviral therapy.
- Drug-induced liver disease can also be broadly categorized **according to morphology:**
    1) Cholestasis: chlorpromazine, nitrofurantoin, erythromycin, and anabolic steroids;
    2) Fatty liver: tetracycline, valproate, and anti-retrovirals;
    3) Hepatitis: halothane, phenytoin, isoniazid, and alpha-methyldopa;
    4) Toxic or fulminant liver failure: carbon tetrachloride and acetaminophen; and
    5) Granulomatous: allopurinol and phenylbutazone.
    6) OCPs cause changes in LFTs without evidence of necrosis or fatty change

- While extrahepatic hypersensitivity manifestations like rash, arthralgias, fever, leukocytosis, and eosinophilia are common in patients with drug-induced liver injury, they are characteristically absent in cases of isoniazid-induced hepatic cell injury—Histologic picture is similar to viral hepatitis

ALCOHOLIC HEPATITIS

Clinical features of alcoholic hepatitis	
Clinical presentation	• Jaundice, anorexia, fever • Right upper quadrant &/or epigastric pain • Abdominal distension due to ascites • Proximal muscle weakness from muscle wasting (if malnourished) • Possible hepatic encephalopathy
Laboratory/ imaging studies	• Elevated AST & ALT, usually <300 U/L • AST:ALT ratio ≥2 • Elevated gamma-glutamyltransferase, bilirubin, &/or international normalized ratio • Leukocytosis, predominantly neutrophils • Decreased albumin if malnourished • Abdominal imaging may show fatty liver

Tender hepatomegaly

Cholangitis: may present with fever, RUQ pain and jaundice—but more severe presentation (eg sepsis) and marked ↑ in ALP (not AST: ALT ratio >2)—diagnosed by RUQ USG

And ↑ ferritin

- Social history for confirming alcohol use and quantification and discussing substance abuse is important in diagnosis—pts with AH have h/o chronic alcohol use (>7drinks/day or 100 g/day)—sometimes develop symptoms after acute ↑ in consumption. In addition, alcoholic liver disease is unlikely with light to moderate alcohol intake (<15 drinks/wk for men, <10/wk for women). A standard drink is equivalent to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof spirits (1 oz = 30 ml)
- Diagnosis: mainly clinical and no further investigation required in pts with consistent history and lab values. Pts with risk factors for viral hepatitis need further investigation (ALT, AST will be >1000 in viral hep and acetaminophen intoxication—usually does not ↑ >500 in acute alcoholic hepatitis as well)
- AST:ALT ratio >/= 2→ thought to be due to hepatic def. of pyridoxal 5' phosphate, an ALT enzyme cofactor—no correlation btw degree of elevation and severity of disease
- Rx: abstinence, supportive (eg hydration and nutrition support) and acid suppression. Prednisone for severe alcoholic hepatitis
- Liver biopsy—helpful if diagnostic uncertainty

NON-ALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease	
Definition	• Hepatic steatosis on imaging or biopsy • Exclusion of significant alcohol use • Exclusion of other causes of fatty liver
Clinical features	• Mostly asymptomatic • Metabolic syndrome • +/- Steatohepatitis (AST/ALT ratio <1) • Hyperechoic texture on ultrasound
Treatment	• Diet & exercise • Consider bariatric surgery if BMI ≥35

AST = aspartate aminotransferase; **ALT** = alanine aminotransferase.

Weight loss and control of metabolic risk factors

- Most common in pts with obesity and diabetes
- Can range from bland steatosis to inflammation and necrosis (steatohepatitis) and fibrosis and cirrhosis
- **Histology:** resembles macrovesicular fat deposition, peripheral displacement of neuclei (same as alcoholic hepatitis)
- **Pathogenesis:** ↑ transport of FFA from adipose tissue to liver, ↓ oxidation of FFA in liver, or ↓ clearance of FFA from liver (due to ↓VLDL production). It is frequently related to **insulin resistance** leading to ↑ peripheral **lipolysis (**insulin ↓ lipolysis in peripheral tissue)**,** TG synthesis, and hepatic uptake of fatty acids. Hepatic FFA→ ↑ oxidative stress and production of proinflammatory cytokines (eg TNF-α) and further contribute to insulin resistance by impairing insulin dependent glucose uptake by liver and ↑ing gluconeogenesis by liver
- **Dx**: Made on the basis of laboratory and imaging studies. Confirmed on liver biopsy.
- Hepatic fibrosis develop in 40% pts. Cirrhosis in 10-15% pts
- It is safe to give statins in NAFLD.

HEPATIC ENCEPHALOPATHY

Clinical features of hepatic encephalopathy	
Precipitating factors	• Drugs (sedatives, narcotics) • Hypovolemia (eg, diarrhea, vomiting, diuretics, high-volume paracentesis) • Excessive nitrogen load (gastrointestinal bleeding, constipation, high-protein diet) • Hypokalemia & metabolic alkalosis • Hypoxia & hypoglycemia • Infection (eg, pneumonia, urinary tract infection, spontaneous bacterial peritonitis) • Portosystemic shunting (eg, surgical shunts)
Clinical presentation	
Stage 1	• Hypersomnia, insomnia, or inverted sleep cycle • Slightly impaired cognition • Mild confusion • Tremor, possible asterixis
Stage 2	• Lethargy with slow responses to stimuli • Moderate confusion • Difficulty with writing, slurred speech
Stage 3	• Marked confusion • Sleeping but arousable
Stage 4	• Stupor or coma
Neuromuscular findings in overt encephalopathy include slurred speech, ataxia, bradykinesia, asterixis, hyperactive deep-tendon reflexes with Babinski & clonus, & nystagmus.	

- Pathogenesis: inability of liver to break down ammonia→ urea. Other toxins may also be responsible. These neurotoxins stimulate inhibitory (e.g. GABA) and impairment of excitatory (e.g. glutamate) pathways in brain
- Dx: ↑ NH3 is diagnostic in symptomatic pts with high clinical suspicion→ but non-specific and may be ↑ in asymptomatic pts
- EEG may show B/L synchronous ↓ wave frequency and ↑ wave amplitude→ non-specific and non-diagnostic

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Management of hepatic encephalopathy

- Supportive care (eg, volume repletion if needed, restraints if agitated, correct electrolytes)
- Adequate nutrition **without** protein-restricted diet unless patient is unable to tolerate protein intake
- Treat precipitating cause (eg, gastrointestinal bleed, hypovolemia, infection, electrolyte abnormalities) Medicines like sedatives
- Lower serum ammonia
  - Lactulose orally or enema if unable to take orally
  - Rifaximin orally if no improvement in 48 hours with lactulose or unable to take lactulose

- Non-absorbable disaccharides (lactulose, lactitol)—preferred: colonic bacteria→ metabolize lactulose to short chain fatty acids (lactic acid, acetic acid)→ converts absorbable ammonia to non-absorbable ammonium (an ammonia trap) and also cause catharsis. Antibiotics (like rifaximin)→↓ ammonia producing bacteria—added to lactulose if pt does not improve in 48 hours or monotherapy in those unable to take lactulose. Catharsis using any laxative may also be beneficial. Neomycin is an alternate therapy in pts unable to take rifaximin.
- Cirrhotic patients—usually malnourished and should not follow a protein-restricted diet. Protein-free diets → cause a negative nitrogen balance → increase mortality. Protein restriction—recommended only in patients unable to tolerate protein intake (ie, recurrent encephalopathy episodes after a high-protein diet).
- Diuretics normally improve ascites and peripheral edema in most pts with cirrhosis. Some pts may become diuretic resistant and unable to mobilize ascites→ instead develop progressive azotemia, electrolyte disturbance (hypokalemia) and HE and still can have significant ascites and peripheral edema
- Poor oral intake→ intravascular volume depletion and worsening of metabolic alkalosis and hypokalemia. Hypokalemia→↑ renal ammonia production. Metabolic alkalosis→ converts ammonium to ammonia. Hence, pts with HE and hypokalemia→ prompt potassium repletion and intravascular volume repletion (eg albumin)

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis	
Clinical presentation	• Temperature ≥37.8 C (100 F) • Abdominal pain/tenderness • Altered mental status (abnormal connect-the-numbers test) • Hypotension, hypothermia, paralytic ileus with severe infection
Diagnosis from ascitic fluid	• PMNs **≥250/mm^3** • Positive culture, often gram-negative organisms (eg, *Escherichia coli*, *Klebsiella*) • Protein <1 g/dL • SAAG ≥1.1 g/dL
Treatment	• Empiric antibiotics - third-generation cephalosporins (eg, cefotaxime) • Fluoroquinolones for SBP prophylaxis

PMN = polymorphonuclear leukocytes; **SAAG** = serum-ascites albumin gradient; **SBP** = spontaneous bacterial peritonitis.

Most common features—abdominal pain less prominent than in other causes of peritonitis

Known as Reitan trail test

Paracentesis is the test of choice for dx—these two are main diagnostic criteria—E. coli and Klebsiella most common followed by streptococcal species

- Keep a low threshold of suspicion
- Pts with cirrhosis are normally hypothermic and >100 F warrants investigation

SOLID LIVER MASSES

Solid liver masses	
Focal nodular hyperplasia	• Associated with anomalous arteries • Arterial flow & central scar on imaging
Hepatic adenoma	• Women on long-term oral contraceptives • Possible hemorrhage or malignant transformation
Regenerative nodules	• Acute or chronic liver injury (eg, cirrhosis)
Hepatocellular carcinoma	• Systemic symptoms • Chronic hepatitis or cirrhosis • Elevated alpha fetoprotein
Liver metastasis	• Single/multiple lesions • Known extrahepatic malignancy

Not associated with OCP use—caused by hyperperfusion from anomalous arteries

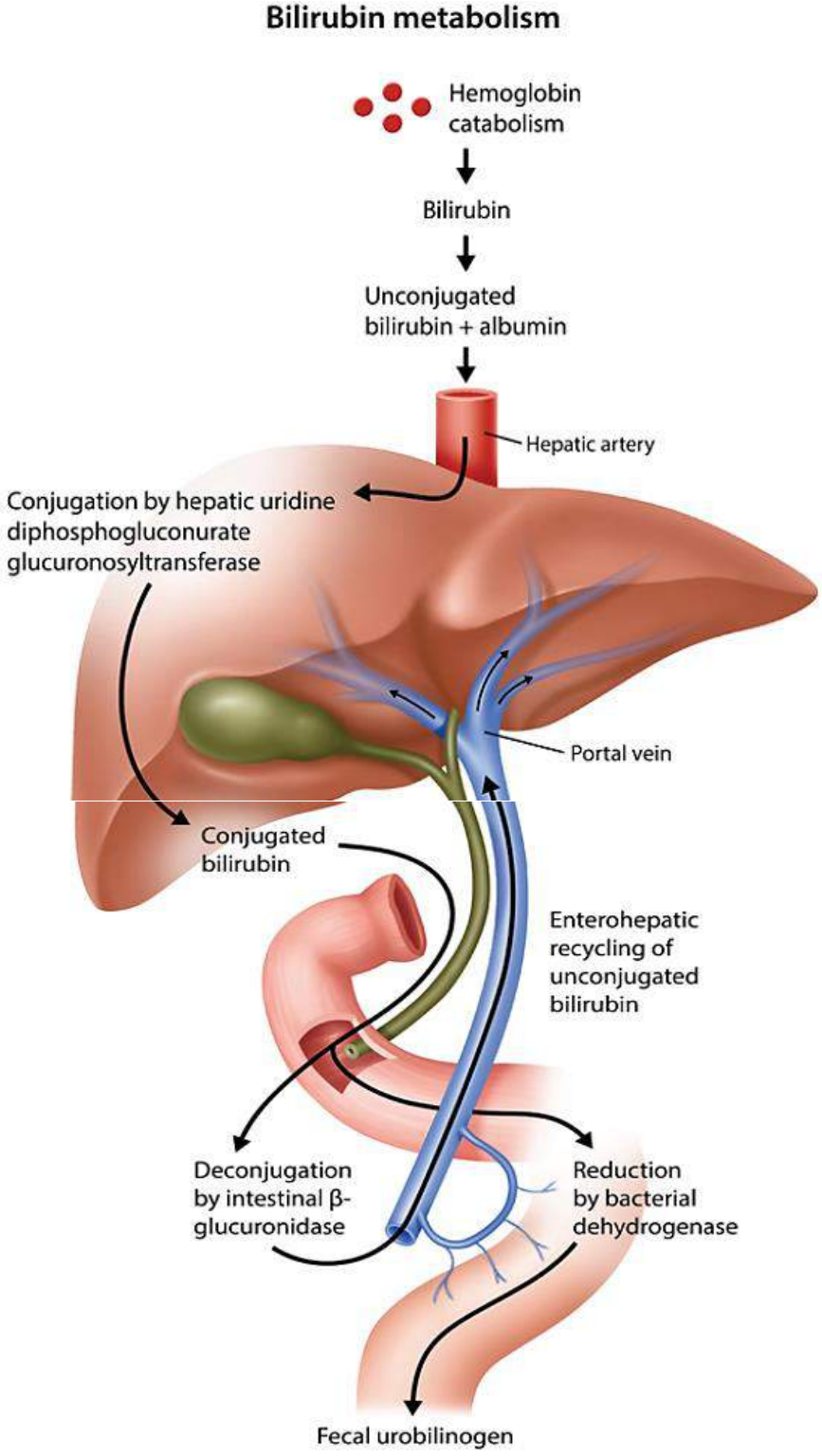
Common in young women

Other risk factors: pregnancy and anabolic steroid use. USG: well-demarcated hyperechoic lesion. CT: early peripheral enhancement. Biopsy: not recommended. Rx: excision

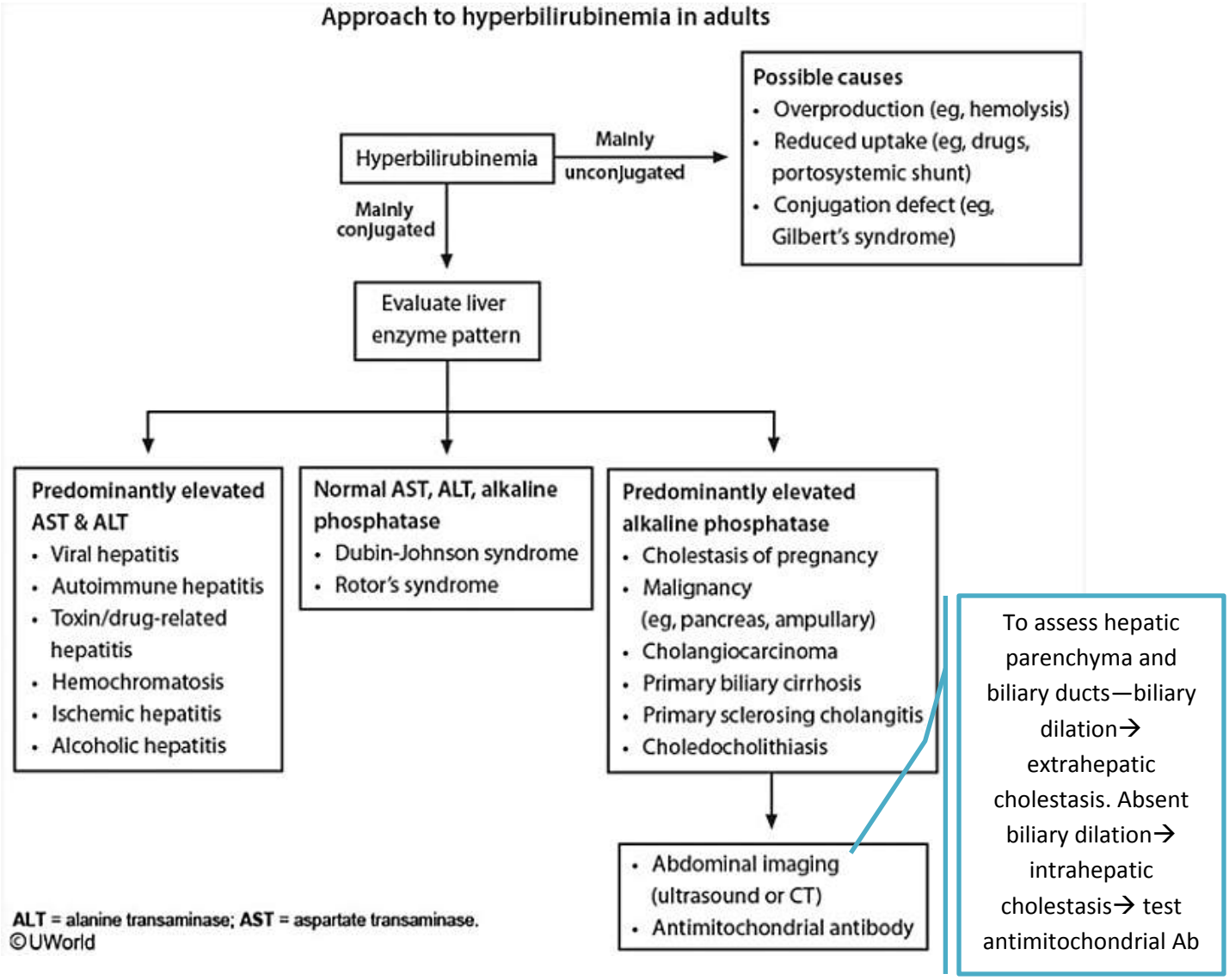
HEPATIC ANGIOSARCOMA:

- Rare liver neoplasm in older men exposed to chemical products like vinyl chloride, inorganic arsenic compounds, thorium dioxide

BILIRUBIN METABOLISM



HYPERBILIRUBINEMIA IN ADULTS



To assess hepatic parenchyma and biliary ducts—biliary dilation→ extrahepatic cholestasis. Absent biliary dilation→ intrahepatic cholestasis→ test antimitochondrial Ab

HERIDITARY HYPERBILIRUBINEMIAS

GILBERT SYNDROME

- ↓ production of UDP-glucoronyltransferase
- Occurs in pts with no apparent liver disease
- Mild unconjugated hyperbilirubinemia (<3mg/dl) thought to be triggered by one of classic stresses like fasting, stress or illness, fat-free diet, physical exertion
- Rx: unnecessary, mode of inheritance should be discussed to prevent unnecessary testing

CRIGGLER NAJJAR SYNDROME

- Very rare, autosomal recessive
- **Type 1**:
  - results in significant neurological impairment (kernicterus) and death—UCB 20-25mg/dl and can rise to 50mg/dl→ not affected by IV phenobarbital
  - normal liver enzymes and histology

- Phototherapy and plasmapheresis—used for short term—curative treatment: liver transplant

- **Type 2:**
  - Less severe—UCB <20mg/dl—no neurological impairment
  - IV Phenobarbital improve bilirubin level
  - Rx: unnecessary in mil cases—periodic phenobarbital or clofibrate ↓ bilirubin level if necessary

DUBIN JOHNSON SYNDROME

- Benign
- Defective liver transport system→ ↑ conjugated bilirubin with direct bilirubin fraction >50% —not associated with hemolysis
- Common in Sephardic Jews—can occur in all races and both men and women
- Icterus evident—rest of PE normal—some may have non-specific Sx like fatigue, abdominal pain, weakness
- Icterus usually mild—only becomes evident in context of trigger like illness, pregnancy or OCP use
- Labs: usually unremarkable including CBC and LFTs - serum bilirubin usually range from 2-5 mg/dl – may be normal or as high as 20-25mg/dl
- Additional insight in evaluation: normal urinary coproporphyrin—they have normal total urinary coproporphyrin but will have 80% coproporphyrin I v/s normal individuals who have similar majority of coproporphyrin III
- Liver is strikingly black
- Histology—normal except dense pigments composed of epinephrine metabolites within lysosomes
- No treatment needed—excellent prognosis

ROTOR SYNDROME

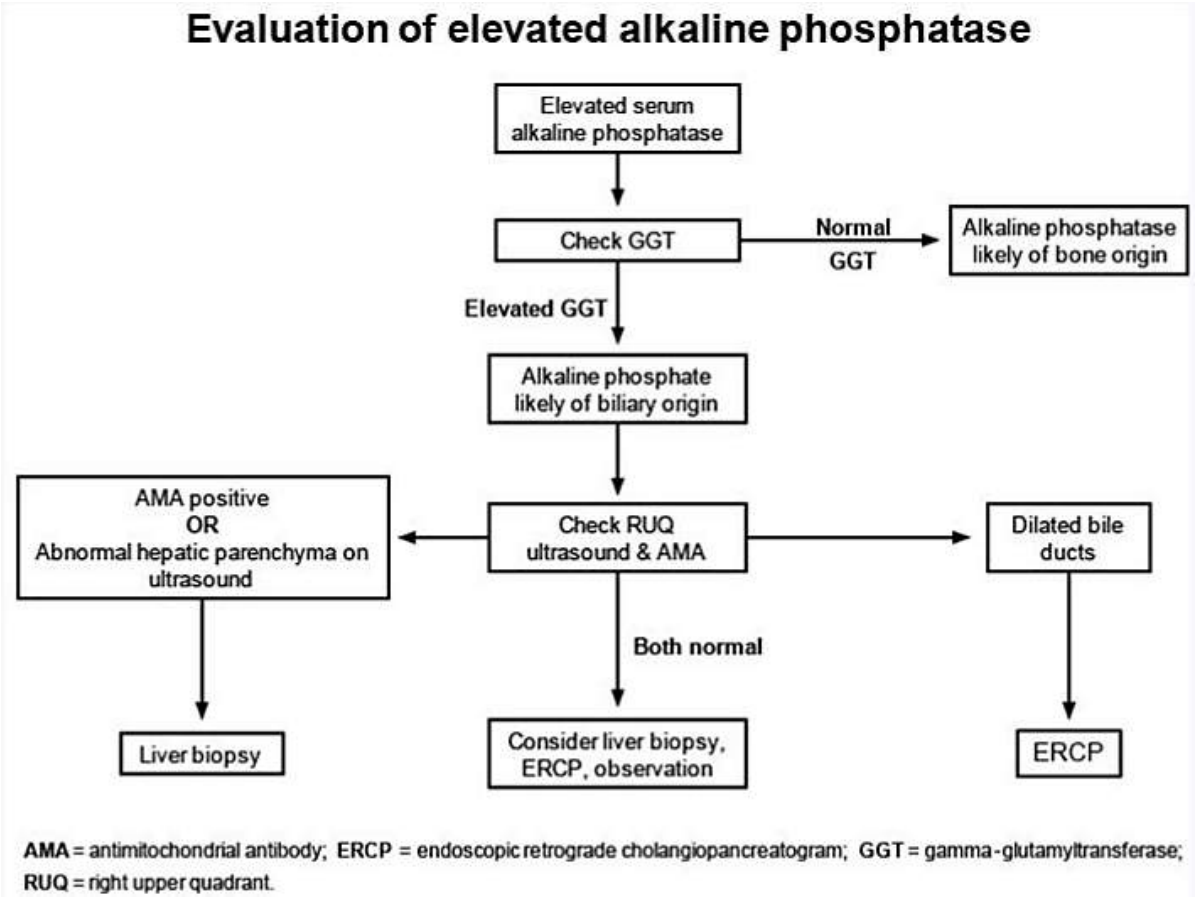
- Benign
- Defect in liver storage of conjugated bilirubin→ leakage in to plasma→ chronic and mild hyperbilirubinemia of both conjugated and unconjugated bilirubin then develop
- Normal LFTs
- No pigmentation

WILSON DISEASE

- Also known as hepatolenticular disease—diagnosed in young age (5-40yrs)
- ↓ formation and secretion of ceruloplasmin and decrease secretion of copper in biliary system→ copper accumulates in hepatocytes→ damages due to generation of free radicals→ copper leaks and deposits in other tissues
- Liver involvement: may present as asymptomatic, chronic hepatitis, fulminant hepatitis, portal HTN or macronodular cirrhosis
- Neuropsychiatric symptoms: Parkinson-like tremors, rigidity, ataxia, slurred speech, drooling, personality changes, depression, paranoia and catatonia
- Also associated with Fanconi syndrome, hemolytic anemia, and neuropathy
- Dx: gold standard liver biopsy (copper >250mcg/gram dry weight), confirmatory: ↓ ceruloplasmin level (<20 mg/dl) +↑ urinary copper excretion + Keyser Fleisher ring
- Rx: copper chelators (d-pencillamine, trientine), oral zinc (prevents copper absorption)—fulminant hepatitis or decompensated liver disease (liver transplantation)

BILIARY TRACT DISEASES

EVALUATION OF ELEVATED ALKALINE PHOSPHATASE



PRIMARY BILIARY CHOLANGITIS/CIRRHOSIS

- Chronic, progressive liver disease→ cholestasis and autoimmune destruction of intrahepatic bile ducts
- Most common in middle aged women—insidious onset
- Sx: pruritis and fatigue—initial sx, as disease progresses→ steatorhhea, jaundice, hepatomegaly, eyelid xanthelasma, portal HTN and osteopenia may develop. May be associated with other autoimmune diseases
- Antimitochondrial antibodies +ve
- Rx: ursodeoxycholic acid (UDCA)—used in a no. of cholestatic disorders, DOC in PBC—start as soon as dx is made whether symptomatic or asymptomatic—not useful in later stages. UDCA is hydrophilic bile acid→ ↓ biliary injury by more hydrophobic endogenous bile acids—also ↑ biliary secretion and has anti-inflammatory and immunomodulatory effects→ delays histologic progression and improve sx and possibly survival
- Advanced disease with severe liver damage or cirrhosis: liver transplantation (definitive cure)

VANISHING BILE DUCT SYNDROME

- Rare
- Progressive destruction of intrahepatic bile ducts
- Histologic hallmark: ductopenia
- Pathophysiology: unknown

- Most common cause of ductopenia: primary biliary cirrhosis. Other causes: failing liver transplantation, Hodgkin's disease, graft-versus-host disease, sarcoid, CMV infection, HIV and medication toxicity

➔ Certain drugs associated with intrahepatic cholestasis: antibiotics (eg macrolides), OCPs, anabolic steroids

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis	
Clinical features	• Fatigue & pruritus • Majority of patients asymptomatic at time of diagnosis • About 90% of patients have underlying inflammatory bowel disease, mainly ulcerative colitis
Laboratory /imaging	• Cholestatic liver function test pattern (serum aminotransferases typically <300 U/L) • Multifocal stricturing/dilation of intrahepatic &/or extrahepatic bile ducts on cholangiography
Liver biopsy	• Fibrous obliteration of small bile ducts with concentric replacement by connective tissue in an "onion-skin" pattern
Complications	• Intrahepatic &/or extrahepatic biliary stricture • Cholangitis & cholelithiasis (cholesterol &/or pigment stones) • Cholangiocarcinoma (10%-15% lifetime risk) • Cholestasis (eg, ↓ fat-soluble vitamins, osteoporosis) • Colon cancer

↑ ALP and bilirubin, hyper-gammaglobulinemia, ↑ serum IgM levels or atypical p-ANCA

i.e. ERCP or MRCP→ beading

Liver biopsy: to determine disease stage and prognosis— obliteration by moderate lymphocytic infiltrate

- As the disease is progressive, and can lead to hepatic failure and portal HTN, mean survival is 12 years after diagnosis if liver transplantation not performed

CHOLELITHIASIS

RISK FACTORS

Gallbladder stasis

- Normal mechanism: proteins and fatty acids in duodenum→ promote release of CCK (cholecystokinin)→ gall bladder contraction
- Pt on TPN or prolonged fasting→ absent normal stimulus for CCK and gallbladder contraction→ gall bladder stasis→ sludge and gall stone formation

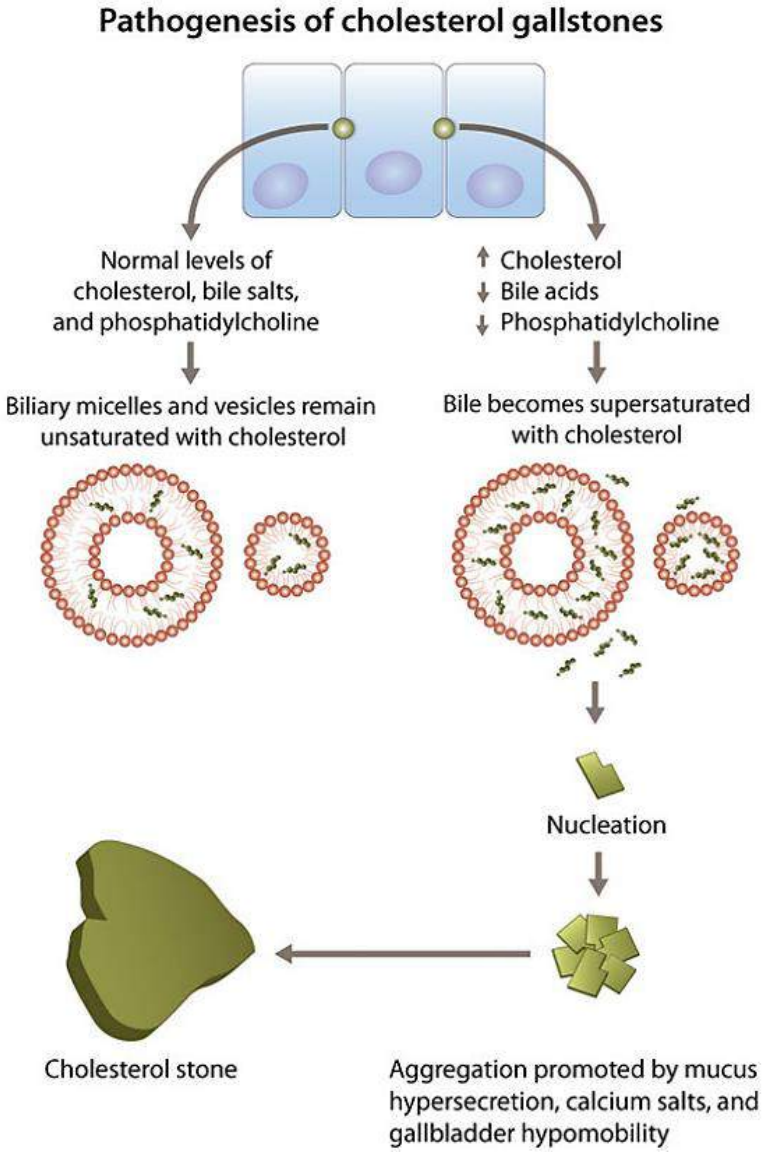
Small bowel (ileal resection) or ileal Crohn disease

- ↓ enterohepatic circulation of bile acids→ altered hepatic bile composition→bile becomes supersaturated with cholesterol→cholesterol gall stone formation due to ↑ concentration of bilirubin conjugates and total calcium in gall bladder

Estrogen induced gall stone formation

- During pregnancy and OCP use
- Estrogen→↑ in cholesterol secretion
- Progesterone→ ↓ bile acid secretion and slows gallbladder emptying

} ↑ cholesterol saturation of bile→ gall stone formation



MANGEMENT OF GALLSTONES

Management of gallstones	
Gallstones without symptoms	• **No treatment** necessary in most patients
Gallstones with typical biliary colic symptoms	• Elective laparoscopic cholecystectomy • Possible ursodeoxycholic acid in poor surgical candidates
Complicated gallstone disease (acute cholecystitis, choledocholithiasis, gallstone pancreatitis)	• Cholecystectomy within 72 hours

Gallstone ileus:

- Dx: confirmed by abdominal CT→ gallbladder wall thickening, pneumobilia and an obstructing stone
- Rx: surgical removal of stone and either simultaneous or delayed cholecystectomy.

BILIARY COLIC

- Secondary to gall stones
- Ingestion of large (esp. fatty) meal→ gall bladder contraction against obstructed cystic duct→ intra-gallbladder pressure ↑→ RUQ or epigastric constant pain (not colicky), N/V, right shoulder/subscapular discomfort→ gall bladder relaxation→ stone falls back→ pain resolves.
- Recurrent and resolution between episodes
- Pain resolves in 4-6 hours, absence of abdominal tenderness, fever and leukocytosis, no signs of inflammation present (unlike cholecystitis)

ACUTE CHOLECYSTITIS

- Gall stone→ obstruct cystic duct (CBD obstruction will cause severe jaundice and very high alkaline phosphatase)→ inflamed gall bladder mucosa→ stasis→ bacterial overload→ ischemia leads to gangrene, perforation, generalized peritonitis, or well-circumscribed abscess. Other potential complications: cholangitis or chronic cholecystitis (in 90% cases gall stones +ve)
- Pain similar to biliary colic but lasts longer than 6 hours—pain is colicky
- Fever, leukocytosis, tenderness to palpation, vomiting. Uncomplicated cholecystitis may lead to mild ↑ in transaminases, total serum bilirubin from 1-4 mg/dl, and serum amylase without obvious CBD or pancreatic disease. Alkaline phosphatase—usually not ↑ without associated cholangitis or choledocholithiasis
- Rx: supportive (NPO, IV antibiotics and analgesics). Laparoscopic cholecystectomy→ shortly after hospitalization and immediately in case of perforation or gangrene. Early removal→↓ disease duration, duration of hospitalization and mortality when compared to delayed (>7 days) cholecystectomy

POSTCHOLECYSTECTOMY SYNDROME

- PCS refers to persistent abdominal pain or dyspepsia (eg, nausea) that occurs either postoperatively (early) or months to years (late) after a cholecystectomy.
- Can be due to biliary (eg, retained common bile duct or cystic duct stone, biliary dyskinesia) or extra-biliary (eg, pancreatitis, peptic ulcer disease, coronary artery disease) causes, functional or sphincter of Oddi dysfunction
- Patients usually notice the same pain they had prior to surgery, new pain just after surgery, or the same pain that never went away.
- Laboratory findings can include elevated alkaline phosphatase, mildly abnormal serum aminotransferases, and dilated common bile duct on abdominal ultrasound. These findings usually suggest common bile duct stones or biliary sphincter of Oddi dysfunction (LFTs ↑ during pain and come to normal level when pain subsides).
- The next step involves endoscopic ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography for final diagnosis and guiding therapy—detect stone→ sphincter of Oddi manometry for sphincter of Oddi dysfunction (↑ pressure in this). Functional pain is diagnosis of exclusion
- Treatment for PCS is directed at the causative factor: ERCP with sphincterotomy is the treatment of choice for sphincter dysfunction

ACALCULOUS CHOLECYSTITIS

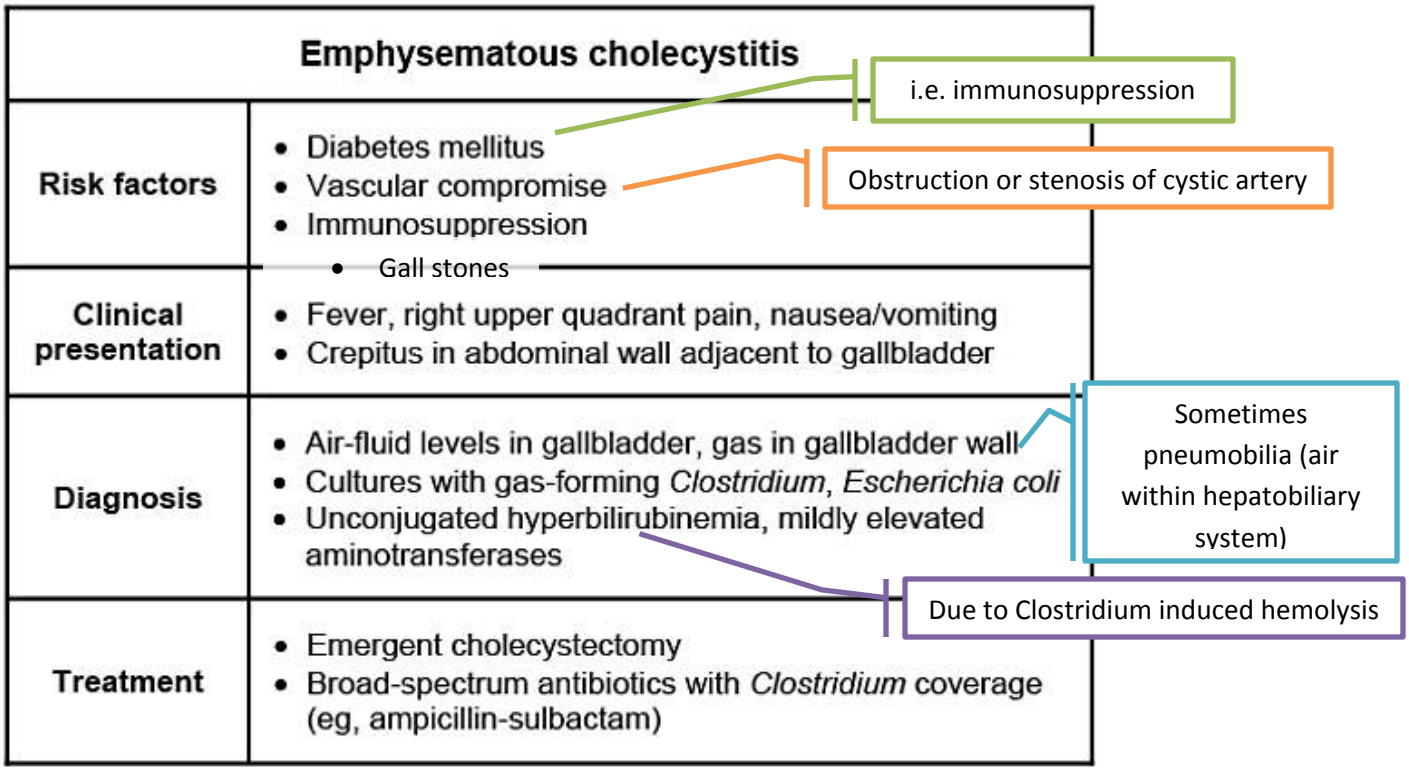
Acalculous cholecystitis	
Risk factors	• Severe trauma, extensive burns, recent surgery (eg, cardiopulmonary, aortic, abdominal) • Prolonged fasting or TPN • Critical illness (sepsis, ICU, mechanical ventilation)
Clinical presentation	• Unexplained fever, vague/RUQ abdominal discomfort, leukocytosis • Possible jaundice, RUQ mass, abnormal LFTs
Diagnosis	• Abdominal ultrasound (preferred) • Cholescintigraphy (HIDA scan) or abdominal CT scan if ultrasound not diagnostic

HIDA = hepatobiliary iminodiacetic acid; **ICU** = intensive care unit; **LFTs** = liver function tests; **RUQ** = right upper quadrant; **TPN** = total parenteral nutrition.

These conditions cause gall bladder stasis or ischemia, with local inflammation that can lead to gall bladder distension, necrosis and 2® bacterial infection by enteric organisms. Complications: gangrene, perforation & emphysematous cholecystitis—sepsis and death can occur

- Radiologic signs: gallbladder wall thickening and distension and presence of pericholecystic fluid
- Rx: immediate antibiotics followed by percutaneous cholecystostomy under radiologic guidance. Cholecystectomy with drainage of any associated abscesses—definitive treatment once pts condition improves

EMPHYSEMATOUS CHOLECYSTITIS



- Life-threatening form of acute cholecystitis due to infection with gas-forming bacteria like Clostridium and some strains of E.coli
- Complications: gangrene and perforation, latter may transiently relieve pain but later results in peritoneal signs

ACUTE CHOLANGITIS

Acute cholangitis	
Clinical presentation	• Fever, jaundice, right upper quadrant pain (Charcot triad) • Mental status changes, hypotension (Reynolds pentad) • Liver failure • Acute kidney injury
Diagnosis	• Biliary dilation on ultrasound or CT scan • ↑ Alkaline phosphatase, gamma-glutamyl transpeptidase, direct bilirubin • Leukocytosis, ↑ C-reactive protein Neutrophilia
Treatment	• Biliary drainage: Endoscopic retrograde cholangiopancreatography with sphincterotomy or percutaneous transhepatic cholangiography Or open surgical decompression • Broad-spectrum antibiotics: Beta-lactam/beta-lactamase inhibitor, third-generation cephalosporin + metronidazole

- If prompt treatment is not done→ septic shock
- Bile duct obstruction from gall stones, malignancy or stenosis→ biliary stasis→ acute cholangitis
- In the setting of stasis→ bile-blood barrier disrupts→ translocation of bacteria and toxins from hepatobiliary system to blood stream

CHOLANGIOCARCINOMA

- Sx of biliary obstruction—jaundice, pruritis, light colored stools and dark urine
- Risk factor: major is primary sclerosing cholangitis

ACUTE PANCREATITIS

Clinical features of acute pancreatitis	
Etiology	• Chronic alcohol use • Gallstones • Hyperlipidemia (types I, IV & V) • Drugs (eg, didanosine, azathioprine, valproic acid) • Infections (eg, cytomegalovirus, *Legionella*, *Aspergillus*) • Trauma • Iatrogenic (post-ERCP) Ischemic/ atheroembolic
Clinical presentation	**Diagnosis requires 2 of the following:** • Acute epigastric abdominal pain often radiating to the back • ↑ Amylase/lipase >3 times normal limit • Abdominal imaging showing focal or diffuse pancreatic enlargement with heterogeneous enhancement with intravenous contrast (CT) or diffusely enlarged & hypoechoic pancreas (ultrasound) **Other findings:** • Nausea, vomiting, leukocytosis • Severe disease with possible abdominal tenderness, fever, tachypnea, hypoxemia & hypotension • ALT level >150 units/L → biliary pancreatitis
Complications	• Pleural effusion • Ileus • Pancreatic pseudocyst/abscess/necrosis • Acute respiratory distress syndrome Renal failure

Perform RUQ USG for gall stones→ non-diagnostic (esp. if stone has passes)→ ERCP→ but typically have ↑ ALT—ERCP should also be considered in pts with >1 episode of acute pancreatitis of unknown origin. HIDA is not used to diagnose pancreatitis rather used for cholecystitis

Serum TG must be >1000 mg/dl to be considered potential cause of pancreatitis. TG >1000 mg/dl→ also leads to eruptive xanthomas→ Dx: fasting lipid profile

Perform these tests in sequence. If these 2 are present then CT need not be performed unless diagnosis is unclear or after failure of conservative rx (to identify infection or necrosis)

CXR abnormal in 1/3rd pts—show atelectasis, elevated hemidiaphragm or pulm. Infiltrates—due to activated pancreatic enzymes (eg trypsin, phospholipase) or cytokine (eg TNF) released from inflamed pancreas

- Chronic alcohol abuse and gall stones account for 75% of all cases
- Early in pancreatitis, the pancreas synthesizes digestive enzymes but cannot secrete them. These enzymes leak out of the acinar cells into the systemic circulation. Amylase rises within 6-12 hours of symptom onset and may remain elevated for 3-5 days. Lipase rises within 4-8 hours of symptom onset but remains elevated longer than amylase (8-14 days). As a result, lipase is more useful and sensitive than amylase for diagnosis (especially in alcoholics and patients presenting later in the disease course)

ACUTE PANCREATITIS 2° TO ATHEROEMBOLISM

- Patients with risk factors for aortic atherosclerosis (e.g. hypercholestrolemia, DM, PVD) who undergo cardiac catheterization or vascular procedure →↑ risk of cholesterol emboli as a result of vascular manipulation
- Emboli can occlude blood vessels and cause following:
  - Skin manifestations: livedo reticularis (reticulated, mottled, discolored skin), blue toe syndrome
  - Kidney manifestations: acute renal failure

- GI manifestations: pancreatitis, mesenteric ischemia

TREATMENT OF UNCORRECTABLE CAUSES OF ACUTE PANCREATITIS

- Uncorrectable causes: ischemia, hypotension, viruses, atheroembolism
- Supportive care: pain control, IV fluids, bowel rest
- Most acute attacks are self-limiting and usually improve in 4-7 days of supportive care
- Pt should be NPO except essential medications like antiplatelet therapy in case of stent placement
- Prophylactic antibiotics are not routinely used in acute pancreatitis—unless there is evidence of necrotizing pancreatitis with local infection

DRUG INDUCED ACUTE PANCREATITIS

- 5% cases of acute pancreatitis
- Medicines causing acute pancreatitis:
  - Anti-seizure medications (valproic acid)
  - Diuretics (furosemide, thiazides)
  - Drugs for IBD (sulfasalazine, 5-ASA)
  - Immunosuppressive agents (azathioprine)
  - HIV related meds (didanosine, pentamidine)
  - Antibiotics (metronidazole, tetracycline)
- Usually mild—N/V, abdominal pain radiating to back
- ↑amylase and lipase
- CT: peripancreatic fluid and fat stranding
- Rx: supportive—fluid and electrolyte replacement

CHRONIC PANCREATITIS

Overview of chronic pancreatitis	
Etiology	• Alcohol use • Cystic fibrosis (common in children) • Ductal obstruction (eg, malignancy, stones) • Autoimmune
Clinical presentation	• **Chronic epigastric pain** with intermittent pain-free intervals • **Malabsorption**—steatorrhea, weight loss • **Diabetes mellitus**
Laboratory results/imaging	• Amylase/lipase can be normal & nondiagnostic • CT scan or MRCP can show calcifications, dilated ducts & enlarged pancreas
Treatment	• Pain management • Alcohol & smoking cessation • Frequent, small meals • Pancreatic enzyme supplements

MRCP = magnetic resonance cholangiopancreatography.

Progressive inflammation of pancreas → irreversible exocrine and endocrine dysfunction

Unlike acute pancreatitis, CP causes patchy inflammation and fibrosis (burned out pancreas)→ normal or slightly ↑ amylase and lipase

- Early CP can present with acute attacks that become continuous as condition progressively worsens
- Stool elastase—marker for pancreatic exocrine function—low levels in CP rather than acute pancreatitis

SEVERE PANCREATITIS

Clinical features of severe pancreatitis	
Clinical presentation	• Fever, tachycardia, hypotension • Dyspnea, tachypnea &/or basilar crackles • Abdominal tenderness &/or distension • **Cullen sign**: Periumbilical bluish coloration indicating hemoperitoneum • **Grey-Turner sign**: Reddish-brown coloration around flanks indicating retroperitoneal bleed
Associated with ↑ risk of severe pancreatitis	• Age >75 • Obesity • Alcoholism • C-reactive protein >150 mg/dL at 48 hours after presentation • Rising blood urea nitrogen & creatinine in the first 48 hours • Chest x-ray with pulmonary infiltrates or pleural effusion • Computed tomography scan/magnetic resonance cholangiopancreatography with pancreatic necrosis & extrapancreatic inflammation
Complications	• Pseudocyst • Peripancreatic fluid collection • Necrotizing pancreatitis • Acute respiratory distress syndrome • Acute renal failure • Gastrointestinal bleeding

- Most pts have mild disease→ recover with conservative management in 3-5 days
- 15-20% develop severe acute pancreatitis, defined as pancreatitis with involvement of at least one organ
- Severe pancreatitis→local release of activated pancreatic enzymes→enters vascular system→↑ vascular permeability within and around pancreas→ large volumes of fluid migrate from vascular system to surrounding retroperitoneum. Systemic inflammation also ensues as inflammatory mediators enter vascular system→ widespread vasodilation, capillary leak, shock and associated end-organ damage
- RX: supportive care with several liters of IV fluid to replace intravascular volume

COMPLICATIONS OF PANCREATITIS

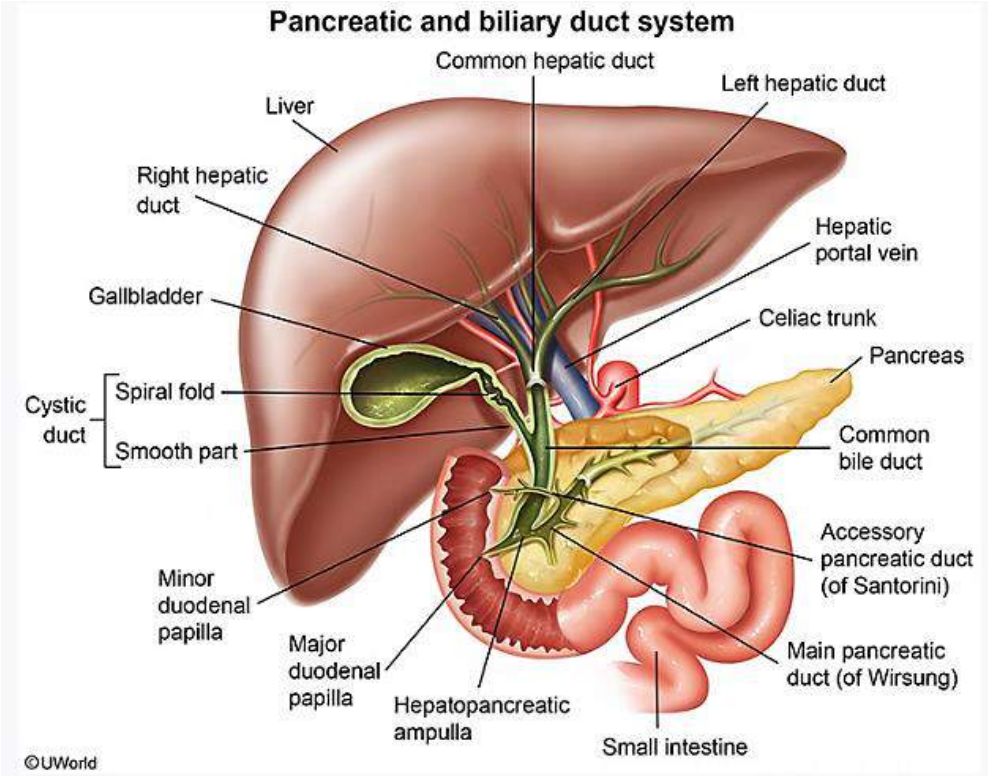
PANCREATIC PSEUDOCYST

- Progressive abdominal distension, abdominal pain, N/V
- CT scan: round, well circumscribed, encapsulated fluid collection (usually no necrosis or solid material), thick fibrous capsule, containing enzyme-rich fluid, tissue and debris
- ↑ serum amylase
- Complications: spontaneous infection, duodenal or biliary obstruction, pseudoaneurysm (due to digestion of adjacent vessels), pancreatic ascites and pleural effusion

- Abdominal imaging confirms diagnosis
- **Rx:**

- **Minimal or no symptoms and without complications (eg pseudoaneurysm)** → expectant management (eg symptomatic therapy and NPO)—preferred initially
- **Significant symptoms (abdominal pain, N/V), infected pseudocyst, evidence of pseudoaneurysm**→ endoscopic drainage

PANCREATIC CANCER



Major risk factors for pancreatic cancer	
Hereditary	• First-degree relative with pancreatic cancer • Hereditary pancreatitis • Germline mutations (eg, BRCA1, BRCA2, Peutz-Jeghers syndrome)
Environmental	• Cigarette smoking (most significant) • Obesity, low physical activity • Nonhereditary chronic pancreatitis

No. of cigarettes smoked α risk of pancreatic cancer—smoking cessation→↓ risk by 25%

- 4th leading cause of cancer death in US
- Adenocarcinoma most common tissue type
- Usually occur after age 45—more common in men and African American pts
- Usually diagnosed late→ high mortality (98% according to some studies)

- Long-standing DM→ risk factor for pancreatic cancer—new onset DM→ often a sign of occult pancreatic CA—treatment of DM has variable effects on CA risk—Insulin and insulin secretagogues (eg sulfonylureas)→ ↑ risk of CA, metformin→↓risk

Pancreatic adenocarcinoma	
Risk factors	• Smoking • Hereditary pancreatitis • Nonhereditary chronic pancreatitis • Obesity & lack of physical activity
Clinical presentation	• Systemic symptoms (eg, weight loss, anorexia) (>85%) • Abdominal pain/back pain (80%) • Jaundice (56%) • Recent-onset atypical diabetes mellitus • Unexplained migratory superficial thrombophlebitis • Hepatomegaly & ascites with metastasis
Laboratory studies	• Cholestasis (↑ alkaline phosphatase & direct bilirubin) • ↑ Cancer-associated antigen 19-9 (not as a screening test) • Abdominal ultrasound (if jaundiced) or CT scan (if no jaundice)

- Presentation and work up vary depending on tumor location
- Classic findings: weight loss and insidious onset abdominal pain- worse at night, with eating and when lying supine

CANCER OF PANCREATIC HEAD

- 60-70%
- Jaundice—bile duct obstruction, ↑ ALP and bilirubin
- Steatorrhea—pancreatic exocrine insufficiency or pancreatic duct blockage
- Can lead to compression of pancreatic duct and common bile duct→ **"double duct sign"** on imaging
- Backup of bile leads to dilation of intra and extrahepatic bile ducts and nontender distended gall bladder **(Courvoisier sign).** left supraclavicular LN enlargement (Virchow's nodes) can be present in metastatic disease
- USG better for detecting pancreatic head tumor and excluding other causes of biliary obstruction (eg choledocholithiasis)→ if unremarkable→ perform CT scan→ non-diagnostic→ ERCP→ ERCP contraindicated→ percutaneous transhepatic cholangiogram (PTC)—(PTC is an invasive procedure in which a needle is inserted into a dilated bile duct and contrast material is injected for bile duct opacification. PTC is used in the evaluation of patients who have previously identified biliary tract dilation but are not candidates for ERCP. PTC also allows for certain therapeutic interventions, including the drainage of infected bile (in patients with cholangitis), extraction of stones in the biliary tract, dilation of benign biliary strictures, or stent placement across malignant strictures.)

CANCER OF PANCREATIC TAIL AND BODY

- Do not present with obstructive jaundice
- CT preferred to rule out other causes

- USG—less visibility of tail and body due to overlying bowel gas and also less sensitive for detecting smaller tumors (<3cm)

MALIGNANT BILIARY OBSTRUCTION

Clinical features of malignant biliary obstruction	
Etiologies	• Cholangiocarcinoma • Pancreatic or hepatocellular carcinoma • Metastatic cancer (eg, colon, gastric)
Clinical presentation	• Jaundice (can be painless) • Pruritus, weight loss, acholic stools with dark urine • **Examination:** Can be normal or show right upper-quadrant mass, tenderness, or hepatomegaly • **Laboratory:** ↑ Direct bilirubin, ↑ alkaline phosphatase & gamma-glutamyl transpeptidase & normal to ↑ AST & ALT
Evaluation	• Abdominal imaging (ultrasound or computed tomography) • Magnetic resonance cholangiopancreatogram or endoscopic retrograde cholangiopancreatogram if imaging is nondiagnostic

PHARMACOLOGY

PPI

S/E:

- C. diff. infection due to prolonged acid suppression (also occurs in prolonged H2 receptor blocker use)
- Prolonged acid suppression→ ↓ calcium absorption→ osteoporosis
- ↑ colonization of pathogens in upper GI tract→ ↑ risk of pneumonia

Contents

WATER-SOLUBLE VITAMIN DEFICIENCIES

Water-soluble vitamins		
Vitamin	**Source**	**Deficiency**
B_1 (thiamine)	Whole grains, meat, fortified cereal, nuts, legumes	• Beriberi (peripheral neuropathy, heart failure) • Wernicke-Korsakoff syndrome
B_2 (riboflavin)	Dairy, eggs, meat, green vegetables	• Angular cheilosis, stomatitis, glossitis • Normocytic anemia • Seborrheic dermatitis
B_3 (niacin)	Meat, whole grains, legumes	• Pellagra (dermatitis, diarrhea, delusions/dementia, glossitis)
B_6 (pyridoxine)	Meat, whole grains, legumes, nuts	• Cheilosis, stomatitis, glossitis, • Irritability, confusion, depression
B_9 (folate, folic acid)	Green leafy vegetables, fruit, meat, fortified cereal/grains	• Megaloblastic anemia • Neural tube defects (fetus)
B_{12} (cobalamin)	Meat, dairy	• Megaloblastic anemia • Neurologic deficits (confusion, paresthesias, ataxia)
C (ascorbic acid)	Citrus fruits, strawberries, tomatoes, potatoes, broccoli	• Scurvy (punctate hemorrhage, gingivitis, corkscrew hair)

- Toxicity of water-soluble vitamins is rare but pyridoxine excess can cause peripheral neuropathy

PEDIATRIC ABDOMINAL WALL DEFECT

Pediatric abdominal wall defects	
Diagnosis	**Clinical features**
Umbilical hernia	• Defect at linea alba covered by skin • Sometimes contains bowel • Umbilical cord inserts at apex of defect
Gastroschisis	• Defect to the right of the cord insertion not covered by membrane or skin • Contains bowel • Umbilical cord inserts next to defect
Omphalocele	• Midline abdominal wall defect covered by peritoneum • Contains multiple abdominal organs • Umbilical cord inserts at apex of defect

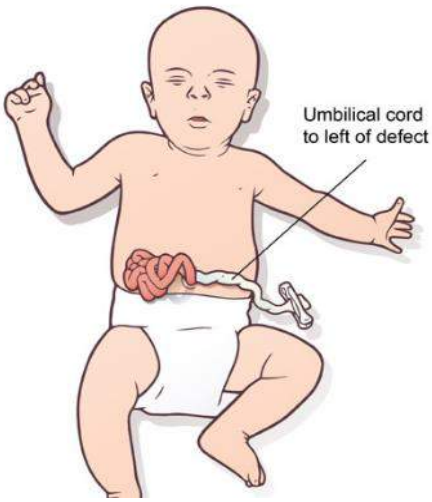
UMBILICAL HERNIA

- Incomplete closure of abdominal muscles around umbilical ring at birth
- Common in African American race, premature birth, Ehler-Danlos syndrome, Beckwith-Weidmann syndrome and hypothyroidism
- Small umbilical hernias typically close spontaneously by concentric fibrosis and scar tissue formation. Spontaneous closure is less likely with large (>1.5 cm diameter) hernias or in patients with underlying medical problems. Surgery is recommended around age 5 for persistent hernias, or sooner if it is bothersome or causing complications

GASTROSCHISIS

- Caused by vascular insult→ bowel herniation
- 2nd trimester USG→ >95% sensitive for abdominal wal defects and maternal serum AFP usually ↑ed
- Gastroschisis→ bowel exposed to amniotic fluid→ inflammation and edema of bowel wall→ ↑ risk of complications (eg necrotizing enterocolitis, short bowel syndrome)
- Dysmotility (ileus, delayed gastric emptying, intolerance to feeds)—occur in >50% cases and may prolong reliance on TPN
- It is isolated defect in >90% cases
- **Rx:** after delivery→ cover exposed bowel with sterile saline dressings and plastic wrap to minimize insensible heat and fluid losses→Place nasogastric tube to decompress bowel and start on antibiotic therapy→prompt surgical repair and can usually be accomplished in a **single-stage closure**

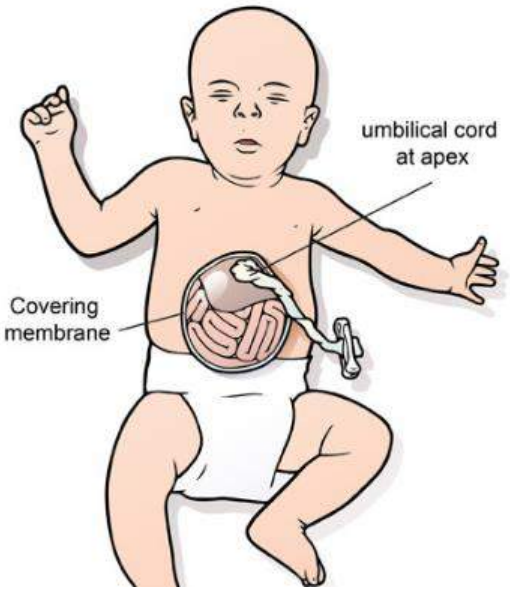
Gastroschisis



OMPHALOCELE

- Approx. half of pts with omphalocele have co-existing other defects like cardiac disease, neural tube defects, or trisomy syndromes
- Rx: surgery immediately after birth by staged closure with a silastic silo

Omphalocele



UMBILICAL GRANULOMA

- Common cause of umbilical mass in newborns
- Appear after umbilical has separated→ present as soft, moist, pink, pedunculated, friable lesion
- Rx: silver nitrate is treatment of choice

DIFFERENTIAL DIAGNOSIS OF CRYING INFANT

Differential diagnosis for a crying infant	
Diagnosis	**Clinical features**
Colic	Crying that occurs in an otherwise healthy infant for ≥3 hours daily (usually evening), ≥3 times a week & for a duration of ≥3 weeks
Gastroesophageal reflux disease	• Arching of the back during or after feeding (Sandifer syndrome) • Frequent spit-ups or vomiting • Poor weight gain
Corneal abrasion	Positive fluorescein examination
Hair tourniquet	Presence of hair that is accidentally tied or wrapped around an extremity or digit
Milk protein allergy	Blood-streaked, mucousy, loose stools or severe constipation
Normal infant crying	• Intermittent crying that resolves with usual consoling methods • Duration <2 hours a day

- Crying time of a normal infant is generally 1-2 hours/day but highly variable

COLIC

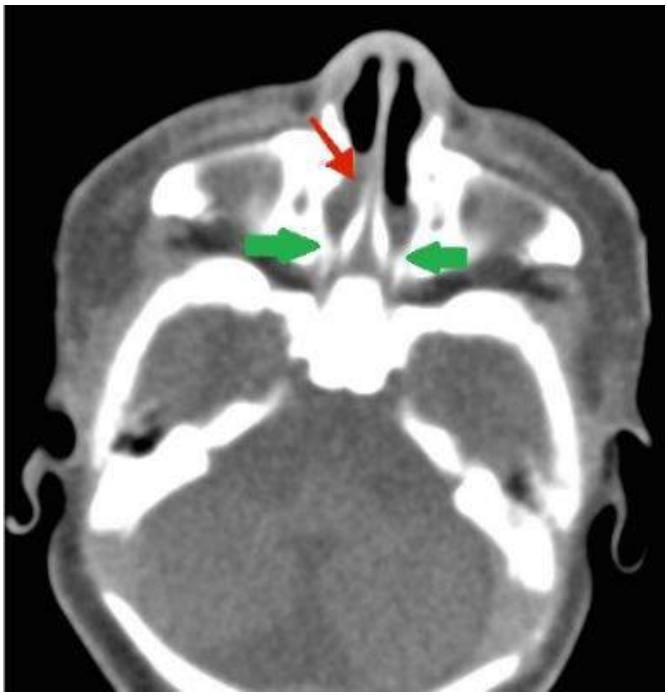
- Usually presents in 1st few wks of life and spontaneously resolves by 4 months
- Generally cries at same time of the day
- Etiology: cause unknown but may be due to overstimulation of baby and parental unfamiliarity with other soothing techniques
- Parents report: difficulty and frustration soothing the baby
- Calming techniques: infant swing, swaddling, minimizing environmental stimuli (eg quiet dark room) and holding and rocking baby
- Review: feeding patterns to assess overfeeding, underfeeding, or an inadequate burping technique
- Colic is associated with ↑ incidence of non-accidental trauma, post-partum depression
- Parents should be emotionally supported and reassured that their child is healthy and review soothing techniques. Breaks should be encouraged including friend or family babysit the child

FOREIGN BODY INGESTION

- Difficulty swallowing, feeding refusal and vomiting→ suspect foreign body ingestion
- Management: depends on object material, location in GI tract, timings of duration and symptoms
- **Coin:** most commonly ingested material
  - Visualized in esophagus and symptomatic or time of ingestion unknown→ remove promptly with **flexible endoscopy** (rigid endo has higher risk of perforation and abrasion—reserved for impacted sharp objects)

- Visualized in esophagus and asymptomatic→ **can observe for 24 hours** after ingestion—as coin lacks sharp border and metal not toxic—those that reach stomach can be allowed to pass spontaneously
- **Radiolucent body:** not visualized on x-ray, CT as next diagnostic procedure
- **Batteries, multiple magnets or sharp objects:** ↑ risk of perforation, obstruction, ischemia→ immediate endoscopy if object is visualized in esophagus. Severe symptoms like hematochezia, melena, and severe abdominal pain→ surgical removal. If battery is distal to esophagus, then almost 90% pass uneventfully→ observe to confirm excretion of battery by stool examination and/or radiographic followup
- Avoid GI series→ as ↓ visualization on endo
- **Tracheobronchial foreign body aspiration:** suspect in toddlers with sudden wheezing, stridor, coughing or dyspnea→ rigid bronchoscopy—procedure of choice

CHOANAL ATRESIA



- **Pathophysiology:** failure of posterior nasal passage to canalize completely, leaving either a bony (90%) or membranous (10%) obstruction—narrowing is at the level of pterygoid plate in posterior nasal cavity
- May be isolated or part of a syndrome (CHARGE syndrome: Coloboma, Heart defects, Atresia choanae, Retardation of growth/development, Genito-urinary abnormalities, and Ear abnormalities/deafness)
- Clinical severity—depends on child's ability to breath from mouth, and whether one or both choanae is/are obstructed
- **C/F:**
  - B/L obstruction: classically presents with **cyclic cyanosis** that worsens when infants cannot breathe through the mouth (eg, during feeding) and recovers when they do (eg, while crying).
  - U/L choanal atresia: may remain undiagnosed until the development of a first URTI
- **Dx:** failure to pass catheter through nares into oropharynx—confirmed by CT scan. In severe cases, air fluid levels may develop at obstruction site
- **Management:**
  1. Place oropharyngeal airway and orogastric tube feeding
  2. Definitive treatment: repairing obstruction with surgery or endoscopy

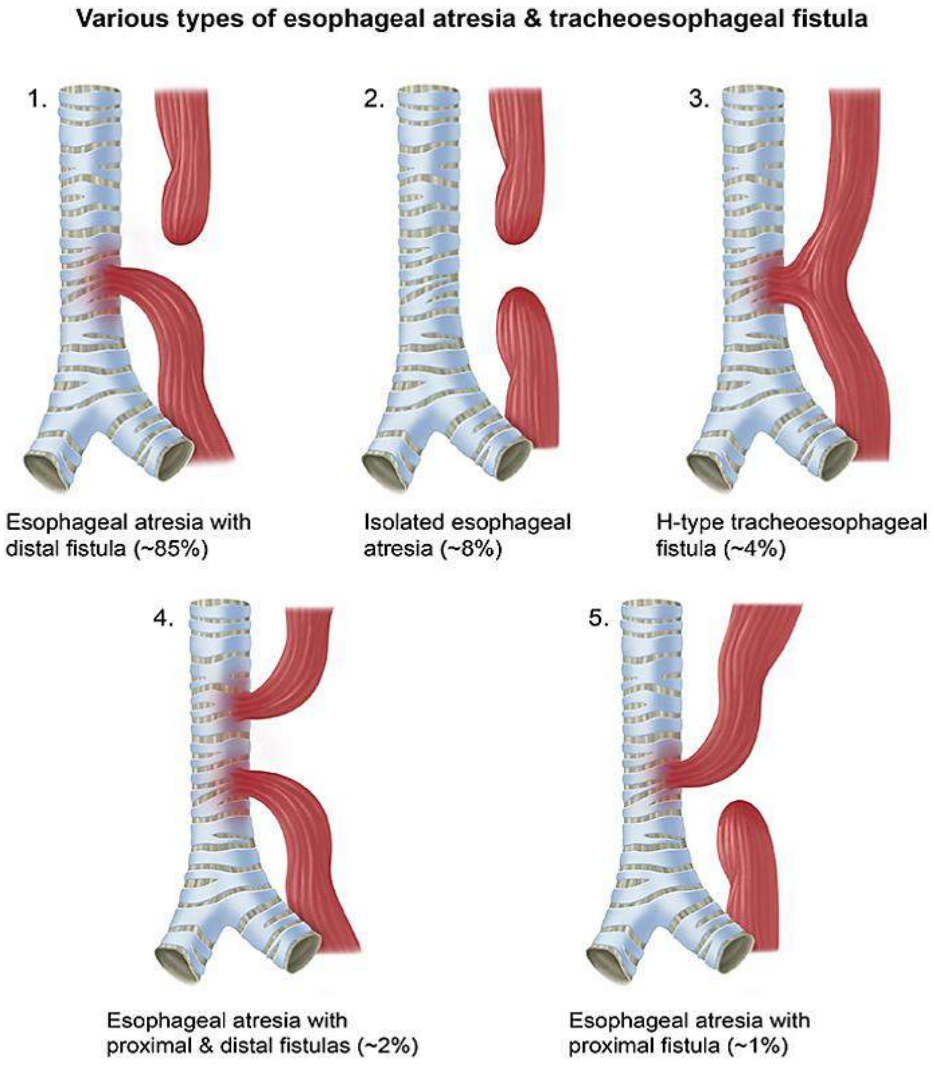
CONGENITAL DIAPHRAGMATIC HERNIA

- Presents as cyanosis and respiratory distress immediately after birth.
- Polyhydramnios can occur as a result of esophageal compression
- However, the deviation of abdominal viscera into the thorax results in a scaphoid-appearing abdomen.
- In addition, x-ray shows a displaced cardiac silhouette, bowel in the thorax, and a gasless abdomen.

ANOMALOUS VASCULAR BRANCHES OF AORTIC ARCH

Anomalous vascular branches of the aortic arch can cause stridor and dysphagia due to compression of the trachea and esophagus. However, naso- or orogastric tubes can be advanced into the stomach.

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA



ESOPHAGEAL ATRESIA WITH TRACHEOESOPHAGEAL FISTULA

- Polyhydramnios due to inability to swallow amniotic fluid
- Excessive drooling, choking, coughing and regurgitation with initial feeding attempts immediately after birth
- Inability to pass naso or orogastric tubes into stomach
- Presence of fistula→ air entry into stomach and intestines with each breath→ abdominal distention

- Gastric fluid can reflux in to esophagus and through fistula to trachea and lungs→ aspiration pneumonia→ respiratory distress, crackles and infiltrates in lungs
- 50% pts with tracheal and esophageal anomalies have additional anomalies→ workup for VACTERL (vertebral, anal atresia, cardiac, tracheoesophageal fistula, renal and limb anomalies) should be considered

ISOLATED ESOPHAGEAL ATRESIA

- Rare and would not cause sudden respiratory distress with feeding

GI BLEEDING

- Divided into upper and lower GI bleeding by ligament of Treitz
- **Upper GI bleeding**: melena (black tarry stools), from stomach and upper small intestine
- **Lower GI bleeding**: hematochezia (bright red blood), from distal small bowel and colon
  - **D/D of hematochezia in toddlers**: hemorrhoids, infectious colitis, intussusception, Meckel's diverticulum (most common) and inflammatory bowel disease.

MILK PROTEIN ALLERGY

Milk- or soy-protein-induced colitis	
Risk factors	• Family history of allergies, eczema, or asthma
Clinical features	• Presents at age 2-8 weeks • Regurgitation or vomiting • +/-Painless bloody stools • +/-Eczema
Treatment	• Elimination of milk & soy from maternal diet of exclusively breastfed infants • Initiation of hydrolyzed formula in formula-fed infants
Prognosis	• Spontaneous resolution by age 1 year

Non- projectile vomiting, poor weight gain

- Condition is exclusive to infants
- Breast milk contains: fats, carbs (eg lactose) and maternal diet derived proteins (eg whey-70%, casein-30%) from milk and soy. Protein content is higher at birth and ↓es over 1st month of life. Whey is more easily digested and improves gastric emptying. Also contains lysozyme, lactoferrin, secretory IgA→ ↑ immunity. Calcium and phosphorus are less in human milk than formula but better absorbed from breastmilk
- Non-IgE mediated immunologic response to proteins in formula or breast milk→ causes rectal and colonic inflammation

- Dx: clinical and confirmed when bleeding ceases in response to dietary changes— visible bleeding ceases in 3 days but occult blood may take up to 2 wks—reassure parents: prognosis is excellent and almost all infants can tolerate dairy and soy products by 1 year
- Due to substantial cross-reactivity—discontinue all dairy and soy products and continue breastfeeding after discontinuation

MECKEL'S DIVERTICULUM

Meckel's diverticulum	
Epidemiology	**Rule of 2s** • 2% prevalence • 2:1 male-to-female ratio • 2% are symptomatic at age 2 • Located within 2 feet of the ileocecal valve
Clinical presentation	• Asymptomatic incidental finding • Painless hematochezia • Intussusception • Intestinal obstruction • Volvulus
Diagnosis	Technetium-99m pertechnetate scan
Treatment	Surgery for symptomatic patients

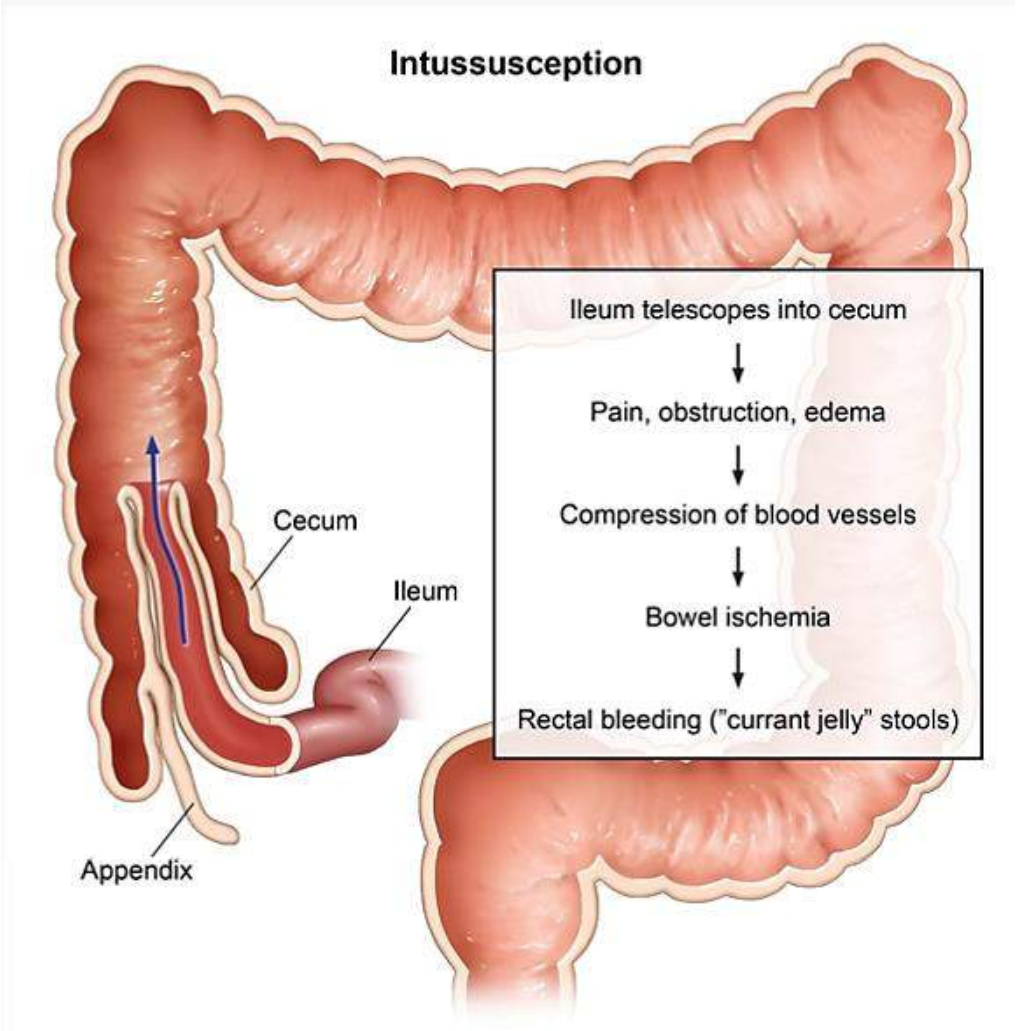
Most common

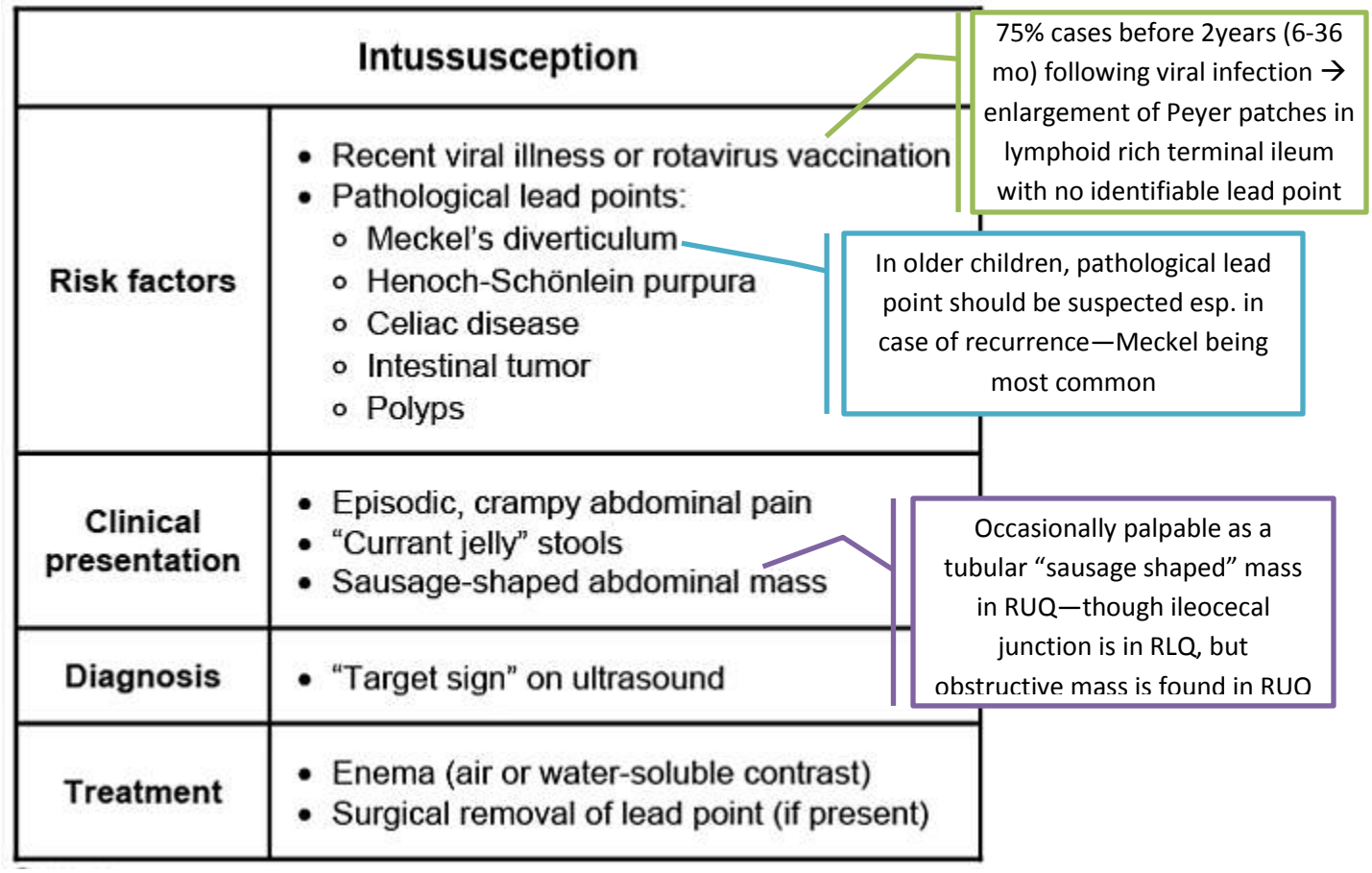
2% become symptomatic—painless hematochezia being most common finding

Tiny amount of IV technetium is given→ gamma camera highlights gastric mucosa and ectopic gastric tissue

- Approx. 85% have heterotropic gastric mucosa and some have pancreatic tissue
- Gastric mucosa secrete HCl→ mucosal ulceration of surrounding small bowel→ bleeding often substantial and causes severe anemia and hemorrhagic shock
- Although bleeding usually stops on its own, surgical resection is necessary to prevent complications
- Intussusception presents as severe, intermittent abdominal pain with or without hematochezia→abdominal USG→diagnostic and therapeutic air enema

INTUSSUSCEPTION





- Ileocolic junction most frequently involved
- Telescoping is intermittent→ periodic pain associated with drawing legs towards abdomen
- Emesis may follow episodes of abdominal pain→ initially non-bilious and later becomes bilious if obstruction persists
- PE: occasionally intussusception is
- Air enema preferred as faster, cleaner and safer than contrast→ unsuccessful, pathological lead point identified or signs of perforation→ laparotomy

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis	
Risk factors	• Prematurity • Very low birth weight (<1.5 kg) • Reduced mesenteric perfusion (hypotension, congenital heart disease) • Enteral feeding (formula > breast milk)
Clinical features	• Systemic: Vital sign instability, lethargy • Gastrointestinal: Vomiting, bloody stools, abdominal distension/tenderness
X-ray findings	• Pneumatosis intestinalis • Portal venous gas • Pneumoperitoneum

Treatment	• Supportive care
	  • Bowel rest
	  • Parenteral hydration/nutrition
	• Broad-spectrum intravenous antibiotics
	• +/- Surgery

Complications	• Septic shock • Intestinal strictures • Short bowel syndrome • Death (up to 40%)

Represents extravasation of bowel gas into damaged bowel wall—double line or train track appearance on xray

Linear branching areas of lucency over liver—portal venous gas—either due to bacteria producing gas in portal vein or by transmigration of gas from bowel wall→mesenteric vein→portal vein

Because of high risk of septic shock

- Common sites: terminal ileum and colon
- Term infants present earlier as enteral feeding starts earlier as compared to pre-term infants
- Commercial formulas and mother's milk→ substrates for bacterial proliferation in gut→ poorly perfused intestinal wall→ ↓ ability to digest and absorb nutrients→ bacterial fermentation→ excessive mucosal inflammation→ translocation of bacteria and gas in to bowel wall—if possible give mother's breastmilk to premature infants as it counteracts some of the problems
- Leukocytosis and metabolic acidosis are signs of inflammation and intestinal ischemia

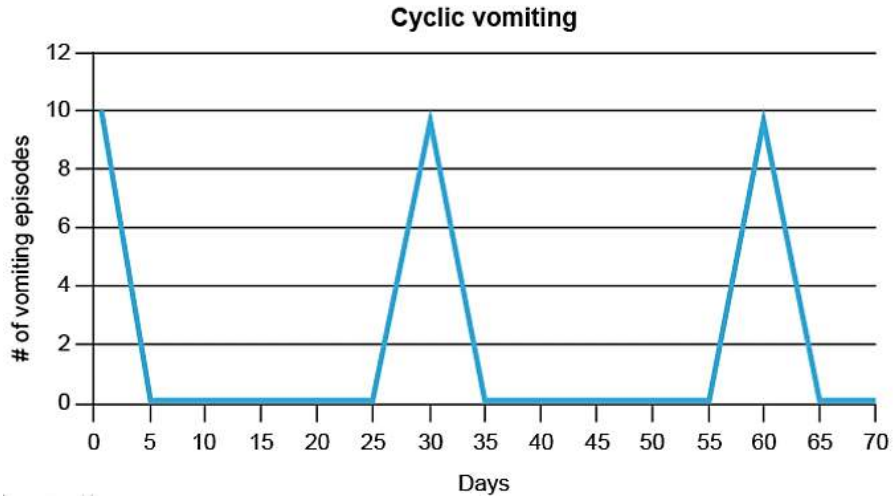
➔ All neonates are frequently colonized by C. diff. but infection is rare in them probably due to lack of toxin receptors

CYCLICAL VOMITING SYNDROME (CVS)

Diagnostic criteria of cyclic vomiting syndrome

- ≥3 episodes in a 6-month period
- Easily recognizable to family (stereotypical)
- Lasts 1–10 days
- Vomiting ≥4 times/hr at peak
- No symptoms in between vomiting episodes
- No underlying condition can be identified

- Recurrent predictable pattern of vomiting



- Family history of migraine headaches is often present
- Etiology: unclear but is thought to be linked to abdominal migraines which generally present as abdominal pain as primary symptom
- Some children progress from CVS to abdominal migraines and migraine headaches
- Complications that may arise from recurrent vomiting: dehydration and anemia
- Rx: hydration, antiemetics (eg ondansetron) and reassurance to parents. Children with FH of migraines are likely to benefit from anti-migraine therapy such as sumatriptan
- Approx. 2/3 have gradual resolution of symptoms in 5-10 years

DIFFERENTIAL DIAGNOSIS OF VOMITING AND REGURGITATION IN INFANTS

Differential diagnosis of regurgitation & vomiting in infants		
Diagnosis	**Clinical features**	**Management**

Gastroesophageal reflux	• Physiologic
	  ○ Asymptomatic
	  ○ "Happy spitter"
		• Reassurance
		• Positioning therapy

	• Pathologic (GERD)
	  ○ Failure to thrive
	  ○ Significant irritability
	  ○ Sandifer syndrome
		• Thickened feeds
		• Antacid therapy
		• If severe, esophageal pH probe monitoring & upper endoscopy

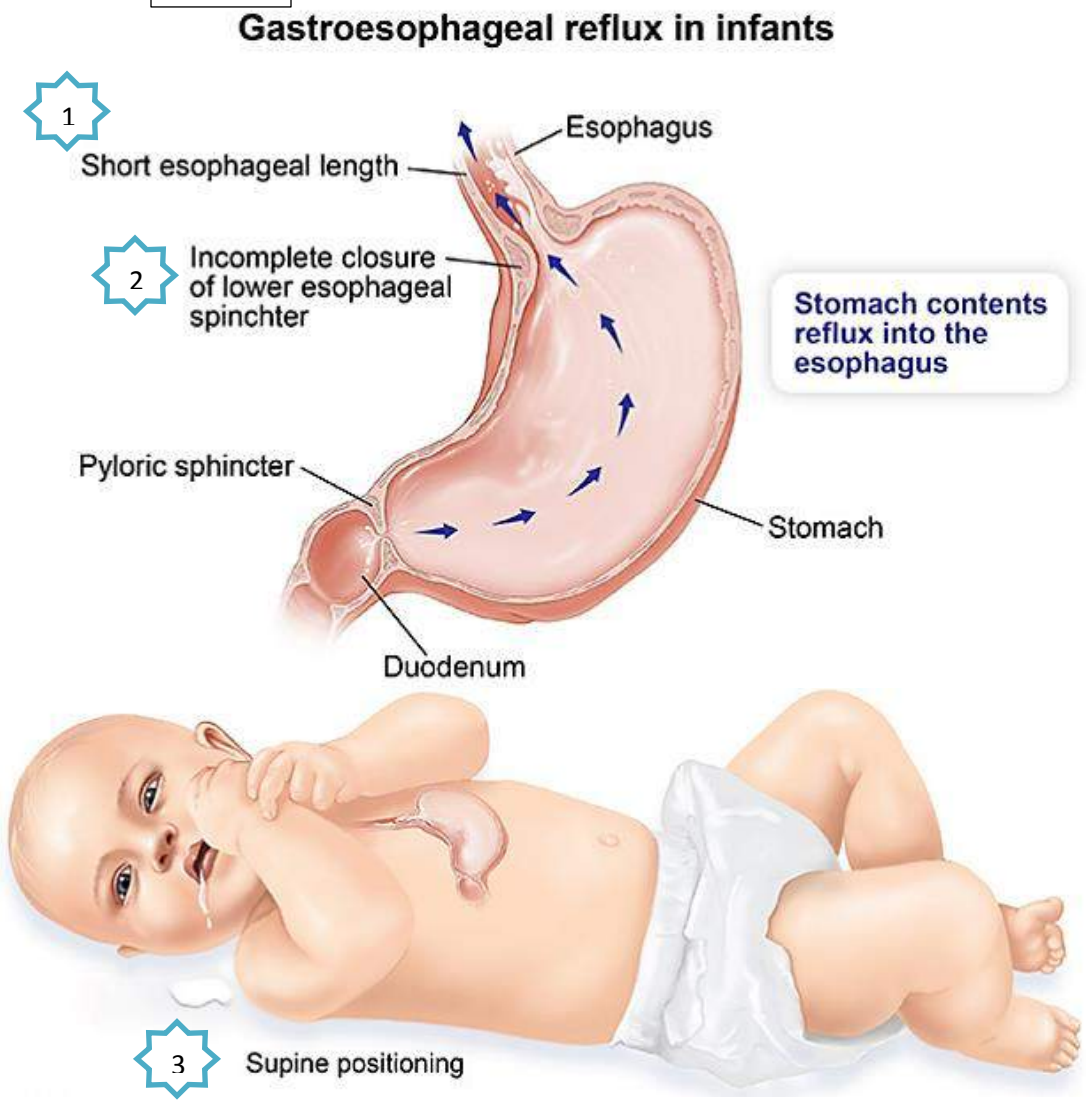
Milk protein allergy	• Regurgitation/vomiting • Eczema • Bloody stools	• Elimination of dairy & soy protein from diet
Pyloric stenosis	• Projectile nonbilious vomiting • Olive-shaped abdominal mass • Dehydration, weight loss	• Abdominal ultrasound • Pyloromyotomy

GERD = gastroesophageal reflux disease.

GASTROESOPHAGEAL REFLUX

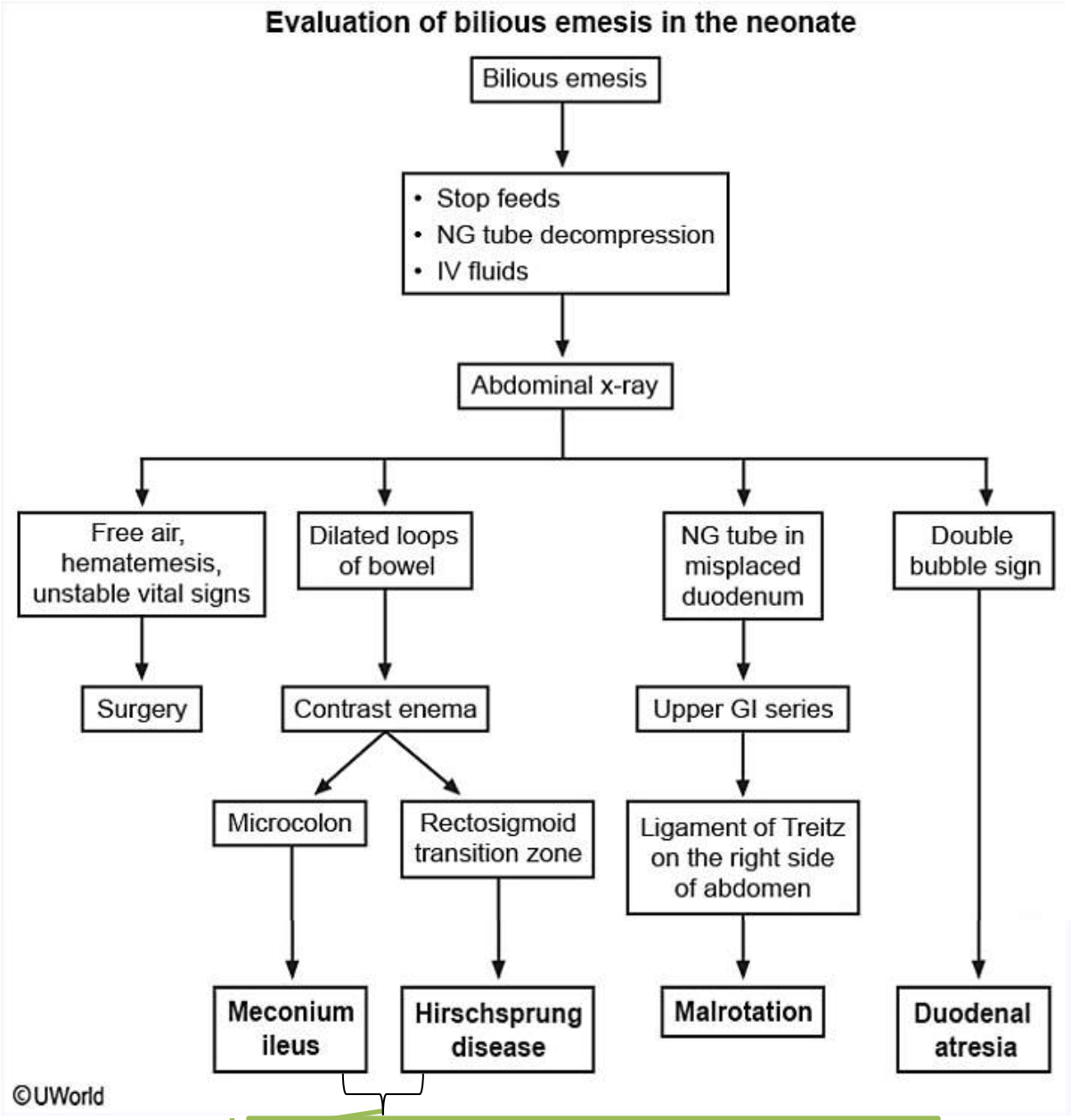
- Extremely common and affects >50% infants
- Infants experience frequent postprandial regurgitation (eg spitting up or spilling) due to physiologic changes among adults and children—differences shown in picture
- If there is normal weight gain, growth and development, no drop in growth percentiles, asymptomatic→ reassurance, supportive measures and education of parents: **frequent, small volume feeds, hold infant upright for 20-30 min** after each feed, place infant in **prone position when awake;** activities that ↑ intraabdominal pressure eg. fastening diaper too tight, brining knees to stomach—avoid
- Improve by age 6 mo (when infant can sit unsupported) and resolves by age 1 year

Causes:



➔ Goat milk is deficient in folate→ macrocytic anemia

BILIOUS EMESIS IN NEONATES



VOLVULUS

- The primary predisposing factor for volvulus in children is malrotation of the midgut during early fetal development.
- Midgut volvulus classically presents in a neonate (age <1 month) with bilious vomiting. Initially, the abdomen is soft and not distended, but ischemia of the twisted bowel can cause bloody stools, bowel perforation, abdominal distension, and peritonitis.
- **Signs of ischemia or systemic decompensation (ie, shock)** are an indication for **emergency laparotomy**.
- **The evaluation of clinically stable neonates with bilious emesis** begins with cessation of enteral feeds, nasogastric (NG) tube decompression, and intravenous (IV) fluids. An x-ray is generally the first step to rule out **pneumoperitoneum,** which would reflect intestinal perforation and immediate need for emergency surgery. Rarely, the diagnosis may be suspected if the NG tube terminates in the abnormally-placed duodenum, but x-ray is usually nonspecific for midgut volvulus.
- If **there is no evidence of free air and the bowel gas pattern** is not suggestive of duodenal atresia ("double bubble") or distal obstruction (dilated loops of bowel), then **an upper gastrointestinal (GI)**

series i.e. fluoroscopy (eg, barium swallow) should be performed. An upper GI series is the fastest and most accurate method of diagnosing malrotation with midgut volvulus. The finding of the Ligament of Treitz on the right side of the abdomen reflects malrotation while contrast in a "corkscrew" pattern indicates volvulus.

- Surgery must be expedited to prevent catastrophic complications. If present, the volvulus is reduced. The **Ladd procedure** consists of fixing the bowel in a non-rotated position to minimize recurrent volvulus risk.

➔ Serial abdominal x-rays are used to follow progression of non-surgical cases like ileus and mild cases of necrotizing enterocolitis—not recommended in suspected cases of surgical conditions like volvulus

SIGMOID VOLVULUS

- C/F: abdominal pain, distension, and constipation due to torsion of the sigmoid colon.
- X-ray shows an inverted U-shaped appearance of the distended sigmoid loop ("coffee bean sign").
- This typically occurs in elderly patients and is exceptionally rare in children

DUODENAL ATRESIA

- Bilious vomiting within 1st 2 days of life
- Common in Down syndrome pts.
- Due to failure to recanalize
- Surgical repair is the treatment (initial Rx in flow sheet)
- Pre-op cardiac assessment is extremely imp as 50% Down syndrome pts have congenital cardiac anomalies esp. VSD or ASD

JEJUNAL AND ILEAL ATRESIA

- Due to vascular accident in utero→ necrosis and resorption of fetal intestine → sealing off and leaving behind blind proximal and distal ends of intestine
- Risk factors: poor gut perfusion from maternal use of vasoconstrictive meds or drugs like cocaine and tobacco. Sometimes meconium ileus/ cystic fibrosis→ inspissated meconium→ localized volvulus→ ischemic necrosis
- Not associated chromosomal abnormalities
- X-ray: **“triple bubble sign”** and **gasless colon**
- Rx: resuscitation and stabilization→surgical correction
- Prognosis: depends on length of affected bowel and pts gestational age and birth weight

INFANTILE HYPERTROPHIC PYLORIC STENOSIS

- Present at: **age 1-2 months (3-5 wks)**
- Classic findings include visible peristaltic waves moving from left to right across upper abdomen just prior to emesis and a palpable abdominal mass.
- The classic "olive-shaped" abdominal mass is palpable in <50% of patients. It is best felt when the patient is calm after emesis as the distended stomach can obscure the mass. However, the abdomen is soft and non-distended because minimal air can pass the gastric outlet.

Infantile hypertrophic pyloric stenosis	
Risk factors	• First-born boy • Erythromycin • Formula feeding
Clinical presentation	• **Projectile nonbilious** emesis • Poor weight gain • Dehydration • **"Olive-shaped" abdominal mass**
Laboratory findings	• **Hypochloremic metabolic alkalosis**
Diagnostic studies	• Abdominal ultrasound
Treatment	• Intravenous rehydration • Pyloromyotomy

Formula feed→ slower gastric emptying and more consumption in less time hence ↑ gastric burden→ may lead to pylorus hypertrophy

After feeding→ followed by hunger "hungry vomiter"

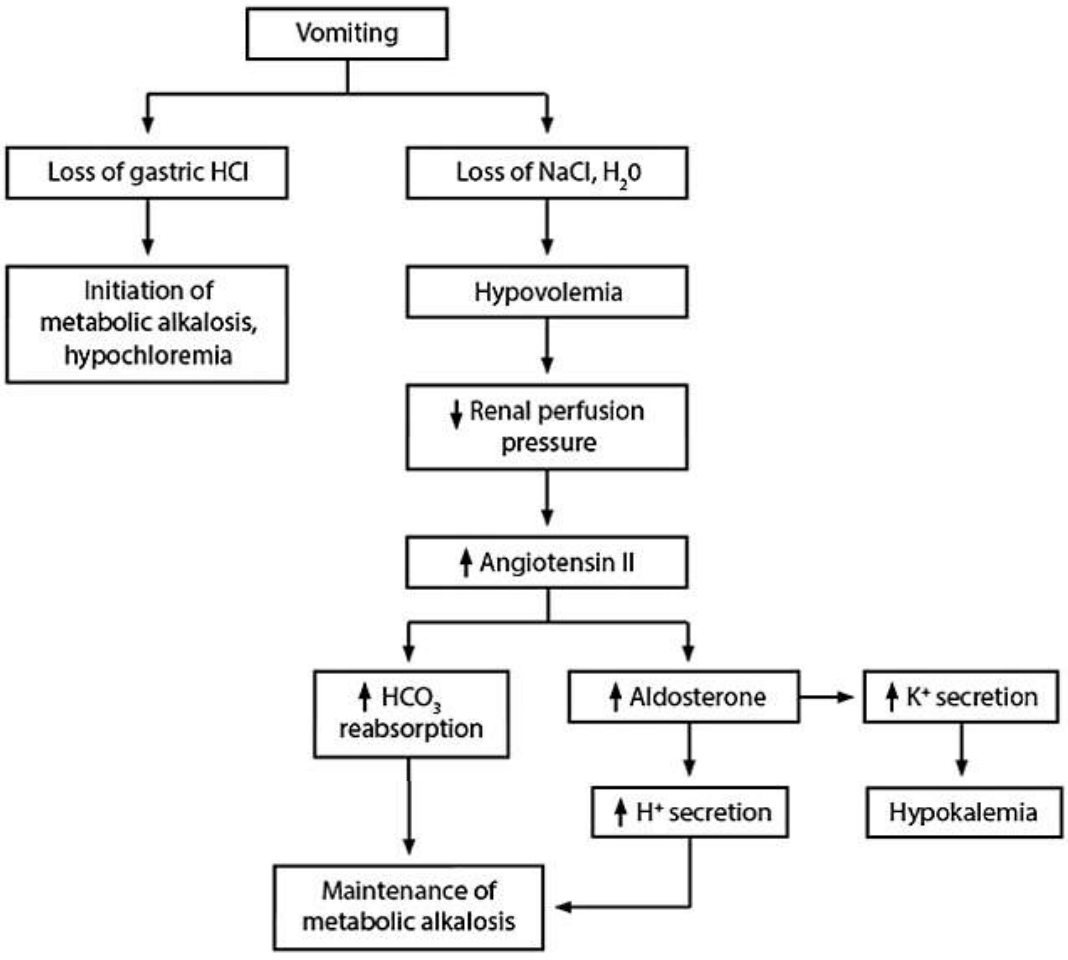
And hypokalemic

USG shows elongated, thickened pylorus

And electrolyte normalization—prior to surgery→ ↓es risk of post-op apnea and improve overall outcomes

LABORATORY DERANGEMENTS IN PYLORIC STENOSIS

Laboratory derangements in pyloric stenosis



CYSTIC FIBROSIS

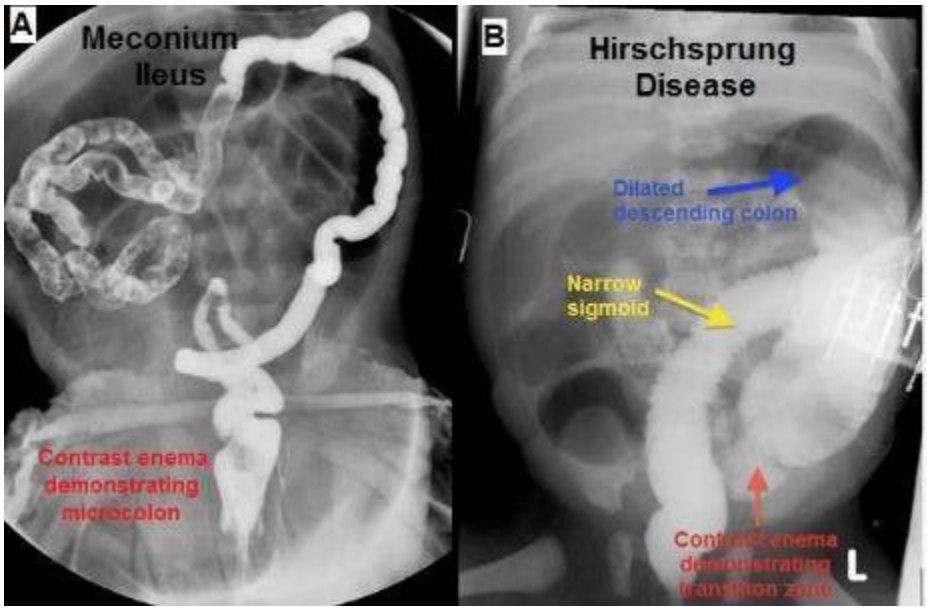
Clinical features of cystic fibrosis	
Respiratory	• Obstructive lung disease → bronchiectasis • Recurrent pneumonia • Chronic rhinosinusitis

Gastrointestinal	• Obstruction (10%-20%)
	  ○ Meconium ileus
	  ○ Distal intestinal obstruction syndrome
	• Pancreatic disease
	  ○ Exocrine pancreatic insufficiency
	  ○ CF-related diabetes (~25%)
	• Biliary cirrhosis

Reproductive	• Infertility (>95% men, ~20% women)
Musculoskeletal	• Osteopenia → fractures • Kyphoscoliosis • Digital clubbing

HIRSCHSPRUNG DISEASE VS MECONIUM ILEUS

Differentiating features of Hirschsprung disease and meconium ileus		
	Hirschsprung disease	**Meconium ileus**
Associated disorder	Down syndrome	Cystic fibrosis
Typical level of obstruction	Rectosigmoid	Ileum
Meconium consistency	Normal	Inspissated
"Squirt sign"	Positive	Negative



- They should be considered in any infant who fail to pass meconium for >48 hours after birth as 99% normal healthy infants pass stool within 48 hours

MECONIUM ILEUS

- 20% pts with CF develop meconium ileus but all pts with meconium ileus have CF
- They also have narrow, underused/underdeveloped colon (microcolon) as obstruction is usually at the level of ileum
- 1st step in management: abdominal x-ray is always 1st step to rule out pneumoperitoneum 2* to perforation→ +ve→ emergency surgery. –ve penumoperitonium→ contrast enema to assess level of obstruction. Administration of hyperosmolar enema (eg, Gastrografin) can potentially break up the inspissated meconium and dissolve the obstruction. Surgery is required if therapeutic enema is unsuccessful
- Almost all CF pts develop sinopulmonary disease→ opacification of all sinuses by 8 mo→ often require surgical debridement of their sinuses
- Men typically infertile due to congenital absence of vas deferens but only 20% females have fertility issues
- 20% develop sensorineural hearing loss due to frequent use of aminoglycosides for G-ve infections (eg Pseudomonas aeruginosa)

HIRSCHSPRUNG DISEASE

- Typically presents with increased rectal tone, "squirt sign" (forceful expulsion of stool after rectal examination)
- X-ray→ no perforation→ contrast enema→ transition zone at junction of narrow rectosigmoid and dilated colon→ rectal biopsy→ equivocal results→ anorectal manometry

CELIAC DISEASE

Celiac disease	
Risk factors	• First-degree relative with celiac disease • Autoimmune thyroiditis • Type 1 diabetes • Down syndrome • Selective IgA deficiency

Symptoms	• Gastrointestinal
	  ○ Abdominal pain
	  ○ Nausea &/or vomiting
	  ○ Diarrhea (rarely, constipation)
	  ○ Flatulence & bloating
	• Extraintestinal
	  ○ Short stature & weight loss
	  ○ Iron deficiency anemia
	  ○ Dermatitis herpetiformis

Diagnosis	• ↑ Tissue transglutaminase IgA • ↑ Anti-endomysial antibodies • Duodenal biopsy showing ↑ intraepithelial lymphocytes & flattened villi

CONSTIPATION

Constipation in children	
Risk factors	• Initiation of solid food & cow's milk • Toilet training • School entry
Clinical presentation	• Straining with passage of hard stools • Crampy abdominal pain • ≤2 defecations/week
Complications	• Anal fissures • Hemorrhoids • Encopresis • Enuresis/urinary tract infections • Vomiting
Treatment	• Increase dietary fiber • Limit cow's milk intake to <24 oz • Laxative • +/- Suppositories, enema

Stool burden ↓ bladder capacity→ urinary incontinence

And sit on toilet after each meal

DEHYDRATION

- Children are vulnerable to dehydration because:
  - ↑ frequency of gastroenteritis
  - High surface area to volume ratio→↑ insensible losses
  - ↓ ability to communicate
- **Management:** initial step is to determine severity—ideal method: determine measured change in weight, 1kg acute weight loss = 1L fluid loss—however, weight changes frequently in children and it is difficult to determine last "well" weight. Hence, severity is determined by history and physical exam and divided into following categories:
  1. **Mild dehydration** (3-5% volume loss): a history of ↓ intake or ↑ fluid loss with minimal or no clinical symptoms
  2. **Moderate dehydration** (6-9% volume loss): ↓ skin turgor, dry mucus membranes, tachycardia, irritability, a delayed capillary refill (2-3 seconds), and ↓ urine output
  3. **Severe dehydration** (10-15% volume loss): cool, clammy skin, a delayed capillary refill (>3 seconds), cracked lips, dry mucous membranes, sunken eyes, sunken fontanelle (if still present), tachycardia, lethargy, and minimal or no urine output. Patients can present with hypotension and signs of shock when severely dehydrated.
- **Rx:**
  - Mild to moderate: oral rehydration is initial step
  - Moderate to severe: immediate IV resuscitation to restore perfusion and prevent end organ damage. Isotonic crystalloid is the only recommended crystalloid in children (normal saline)—hypotonic solutions are not recommended as can cause cerebral edema or electrolyte abnormalities. Dextrose solutions not given in initial therapy but should be added in maintenance therapy

REYE SYNDROME

Reye syndrome	
Pathophysiology	Microvesicular fatty infiltration & hepatic mitochondrial dysfunction
Etiology	Pediatric aspirin use in the setting of influenza or varicella infection
Clinical features	• Acute liver failure • Encephalopathy
Laboratory findings	• ↑ Transaminases • ↑ PT, INR, PTT • ↑ Ammonia

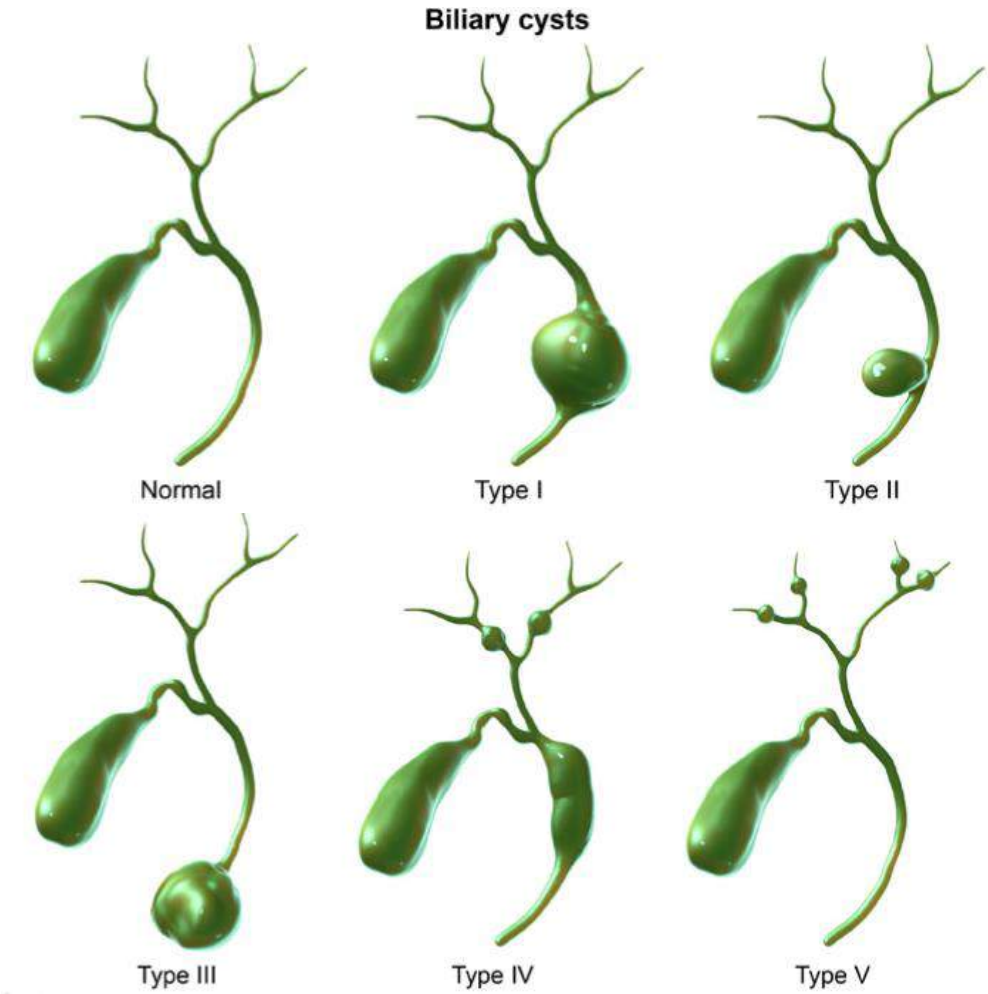
- Age <15 years
- Biopsy of liver, brain and kidney→ microvesicular steatotsis
- Rx: supportive

BILIARY CYSTS OR CHOLEDOCHAL CYSTS

- Congenital or acquired dilation of biliary tree.
- May be single, multiple, intra or extrahepatic

Biliary cysts	
Pathogenesis	• Type I cysts (most common): extrahepatic, single cystic dilatation of the bile duct
Clinical manifestations	• Classic triad of pain, jaundice & palpable mass • Majority of cysts present at age <10 years
Diagnosis	• Visualization on ultrasonography • ERCP → If obstruction is suspected
Treatment	• Surgical resection to relieve obstruction & prevent malignant transformation

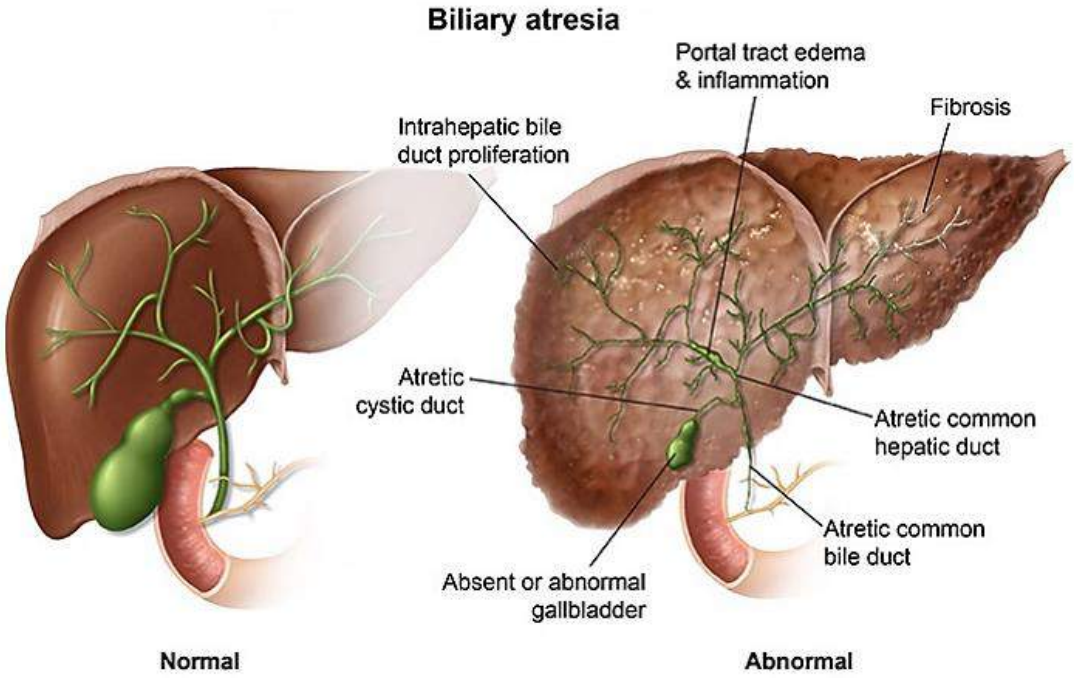
ERCP = endoscopic retrograde cholangiopancreatography.



- Jaundice is due to obstructive cholestasis
- Clinical presentation varies with age:
  - Infants: jaundice and acholic stools, a presentation that resembles biliary atresia
  - Older children: may have pancreatitis
  - Adults: vague epigastric or RUQ abdominal pain or cholangitis (cholangitis presents with fever)
- Biliary cysts can transform in to cholangiocarcinoma

BILIARY ATRESIA

Biliary atresia	
Clinical features	Initially well-appearing, followed by development of the following over 1-8 weeks: • Jaundice • Acholic (pale) stools or dark urine • Hepatomegaly • Conjugated hyperbilirubinemia • Mild elevation in transaminases
Diagnosis	• Ultrasound: absent or abnormal gallbladder (1st) • Hepatobiliary scintigraphy: failure of tracer excretion • Liver biopsy: expanded portal tracts with bile duct obstruction & proliferation; portal tract edema, fibrosis & inflammation • Intraoperative cholangiogram (gold standard): biliary obstruction
Treatment	• Hepatoportoenterostomy (Kasai procedure) • Liver transplant

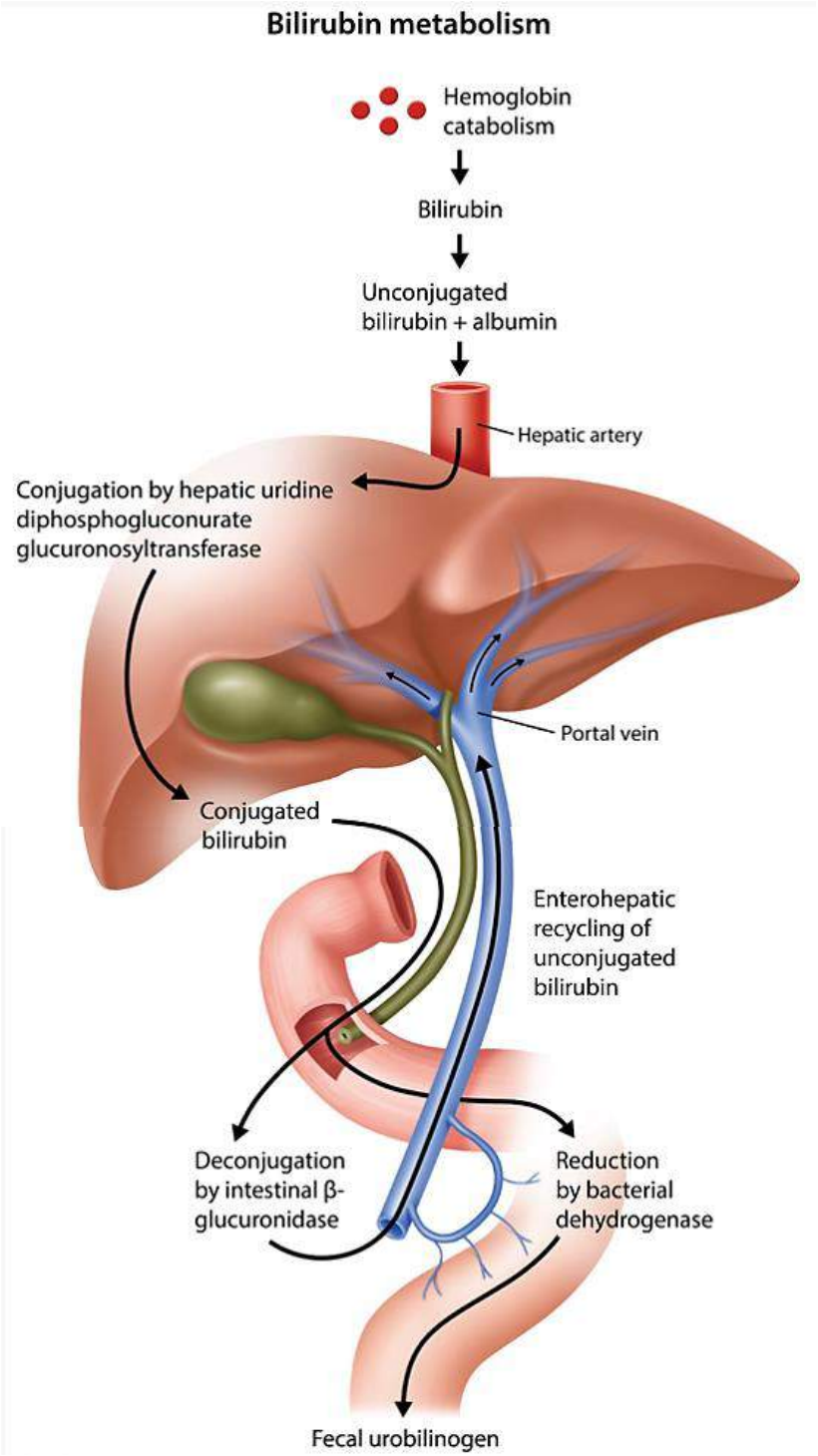


- Progressive obliteration of extrahepatic biliary ducts connecting the liver to small bowel—most common indication of pediatric liver transplant
- Presents in 1st 2 months with obstructive jaundice and acholic stools—conjugated hyperbilirubinemia is always pathological

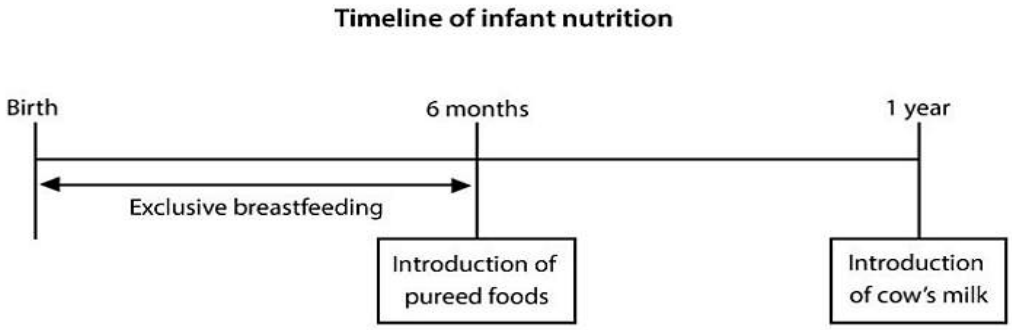
- Conjugated hyperbilirubinemia: defined as >2mg/dl of direct bilirubin or >20% of total bilirubin
- Without treatment: liver will become inflamed (eg hepatomegaly, hepatitis) and ultimately fibrose. Fatal without intervention
- Virtually all pts will require liver transplantation but Kasai procedure will buy time for growth and ↓ mortality and morbidity from transplantation

PHYSIOLOGIC JAUNDICE

- Appear after 1st 24 hours (days 2-4 of life)
- Unconjugated hyperbilirubinemia due to several physiologic differences in bilirubin metabolism
  1. At birth, RBC conc. Is ↑ (Hct 50-60%), short RBC life span (~90 days)→ ↑ Hb turnover and ↑ bilirubin
  2. Bilirubin clearance is slow as hepatic uridine diphosphoglucoronate glucuronosyltransferase (UGT) does not reach adult level until 2 wks of life—Asian newborns have ↓ UGT activity as compared to other ethnicities
  3. Sterile newborn gut cannot breakdown bilirubin into urobilinogen to be excreted in stool→↑ enterohepatic recycling of bilirubin → more bilirubin resorbed in gut until gut is colonized and produces more bacterial enzymes for reduction into urobilinogen
- Usually benign and resolves in 1-2 wks
- Monitor for persistent or worsening jaundice as high levels can cause brain damage
- Suggest: frequent feeding for gut colonization by bacteria and fecal excretion. Natural sunlight can ↓ bilirubin but not recommended cox of risk of sunburn
- Sometimes rapidly progressing hyperbilirubinemia is treated with **phototherapy** to prevent kernicterus development—given if unconjugated bilirubin >20mg/dl
- Exchange transfusion needed if total bilirubin levels >25 mg/dl or there are signs of neurological impairment


Bilirubin metabolism
Hemoglobin catabolism
Bilirubin
Unconjugated bilirubin + albumin
Hepatic artery
Conjugation by hepatic uridine diphosphogluconurate glucuronosyltransferase
Portal vein
Conjugated bilirubin
Enterohepatic recycling of unconjugated bilirubin
Deconjugation by intestinal β-glucuronidase
Reduction by bacterial dehydrogenase
Fecal urobilinogen

TIMELINE OF INFANT NUTRITION



- Full term infants don't develop iron def. anemia until 4-6 mo of life as they are born with robust iron stores
- Preterm infants, maternal iron def. and early introduction of cow's milk before 12 months age→ ↑ risk of iron deficiency
- Exclusive breastfeeding→ ↑ risk of vitamin D deficiency
- Hence, preterm, exclusively breastfed infants should be given iron and vitamin D supplementation
- Iron supplementation should be started at birth and continue till 1 year age in preterm infants
- Vitamin D: 400 IU daily should be started within 1st month of life in exclusively breastfed infants
- B12 supplementation is recommended to exclusively breastfed infants whose mother is a strict vegetarian
- Pureed fruits and vegetables should be introduced 1st followed by pureed proteins like meat
- There is no evidence suggesting that early introduction of highly allergenic foods such as eggs is associated with an increased risk of allergies; these foods can be introduced any time after age 6 months.
- Although some fruit juices contain vitamins, the AAP (American Association of Pediatrics) does not recommend routine introduction of juice into an infant's diet. For families who choose to offer juice, no more than 4-6 ounces per day should be given (after age 6 months) and it should never be given in a bottle given the significantly increased risk of dental caries.

BREASTFEEDING

Breastfeeding benefits & contraindications		
	Benefits	**Contraindications**
Maternal	• More rapid uterine involution & decreased postpartum bleeding • Faster return to prepartum weight • Improved child spacing • Improved maternal-infant bonding • **Reduced risk of breast & ovarian cancer**	• Active untreated **tuberculosis** (mothers may breastfeed after 2 weeks of anti-tuberculin therapy) • Maternal **HIV infection** (in developed countries where formula is readily available) • Herpetic breast lesions • Varicella infection <5 days prior to or within 2 days of delivery • Specific maternal medications • Chemotherapy or ongoing radiation therapy • Active abuse of **street drugs** or **alcohol**

Infant	• Improved **immunity**
	• Improved gastrointestinal function
	• **Prevention** of infectious diseases:
	  ◦ **Otitis media**
	  ◦ Gastroenteritis
	  ◦ **Respiratory illnesses**
	  ◦ Urinary tract infections
	• Decreased risk of childhood cancer, type I diabetes mellitus & necrotizing enterocolitis
		• **Galactosemia**

- Exclusive breastfeeding is the ideal form of nutrition for 1st 6 months and is highly recommended. Vitamin D supplementation is recommended till solids are started

BREASTFEEDING FAILURE JAUNDICE VS BREAST MILK JAUNDICE

- Hyperbilirubinemia that occurs is indirect (unconjugated) and may rise as high as 10-30 mg/dl.

Breastfeeding failure jaundice vs breast milk jaundice			
Diagnosis	**Timing**	**Pathophysiology**	**Clinical features**
Breastfeeding failure jaundice	First week of life	Lactation failure resulting in: • Decreased bilirubin elimination • Increased enterohepatic circulation	• Suboptimal breastfeeding • Signs of dehydration
Breast milk jaundice	Starts at age 3-5 days; peaks at 2 weeks	High levels of β-glucuronidase in breast milk deconjugate intestinal bilirubin & increase enterohepatic circulation	• Adequate breastfeeding • Normal examination

BREASTFEEDING FAILURE JAUNDICE

- Caused by both maternal and infant factors
  - Maternal: inadequate milk supply, cracked/clogged nipples, engorgement, infrequent feeding (e.g. 4 hours feeding interval)
  - Infant: poor latch, ineffective suck, falling asleep factors
- Normal infants: pass dark, sticky meconium during 1st 2 days of life after which they should transition to yellowish or green stool of ingesting adequate milk—inadequate stooling→ ↓ bilirubin excretion and ↑ enterohepatic circulation of bilirubin
- Normal infant: during 1st week of life, normal no. of wet diapers=infants age in days eg. 4 days old child=>/= 4 wet diapers
- **Signs of dehydration:** weight loss, ↓ urine output, brick red urate crystals in diaper
- **Rx:** best treatment in otherwise healthy full-term newborns—↑ frequency and duration of feeds to stimulate milk production, maintain adequate hydration, and promote bilirubin excretion in feces. Neonates should breastfeed ~8-12 times a day (every 2-3 hours) for >10-20 minutes per breast during the first month of life.
- Closely monitor to ensure baby is fed adequately (remonitor in 2 days) and that his bilirubin level is decreasing. If the bilirubin continues to rise despite efforts to optimize lactation, formula supplementation may be necessary. However, discontinuing breastfeeding and switching to formula will further decrease the mother's milk supply and prevent the infant from receiving the benefits of breastfeeding, which include improved infant immunity and mother-infant bonding

BREAST MILK JAUNDICE

- It is generally a benign condition, but in rare cases phototherapy may be indicated

BECKWITH-WIEDEMANN SYNDROME (BWS)

Beckwith-Wiedemann syndrome	
Pathogenesis	• Deregulation of imprinted gene expression in chromosome 11p15
Physical examination	• Fetal macrosomia, rapid growth until late childhood • Omphalocele or umbilical hernia • Macroglossia • Hemihyperplasia
Complications	• Wilms tumor • Hepatoblastoma
Surveillance	• Serum alpha fetoprotein • Abdominal/renal ultrasound

- Sporadic or inherited alteration in gene 11p15→ encodes insulin-like growth factor 2—growth promoting hormone similar to insulin
- Some may have visceromegaly
- Newborns must be monitored for hypoglycemia as fetal hyperinsulinemia can cause significant hypoglycemia—usually transient and older asymptomatic pts usually do not require monitoring
- **Screening for Wilms tumor and hepatoblastoma:**
  - **AFP and abdominal USG:** every 3 months from birth to age 4 years
  - **Abdominal USG:** every 3months from 4-8 years
  - **Renal USG:** from age 8 through adolescence
- **Isolated hemihyperplasia:** are also at ↑ risk of Wilms tumor and hepatoblastoma and require screening as above

Contents

DIFFERENCE BETWEEN SMALL BOWEL OBSTRUCTION AND ILEUS

Small bowel obstruction versus ileus		
	Small bowel obstruction	**Ileus**
Etiology	• Prior surgery (weeks to years)	• Recent surgery (hours to days) • Metabolic (eg, hypokalemia) • Medication induced
Abdominal examination	• Distension • Increased bowel sounds	• Possible distension • Reduced/absent bowel sounds
Small bowel dilation	Present	Present
Large bowel dilation	Absent	Present

SMALL BOWEL OBSTRUCTION

Small bowel obstruction	
Clinical presentation	• Colicky abdominal pain, vomiting • Inability to pass flatus or stool • Hyperactive bowel sounds • Distended & tympanic abdomen
Diagnosis	• Dilated loops of bowel with air-fluid levels • Partial: Air in colon • Complete: Transition point (abrupt cutoff), no air in colon
Complications	• Ischemia/necrosis (strangulation) • Bowel perforation
Management	• Bowel rest, nasogastric tube suction, intravenous fluids • Surgical exploration for signs of complications

↑ amylase and mild leukocytosis may be present

However, as SBO progresses, sounds may become diminished and if ischemia occurs, they may disappear completely

- Categorized by anatomical location (i.e. proximal vs mid/distal) or simple vs strangulated
- **Complete proximal obstruction:**
  - Early vomiting
  - Abdominal discomfort
  - Abnormal contrast filling on x-ray
- **Mid or distal obstruction:**
  - Colicky abdominal pain
  - Delayed vomiting
  - Prominent abdominal distention
  - Constipation-obstipation (obstipation is severe or complete constipation)
  - Hyperactive bowel sounds
  - Dilated loops of bowel on abdominal x-ray
- **Simple:** luminal occlusion→ no need of antibiotics
- **Strangulation/complicated:** loss of blood supply to the bowel wall→ ↑ risk of ischemia, strangulation, necrosis
  - may have peritoneal signs (eg. rigidity, rebound), change in character of pain
  - signs of shock: fever, tachycardia, leukocytosis, significant metabolic acidosis are late findings→ emergency abdominal exploration—if not done ↑ risk of perforation and ↑ mortality rate
- **Cause:** Adhesions—more common cause, may be congenital in children (eg Ladd bands), but commonly arise from abdominal operations or inflammatory processes

PARALYTIC ILEUS

- N/V, failure to pass stool or flatus (obstipation)
- Some degree occurs following most abdominal procedures but Sx >3-5 days post-op→ prolonged or pathological post-op ileus (PPI). Other causes: retroperitoneal/ abdominal hemorrhage or inflammation, intestinal ischemia and electrolytes abnormalities
- **Pathophysiology:** increased splanchnic nerve sympathetic tone following peritoneal instrumentation, local release of inflammatory mediators, and postoperative opiate analgesic use (which causes decreased gastrointestinal motility and disordered peristalsis).
- **Prevention:** epidural anesthesia, minimally invasive surgery, and judicious perioperative use of intravenous fluids (to minimize gastrointestinal edema).
- **Dx:** clinical mainly and abdominal x-ray findings→ dilated loops of bowel and no transition point
- **Rx:** mainly conservative and includes bowel rest, supportive care and treatment of secondary causes

DUMPING SYNDROME

Dumping syndrome	
Symptoms	• Abdominal pain, diarrhea, nausea • Hypotension/tachycardia • Dizziness/confusion, fatigue, diaphoresis
Timing	• 15-30 minutes after meals
Pathogenesis	• Rapid emptying of hypertonic gastric contents
Initial management	• Small/frequent meals • Replace simple sugars with complex carbohydrates • Incorporate high-fiber & protein-rich foods

Drink fluid between rather than during meals

- Common postgasterectomy complication—occur in 50% cases
- Loss of normal action of pyloric sphincter due to injury or surgical bypass→ rapid emptying of hypertonic gastric contents in to duodenum and small intestine→ fluid shift from intravascular space to small intestine→ hypotension, stimulation of autonomic reflexes and release of intestinal VIP,
- **Dx:** clinical, although upper GI x-ray series or gastric emptying studies may be helpful if diagnosis is unclear
- **Sx** diminish over time. Minority with refractory symptoms may benefit from trial of octreotide or reconstructive surgery, but usually not needed

PERITONITIS

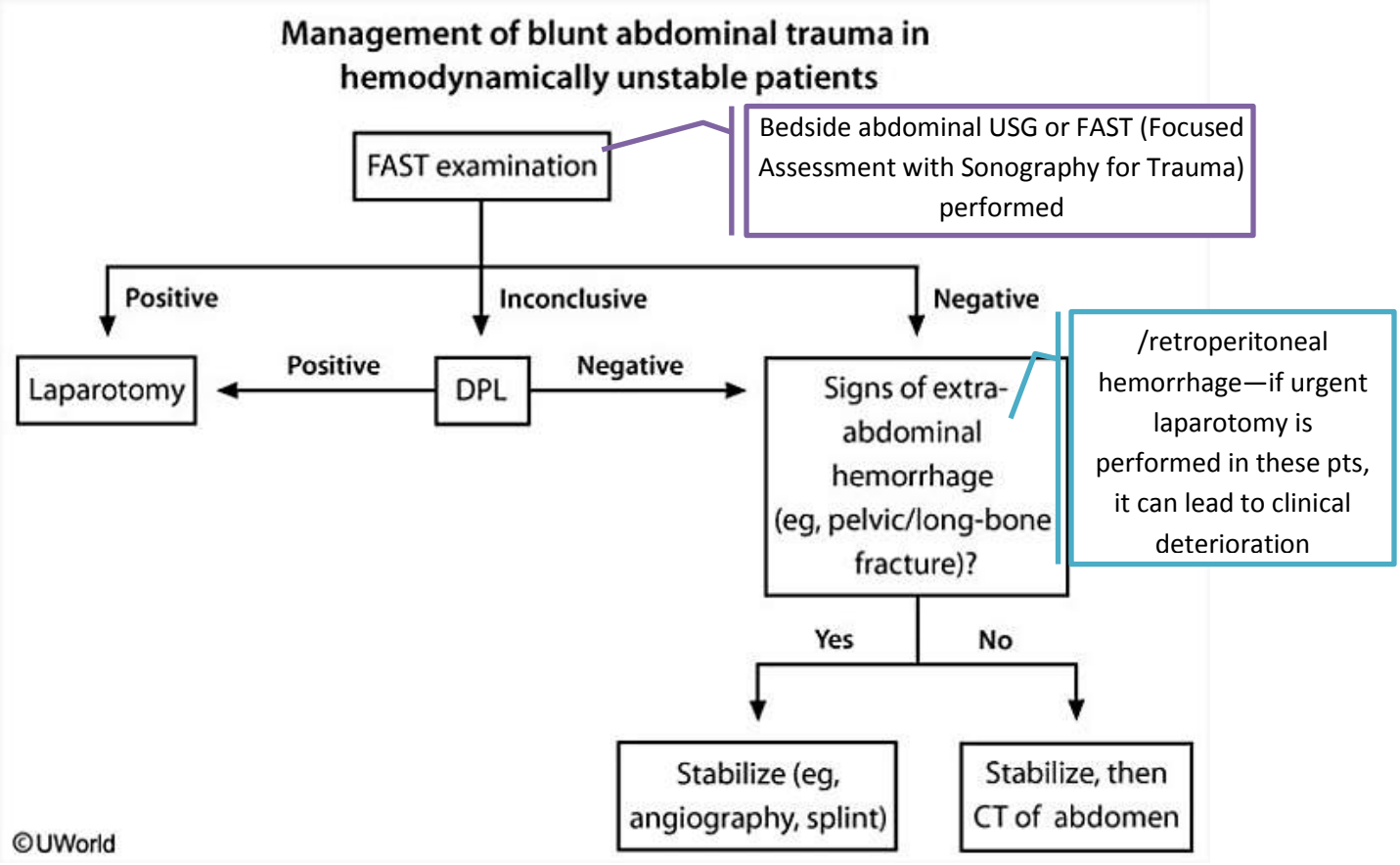
- **Management:**

1. Pre-op nasogastric decompression
2. IV fluids & antibiotics
3. If a pt is on warfarin→ reverse anticoagulation by restoring vitamin K dependent clotting factors with fresh frozen plasma (FFP)
4. Emergent laparotomy

BLUNT ABDOMINAL TRAUMA

- Most commonly injured organs: liver and spleen. Retroperitoneal organs like pancreas and duodenum are less commonly affected
- Hypotension after BAT suggest solid organ or vascular injury
- Splenic laceration but hemodynamically stable and no evidence of other intraabdominal injury→ maybe non-operative management
- Signs of splenic laceration may appear late and initial evaluation may be unremarkable
- Hemodynamically stable→ FAST→ negative→CT with contrast is the diagnostic modality of choice as it identifies splenic laceration with good accuracy. Also determines need for surgery, esp. if spleen contrast extravasation is present
- Hemodynamic instability even after fluid resuscitation→ urgent laparotomy

MANAGEMENT OF BLUNT ABDOMINAL TRAUMA IN HEMODNAMICALLY UNSTABLE PATIENT



- **Features suggestive of intra-abdominal injury:** hypovolemic shock, seatbelt sign, abdominal distention/ guarding, rebound tenderness, concomitant femur fracture
- **FAST=** A convenient and effective test is bedside ultrasonography to detect free intraperitoneal fluid in the hepatorenal space, splenorenal recess, and inferior portion of the intraperitoneal cavity. When combined with evaluation of the pericardium, this is known as the focused assessment with sonography for trauma (FAST) examination
- **DPL=** diagnostic peritoneal lavage→ determines presence of intraabdominal hemorrhage—if aspiration of 10ml of peritoneal fluid shows blood→ intraabdominal injury is likely--- if no gross blood found→ perform peritoneal cavity lavage with normal saline→ effluent sent to lab for analysis (RBCs)

DUODENAL HEMATOMA

- Most commonly follow direct blunt abdominal trauma
- More common in children
- Blood collects between submucosal and muscular layer of duodenum→ obstruction→ epigastric pain and vomiting
- CT with oral contrast—investigation of choice
- **Management:** resolve spontaneously in 1-2 weeks—intervention of choice: nasogastric suction and parenteral nutrition→ fails→ surgery (focused laparotomy or laparotomy to evacuate hematoma)

PANCREATIC LACERATION

- Blunt abdominal trauma→ compression of pancreatic neck &/or body against vertebral column over which it lies→ pancreatic contusion, crush injury, laceration or transection may result
- Abdominal CT done immediately after trauma→ may not detect pancreatic injury
- Serial CT scans required to detect evolution of injury i.e. enlargement of gland, parenchymal disruption, areas of diminished contrast perfusion, peripancreatic fluid collection
- Amylase values are non-specific→ do not aid in diagnosis
- If blunt traumatic pancreatic injury is undetected initially, devitalized tissue or a pseudocyst resulting from such injury can become secondarily infected→ fever, chills, deep abdominal pain
- Pancreatic abscess→ serious complication with ↑ mortality
- RX: immediate placement of percutaneous drainage catheter, culture of drained fluid and surgical debridement

APPENDICITIS

Examination signs in appendicitis		
Sign	**Findings**	**Significance**
Peritoneal signs • Rebound tenderness • Involuntary guarding • Abdominal rigidity	Acute increase in pain after removing the hand from applying pressure Tensing of abdominal wall muscles during palpation of abdomen Persistent tension of abdominal wall muscles	Peritoneal irritation (rupture or impending rupture)
Psoas sign	RLQ pain with extension of right thigh	Abscess adjacent to psoas or retrocecal appendix
Obturator sign	RLQ pain with internal rotation of right thigh	Pelvic appendix or abscess
Rovsing's sign	RLQ pain with LLQ palpation & retropulsion of colonic contents	Acute appendicitis
Rectal tenderness	Right pelvic pain during rectal examination, especially with pressure on right rectal wall	Pelvic appendix or abscess

APPENDICEAL ABSCESS

- If present > 5 days→ can lead to contained abscess
- CT scan for diagnosis
- If stable→ bowel rest, IV antibiotics and possibly percutaneous drainage of abscess—urgent surgery has ↑ risk of complications
- Pt may return 6-8 wks later for elective appendectomy (interval appendectomy)

PSOAS ABSCESS

Psoas abscess	
Clinical presentation	• Subacute fever, abdominal/flank pain radiating to groin • Anorexia, weight loss • Abdominal pain with hip extension (psoas sign)
Diagnosis	• CT scan of the abdomen & pelvis • Leukocytosis, elevated inflammatory markers • Blood & abscess cultures Thrombocytosis
Treatment	• Drainage • Broad-spectrum antibiotics

- May occur from hematologic seeding from distant infection or direct spread from intraabdominal infection (eg diverticulitis, vertebral osteomyelitis)
- Risk factors: HIV, IV drug abuse, diabetes, Crohn disease
- Can present with non-specific symptoms so it should also be considered as part of evaluation for fever of unknown origin
- Deep palpation is needed to elicit pain
- In pts with unexplained PA, colonoscopy may be needed to find out the source of abscess
- Retrocecal appendicitis can also cause psoas sign but pain is elicited by rectal exam and not localized to RLQ

PILONIDAL DISEASE

- Common in young males with larger amount of body hair
- **Etiology of pilonidal cyst/sinuses:** unknown but believed to develop following chronic activity involving sweating and friction of the skin overlying the coccyx within the superior gluteal cleft. Infection of hair follicles in this region may spread subcutaneously→ form abscess→ ruptures→ pilonidal sinus tract. Chronic sinus tract may then collect hair and debris resulting in recurrent infections and foreign body reactions
- When sinus becomes acutely infected→ pain, swelling, purulent discharge occur in midline postsacral intergluteal region (sacrococcygeal skin)
- Rx: drainage of abscess and excision of sinus tract

ANAL FISSURES

Anal fissures	
Etiology	• Local trauma (eg, constipation, prolonged diarrhea, anal sex) • Inflammatory bowel disease (eg, Crohn disease) • Malignancy
Clinical presentation	• Pain with bowel movements • Bright red blood on toilet paper or stool surface • Most common at posterior anal midline • Chronic fissure may have skin tag at distal end
Treatment	• High-fiber diet & adequate fluid intake • Stool softeners • Sitz baths • Topical anesthetics & vasodilators (eg, nifedipine, nitroglycerin)

Longitudinal tear in anal canal distal to dentate line

POST-OP CHOLESTASIS

- Benign condition—often develops after major surgery characterized by hypotension, extensive blood loss in tissues, and massive blood replacement.
- Jaundice is thought to develop secondary to three factors:
  1. Increased pigment load (caused by the transfusion);
  2. Decreased liver functionality (caused by hypotension); and
  3. Decreased renal bilirubin excretion (caused by tubular necrosis).
- Generally, jaundice is evident by the second or third day after a prolonged surgery, with the bilirubin levels peaking at 10-40 mg/dl by the tenth postoperative day.
- Alkaline phosphatase levels can also be markedly elevated, the AST and ALT levels are typically normal or only mildly elevated.

Contents

LIVER DISORDERS UNIQUE TO PREGNANCY

Liver disorders unique to pregnancy		
Disorder	**Presentation**	**Laboratory abnormalities**
ICP	• Intense pruritus	• Elevated bile acids • Elevated levels of liver aminotransferases • Diagnosis of exclusion
HELLP	• Preeclampsia • Right upper-quadrant pain • Nausea/vomiting	• Hemolysis • Moderately elevated liver aminotransferases • Thrombocytopenia
AFLP	• Malaise • Right upper-quadrant pain • Nausea/vomiting • Sequelae of liver failure	• Hypoglycemia • Mildly elevated liver aminotransferases • Elevated bilirubin • Possible disseminated intravascular coagulopathy

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

- Functional disorder of bile formation
- Develops in 2nd or 3rd trimester of pregnancy
- **Etiology** unclear—but thought to be hormonal (e.g. ↑ levels of estrogen and progesterone later in pregnancy), genetic and environmental factors influence
- **C/F:** intense itching, often intolerable, generalized pruritus esp. at palms and soles and worsens at night, evidence of skin excoriations maybe present on examination, <10% have jaundice and require further workup
- **Labs:** total bile acids ↑-- maybe the only abnormal lab, LFTs sometimes suggestive of cholestasis with ↑ alkaline phosphatase and total and direct bilirubin (although alkaline phosphatase is ↑ in normal pregnancy. Serum aminotransferases may be 10x ↑ (>1000 at times)—need viral serology
- **Rx:** symptom relief and pruritis follows weeks after delivery. Ursodeoxycholic acid—frequently prescribed to ↑ bile flow and relieve itching. Maternal prognosis is generally good. However, early delivery is recommended once fetal maturity is achieved to avoid fetal complications (eg, intrauterine demise, neonatal respiratory distress syndrome)

ACUTE FATTY LIVER OF PREGNANCY (AFLP)

- Rare, serious illness that may present in 3rd trimester

- Ultimately develop liver failure and extrahepatic manifestations like ascites, jaundice, hypoglycemia, encephalopathy, severe coagulopathy and acute kidney injury—pruritus is not a common feature of AFLP
- Labs: consistent with liver failure

PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY

- Skin condition that develops in the third trimester.
- Classic finding on abdominal examination is red papules within striae with sparing around the umbilicus, sometimes extending to the extremities. The palms, soles, and face are rarely involved, helping to distinguish it from ICP. There are no laboratory or liver abnormalities associated with PUPPP.

ACUTE APPENDICITIS IN PREGNANCY

- May lead to ruptures appendix if diagnosis delayed 24-48 hours
- N/V mimic pregnancy sx. RLQ pain is most common feature but location may be higher depending on gestational age of pregnancy
- Fever may or may not be present
- ↑ leukocyte count may be present in appendicitis or normal pregnancy
- USG with graded compression technique (non-compression n dilation of appendix—diagnostic)—best initial diagnostic technique and to rule out other causes—non-visualization does not exclude appendicitis
- If USG is non-diagnostic→ MRI is done to assess further for possible appendicitis
- USG non-diagnostic, MRI not available→ only then CT can be performed→ diagnostic laparoscopy with last option (lower midline vertical laparotomy)

Contents

GAIT DISORDERS

Gait disorders			
Type of gait	**Description**	**Associated signs**	**Causes**
Cerebellar	**Ataxic:** Staggering, wide-based	Dysdiadochokinesia, dysmetria, nystagmus, Romberg sign	• Cerebellar degeneration • Stroke • Drug/alcohol intoxication • Vitamin B_{12} deficiency
Gait apraxia (frontal gait)	**Magnetic (freezing):** Start & turn hesitation	Dementia, incontinence, frontal lobe signs	• Frontal lobe degeneration • Normal pressure hydrocephalus
Parkinsonian	Short steps, shuffling	Bradykinesia, resting tremor, postural instability, decreased arm swing	• Parkinson disease
Steppage	**Footdrop**, excessive hip & knee flexion while walking, slapping quality, falls	Distal sensory loss & weakness	• Motor neuropathy
Vestibular	Unsteady, falling to one side	Normal sensation, reflexes & motor strength; nausea, vertigo	• Acute labyrinthitis • Ménière disease

cerebellar degeneration:
- common among chronic alcohol abusers
- **Sx:** gait instability, truncal ataxia, Nystagmus, intention tremor and hypotonia.

PE: pendular knee reflex - persistent swinging movements of the limb after eliciting the DTR.

Qid: 4618

CEREBELLAR

- Due to lesion of vermis (truncal ataxia) or the cerebellar hemispheres (limb ataxia)
- Swaying from side to side, impaired tandem gait and titubation (truncal tremor—forward and backward movement of trunk)
- Ipsilateral ataxia esp. if tumor is located within one hemisphere→ fall towards side of lesion even with eyes open. Other features: intension tremor, ipsilateral muscular hypotonia, and marked difficulty in coordination and performing rapid, alternating movements. Obstruction of CSF flow by tumor→ ↑ICP→ headache, papilledema, nausea and vomiting

GAIT APRAXIA (BRUNS ATAXIA)

- Due to damage of cortico-cortical fibers as in NPH—slow, broad-based shuffling gait
- Strength, coordination and sensory functions are intact. Memory loss is very slow and progressive

- Dx: clinically or radionuclide CSF studies. MRI or CT shows dilated ventricles (due to ↓ CSF absorption). Opening pressure NL
- If symptoms improve on repeated large volume LP (spinal tap), then ventriculoperitoneal shunts can be considered definitive treatment

STEPPAGE GAIT

- Can be due to: L5 radiculopathy or common peroneal nerve neuropathy

L5 radiculopathy:

- Back pain radiating to foot, often weakness of foot inversion and plantar flexion

Common peroneal nerve neuropathy:

- Due to compression of nerve on lateral aspect of fibula (eg due to prolonged crossing of legs or squatting)
- Associated with paresthesia and sensory loss over dorsum of foot but normal foot inversion and plantar flexion

- **Dx:** clarified by EMG and nerve conduction studies

SPASTIC ATAXIA

- Pyramidal tract or corticospinal tract (CST) lesions can cause spastic ataxia.
- The gait appears stiff or rigid with circumduction (the spastic leg is abducted and advanced while in extension and internal rotation) and plantar flexion of the affected limb

SENSORY NEUROPATHY

- Patients with loss of proprioception due to sensory neuronopathy may have postural or gait instability and a wide-based gait. Patients may stomp their feet against the floor (slap gait) to help them know where their lower limbs are relative to the ground.

ALTERED MENTAL STATUS

Causes of altered mental status	
Drugs/ toxins	• Prescription drugs (eg, opioids, lithium, antipsychotics) • Drugs of abuse (eg, ethanol, hallucinogens) • Drug withdrawal (eg, ethanol, benzodiazepines)
Infections	• Sepsis, systemic infections • Meningitis, encephalitis, brain/epidural abscess
Metabolic	• Electrolyte disturbances Hypernatremia • Hypo/hyperglycemia • Endocrine (eg, hypo/hyperthyroid, pituitary, adrenal) • Hypoxemia, hypercarbia • Nutritional (eg, thiamine, vitamin B_{12} deficiency) • Hepatic or renal failure
Central nervous system	• Seizure, head injury • Hypertensive encephalopathy • Psychiatric disorders

BP >/= 180/120 mmHg

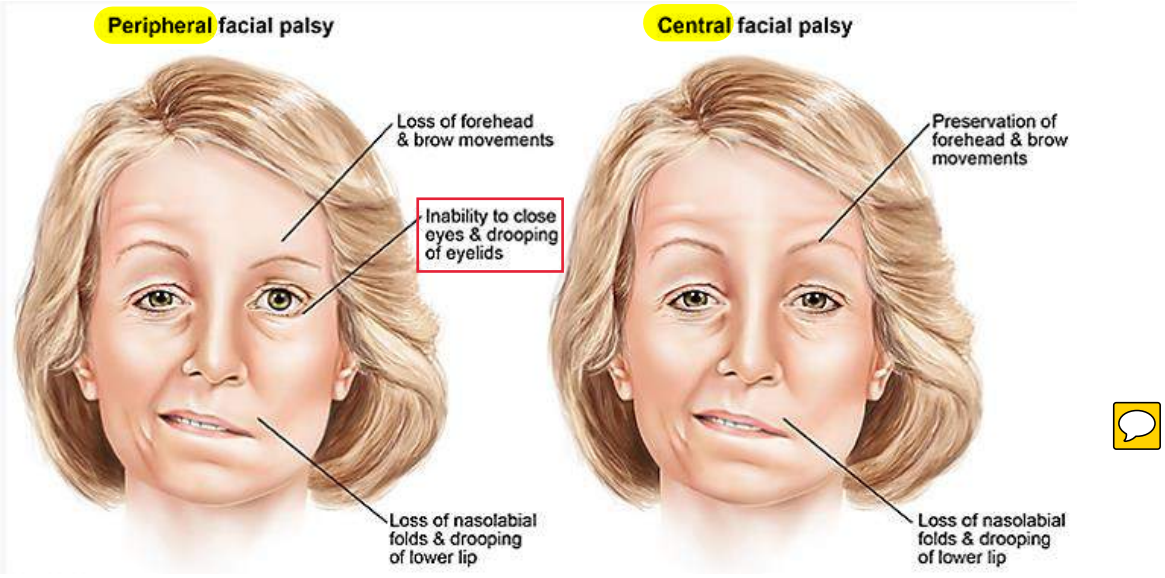
- Altered mental status→ suggest widespread dysfunction of cerebral cortex and/or reticular activating system
- When the cause of AMS is not apparent after initial assessment, empiric treatment for likely causes (eg, WE) is often appropriate.

DIFFERENCE BETWEEN UPPER AND LOWER MOTOR NEURON LESION

Upper motor neuron signs	• Spastic paralysis • Clasp-knife rigidity • Hyperreflexia • Babinski sign
Lower motor neuron signs	• Flaccid paralysis • Hypotonia • Hyporeflexia • Muscle atrophy & fasciculations

CRANIAL NERVES LESIONS

FACIAL NERVE INJURY

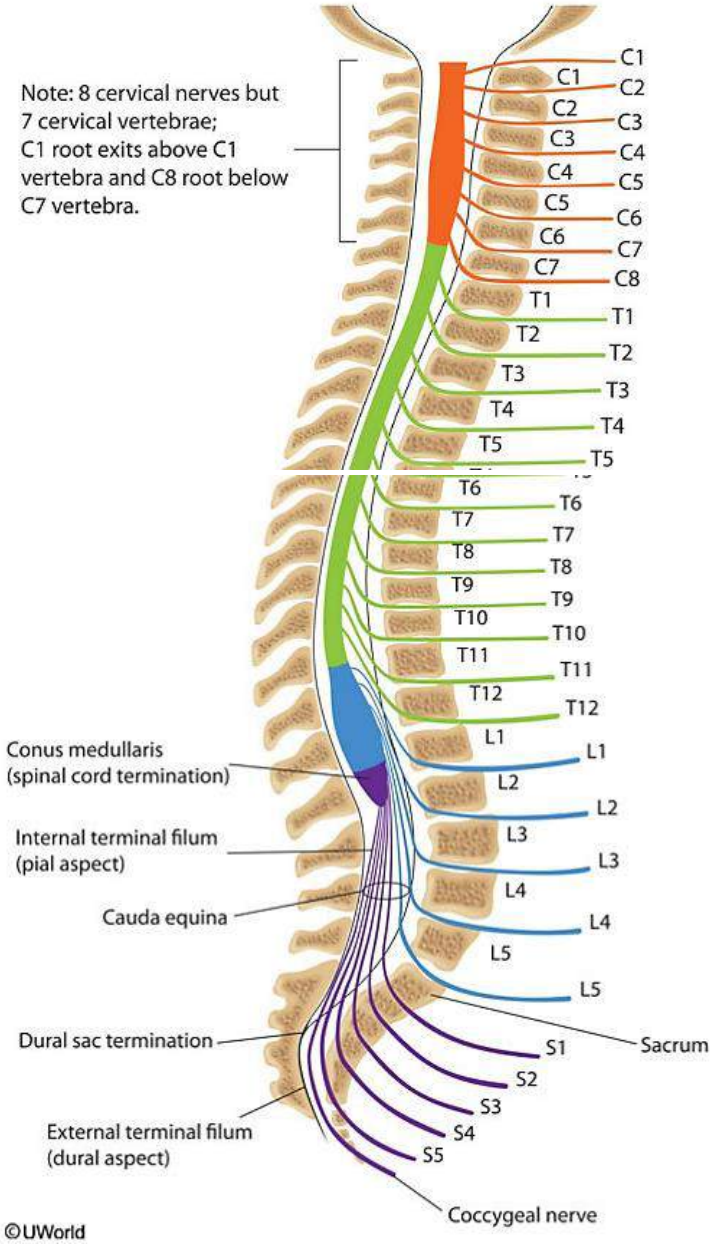


- **Bell's palsy:** acute peripheral neuropathy of CN VII (lesion below the pons i.e. below facial nucleus)—in addition to above findings, may also ↓ tearing, hyperacusis, and/or loss of taste sensation over anterior 2/3rd of tongue
  - Acute onset of symptoms (</= 2 days), maximum clinical paralysis apparent within 3 wks. For most pts, partial or complete recovery occurs within 6 months
- Forehead muscle sparing→ indicative of intracranial lesion→ brain imaging to evaluate ischemia or tumor
- Lesions in the central nervous system occurring above the facial nucleus (ie, above the pons) can result in contralateral hemianesthesia or hemiparesis, and dysarthria. Upper facial weakness can occur with central lesions, however these lesions must occur at the level of the facial nucleus or exit of the fascicle of the facial nerve at the pontomedullary junction.

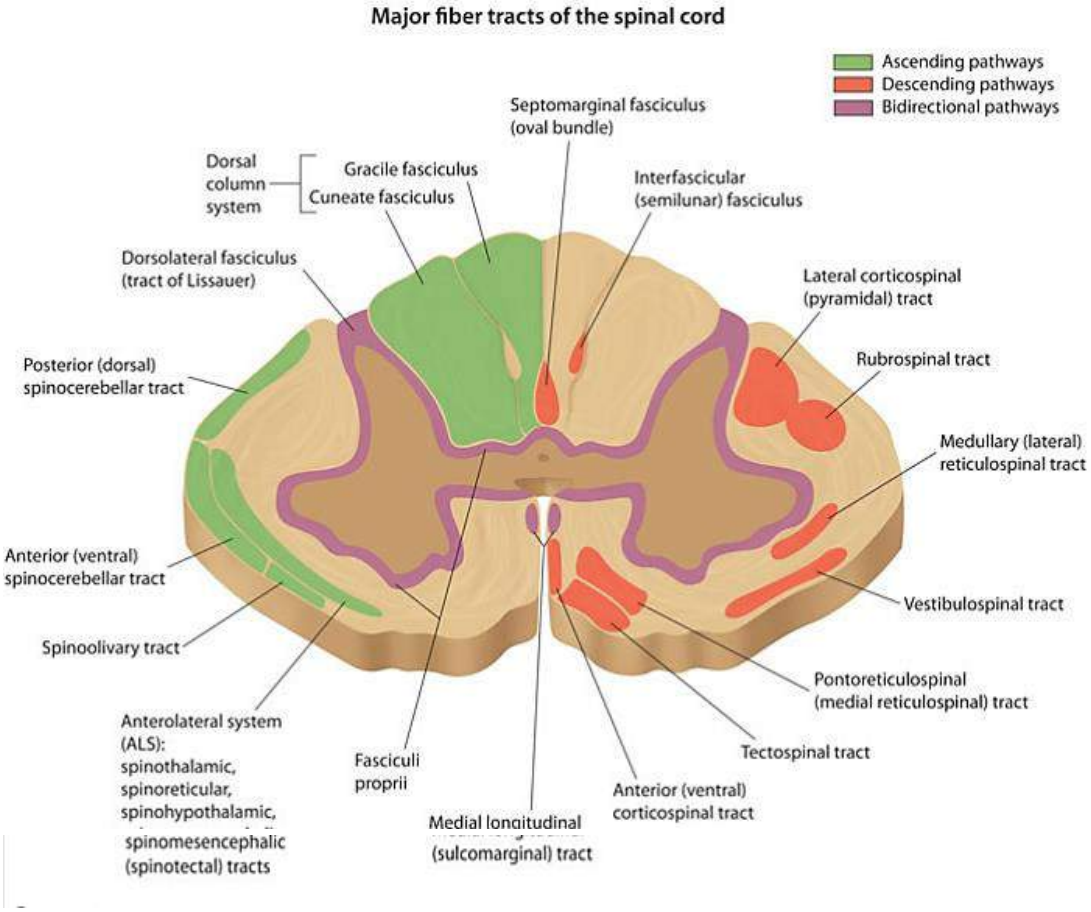
Patients with Bell's palsy present with acute onset of symptoms (≥ 2 days) with maximum clinical paralysis apparent within 3 weeks. For most patients, partial or complete **recovery occurs within 6 months**.

SPINAL CORD LESIONS

Relation of spinal nerve roots to vertebrae

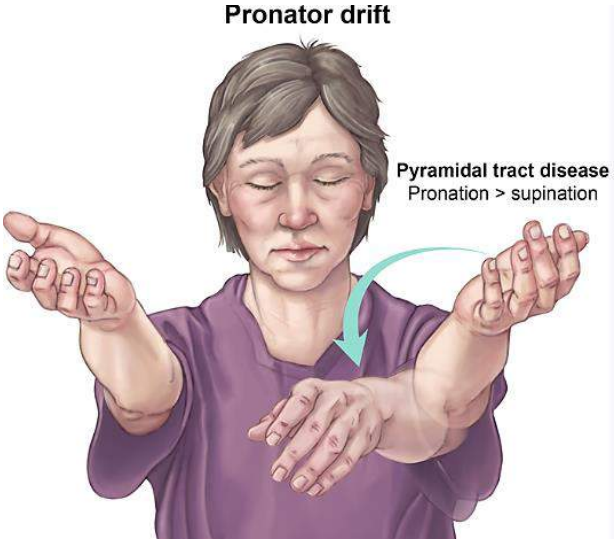


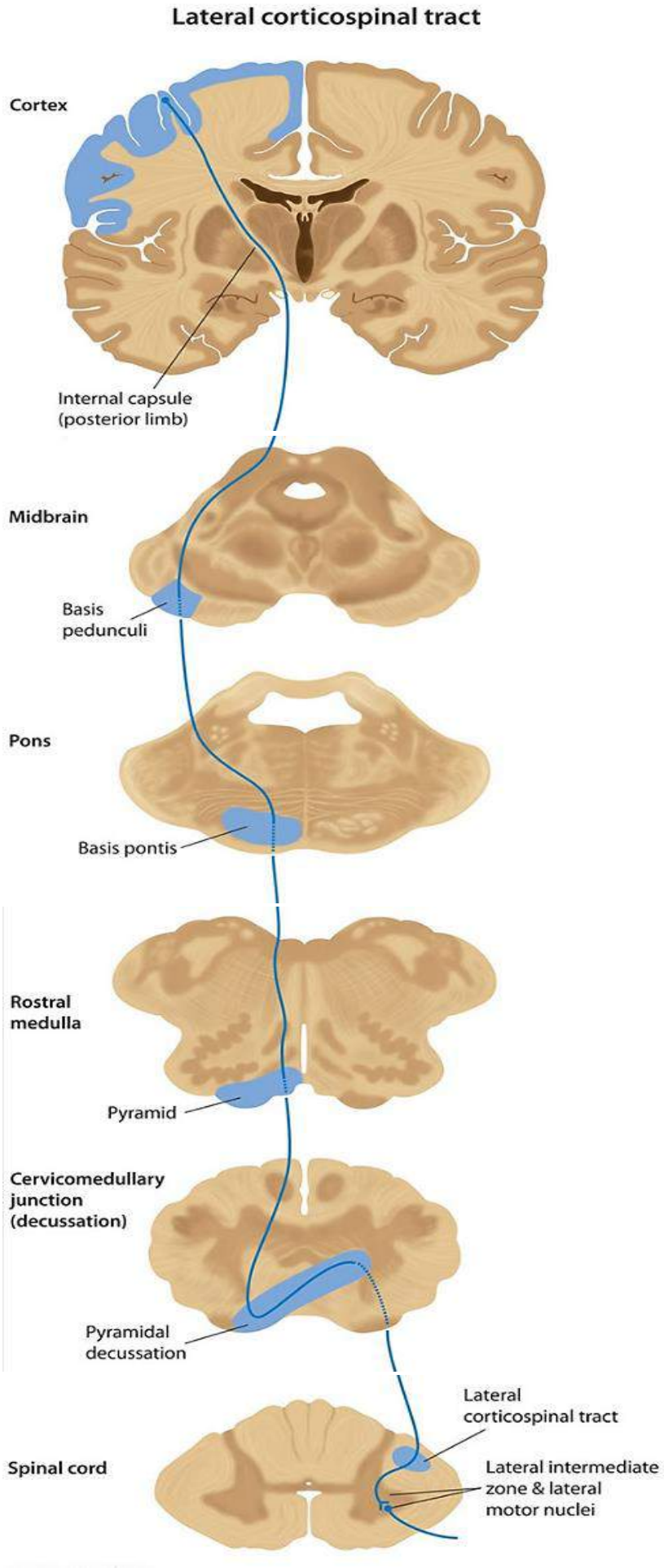
MAJOR FIBER TRACTS OF SPINAL CORD



LESION OF CORTICOSPINAL TRACT OR UMN LESION

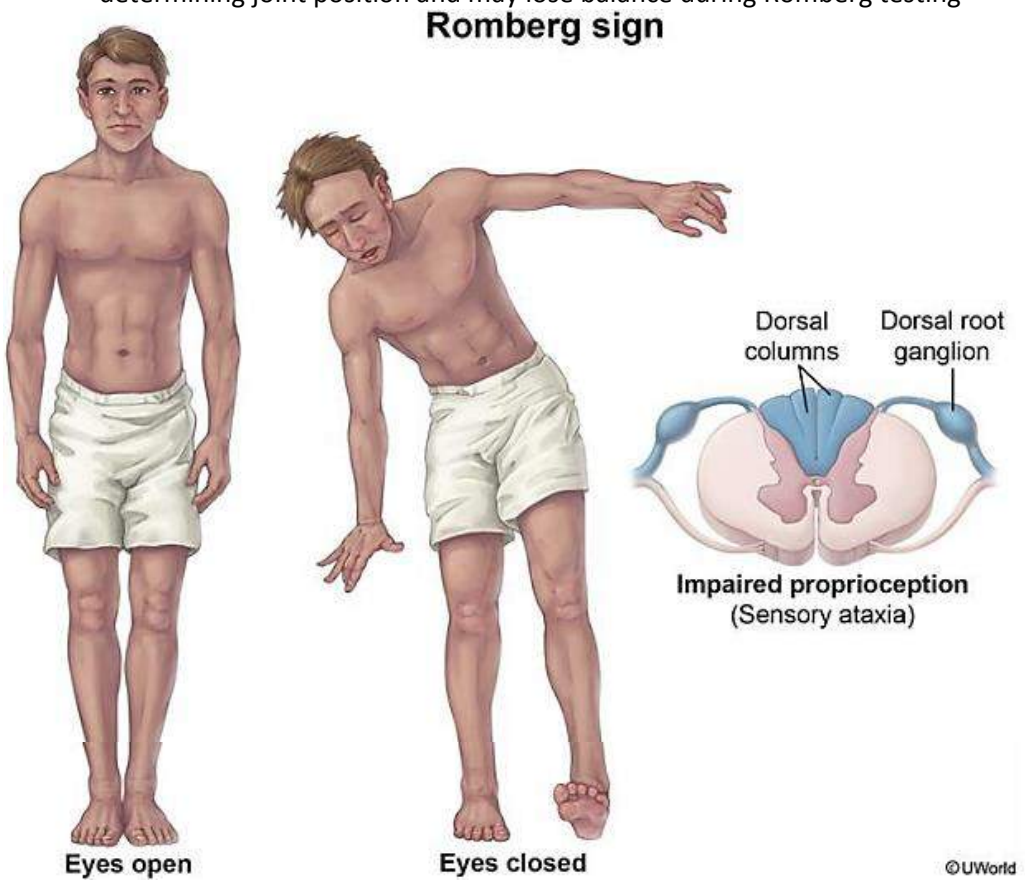
- **Pronator drift:** physical exam finding sensitive and specific for pyramidal/corticospinal tract or UMN lesion
  - Useful in pts with subtle deficits as it can accentuate pyramidal motor weakness
  - Outstretch arms with palms upwards and eyes closed (so that only proprioception is used to maintain arm position)
  - UMN lesion causes more weakness in supinator than pronator muscles of upper limbs→ arm drifts downwards and palm turns (pronates) towards the floor
- Clasp knife rigidity—velocity dependent resistance to passive movement of limb




Lateral corticospinal tract
Cortex
Internal capsule
(posterior limb)
Midbrain
Basis
pedunculi
Pons
Basis pontis
Rostral
medulla
Pyramid
Cervicomedullary
junction
(decussation)
Pyramidal
decussation
Lateral
corticospinal tract
Spinal cord
Lateral intermediate
zone & lateral
motor nuclei

TEST FOR PROPRIOCEPTION DEFECT

- Proprioception is evaluated by passively moving the distal phalange of a digit up and down and having patients identify the direction of movement with their eyes closed.
- Also assessed with the Romberg test in which patients are observed for unsteadiness as they stand with their feet together, arms to the sides, and eyes closed.
- Patients with impaired proprioception (eg, vitamin B, deficiency, tabes dorsalis) have difficulty determining joint position and may lose balance during Romberg testing



SPINAL CORD COMPRESSION

Spinal cord compression	
Causes	• Spinal injury (eg, motor vehicle accident) • Malignancy (eg, lung, breast, prostate cancers; myeloma) • Infection (eg, epidural abscess)
Signs & symptoms	• Gradually worsening severe local back pain • **Pain worse** in the recumbent position/at **night** • Early signs: Symmetric lower-extremity weakness, hypoactive/absent deep-tendon reflexes • Late signs: Bilateral Babinski reflex, decreased rectal sphincter tone, paraparesis/paraplegia with increased deep-tendon reflexes, sensory loss
Management	• Emergency MRI • Intravenous glucocorticoids • Radiation-oncology & neurosurgery consultations

Renal

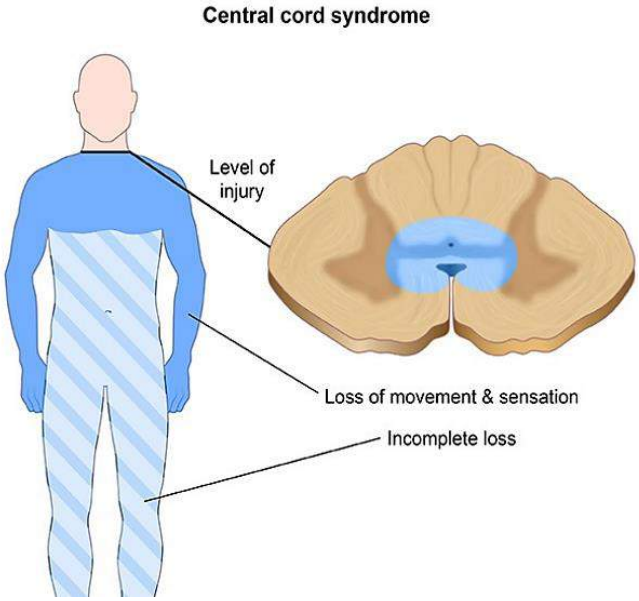
Spinal shock

Gait ataxia

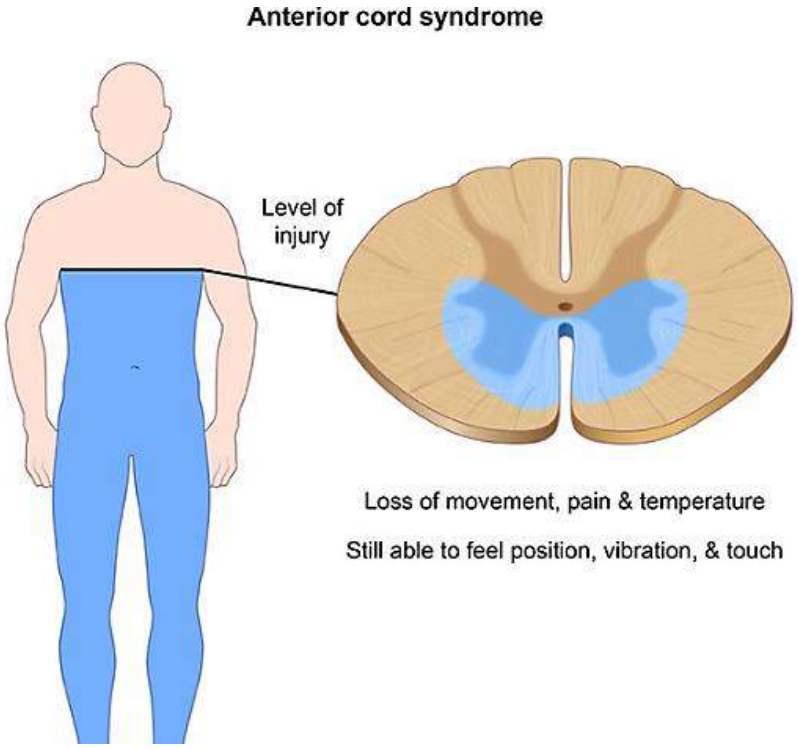
- Injury to descending autonomics in reticulospinal tract (urinary retention/ bladder flaccidity/ bladder shock)—bowel/ bladder disturbance are late findings
- Thoracic spine is most frequently involved level (60%) followed by lumbar spine
- Pain is usually worse in the recumbent position (due to distension of the epidural venous plexus when lying down) in contrast to back pain from degenerative joint disease, which improves with recumbency
- Urgent surgical intervention is necessary to prevent permanent disability

CENTRAL CORD SYNDROME (CCS)

- Occur with hyperextension injuries in elderly pt with pre-existing degenerative changes in cervical spine
- Causes damage to central portion of anterior spinal cord—specifically central portion of corticospinal tracts and decussating fibers of lateral spinothalamic tract
- Weakness more in upper extremities than lower—as motor fibers serving arms are closer to the central part of corticospinal tract
- May have occasional selective loss of pain and temperature sensation due to damage to spinothalamic tract



ANTERIOR CORD SYNDROME

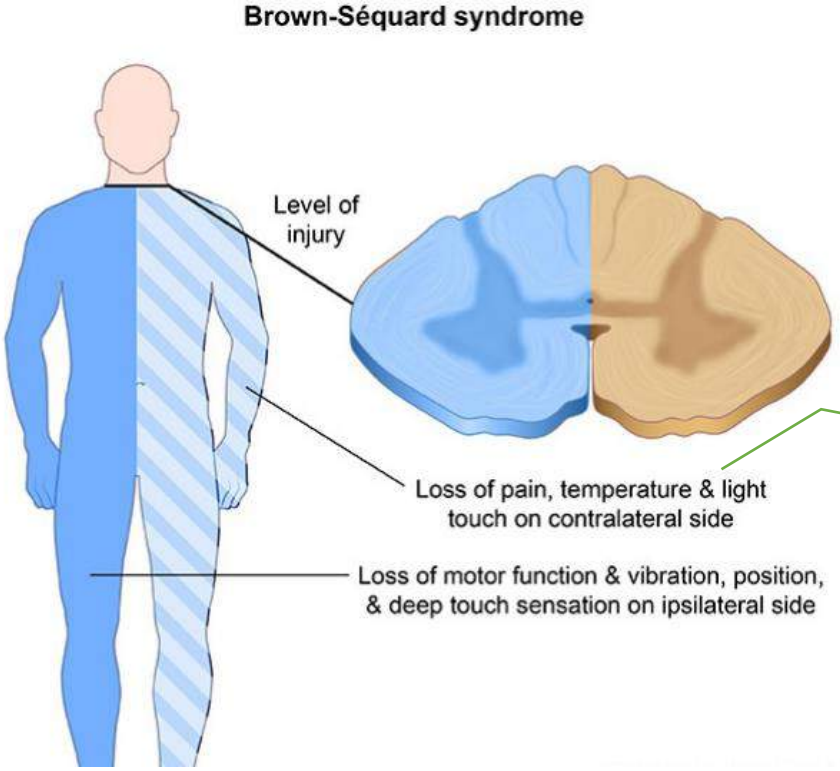


- B/L spastic paresis—initially flaccid paralysis due to spinal shock
- Usually due to occlusion of **anterior spinal artery** **(ASA-** supplies anterior 2/3rd of spinal cord)**, aortic surgery or dissection**—commonly associated with burst fracture of vertebra. ASA depends on blood supply from radicular arteries that originate from thoracic aorta, such as artery of Adamkiewicz
- Disruption of intermediolateral column and its descending autonomic tracts→ autonomic dysfunction—bowel and bladder dysfunction (eg urinary retention)
- MRI is the best test to study extent of neurologic damage

POSTERIOR (DORSAL) CORD SYNDROME

- B/L loss of vibration and proprioception
- Often with weakness, paresthesias, and urinary incontinence or retention
- Due to multiple causes, Multiple sclerosis and vascular disruption (eg vertebral artery dissection) are most common

BROWN SEQUARD SYNDROME



2 levels below the level of lesion

CAUDA EQUINA AND CONUS MEDULLARIS SYNDROME

Cauda equina syndrome	Conus medullaris syndrome
Usually bilateral, severe **radicular pain**	Sudden-onset severe back pain
Saddle hypo/anesthesia	Perianal hypo/anesthesia
Asymmetric motor weakness	**Symmetric** motor weakness
Hyporeflexia/areflexia	**Hyperreflexia**
Late-onset bowel & bladder dysfunction	Early-onset bowel & bladder dysfunction

CAUDA EQUINA SYNDROME

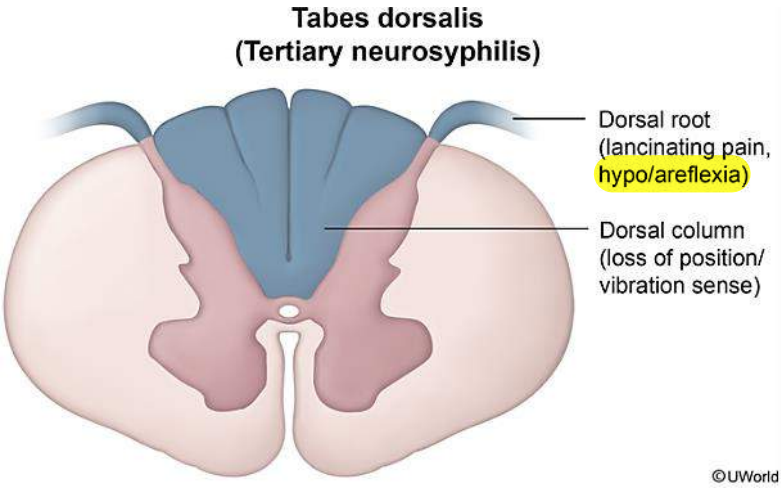
- Due to compression of spinal nerve roots by disk herniation or rupture, tumor, spinal stenosis, infection, hemorrhage, or iatrogenic injury
- Spinal cord ends at level of L1-L2 and lumbosacral nerve roots below this level form cauda equine, which float in CSF
- Cauda equine provide sensory innervation to saddle area, motor innervation to sphincters (anal and urethral), and parasympathetic innervation to bladder and lower bowel→ lower motor neuron signs (in contrast conus medullaris→ both UMN and LMN signs)
- **Management:** emergency MRI, neurosurgical evaluation, and possibly IV glucocorticoids (same management for conus medullaris syndrome)

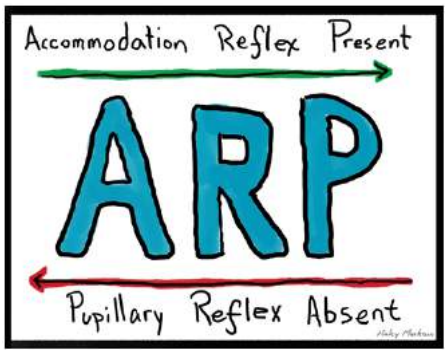
AMYOTROPHIC LATERAL SCLEROSIS

- Neurodegenerative disease

- Signs of UMN and LMN degeneration
- **Rx:** Riluzole—glutamate inhibitor→ does not arrest underlying pathological process, may prolong survival and time to tracheostomy→ S/E: dizziness, nausea, weight loss, elevated liver enzymes and skeletal weakness

TABES DORSALIS



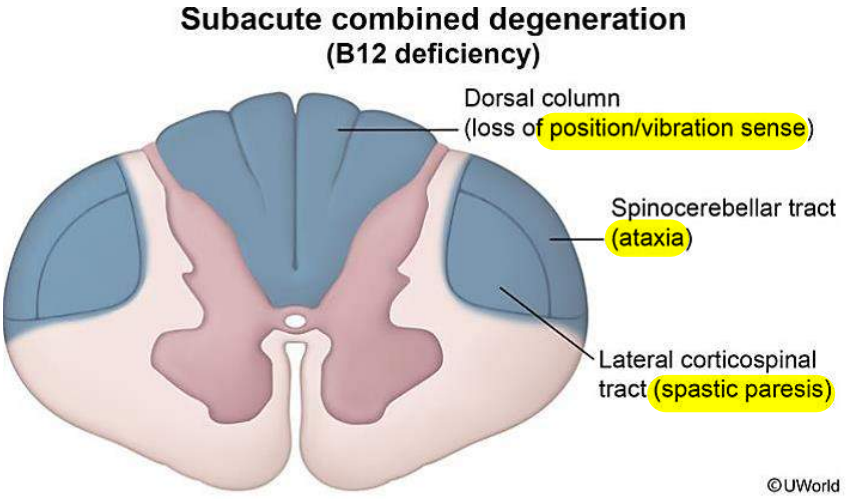


Features of tabes dorsalis	
Epidemiology	• Increased incidence of syphilis in men who have sex with men & HIV-infected patients • HIV-positive patients develop neurosyphilis more rapidly
Pathogenesis	• *Treponema pallidum* spirochetes directly damage the dorsal sensory roots • Secondary degeneration of the dorsal columns
Clinical findings	• Sensory ataxia • Lancinating pains • Neurogenic urinary incontinence • Associated with Argyll Robertson pupils

Brief, shooting or burning pain in face, back or extremities

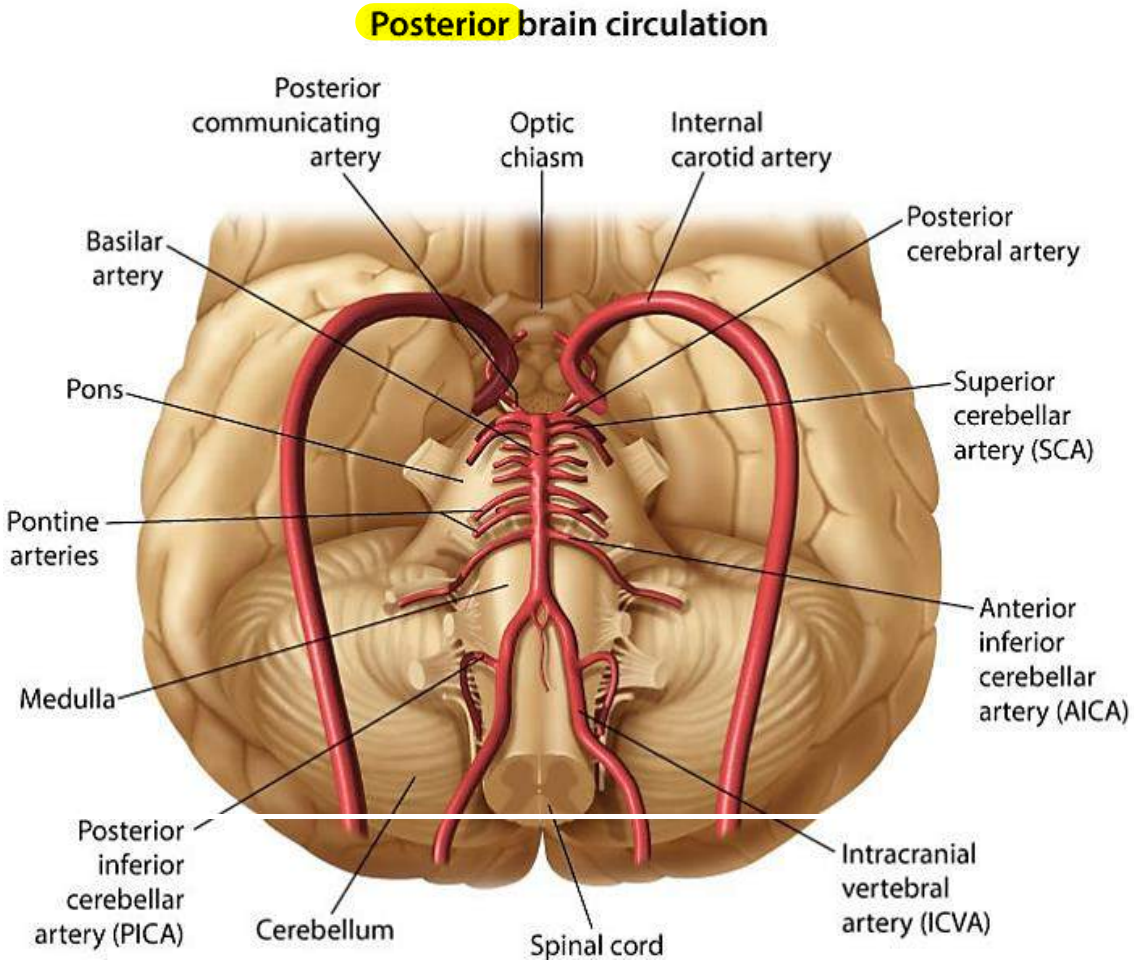
- **Posterior spinal column**: impaired vibration and proprioception, sensory ataxia (walks with legs wide apart, feet are lifted higher than usual and slapping sound comes when feet come in contact with ground) and instability during Romberg test
- **Dorsal sensory roots**: impaired pain and temperature and ↓/absent DTRs
- **Argyll Robertson pupil**: miotic, irregular, normal pupillary constriction with accommodation but not with light
- **Rx**: IV penicillin for 10-14 days

SUBACUTE COMBINED DEGENERATION (VITAMIN B12 DEFICIECNY)



- Progressive symmetric polyneuropathy, more in legs than arms
- Dorsal spinal column (numbness/paresthesia, impaired proprioception/vibration and consequent gait ataxia)→ corticospinal tract (spastic weakness and hyperreflexia)
- Other consequences: peripheral neuropathy, memory loss and dementia
- Labs: CBC, vitamin B12 levels, serum methylmalonic acid (more sensitive than vitamin levels)

BRAINSTEM LESIONS



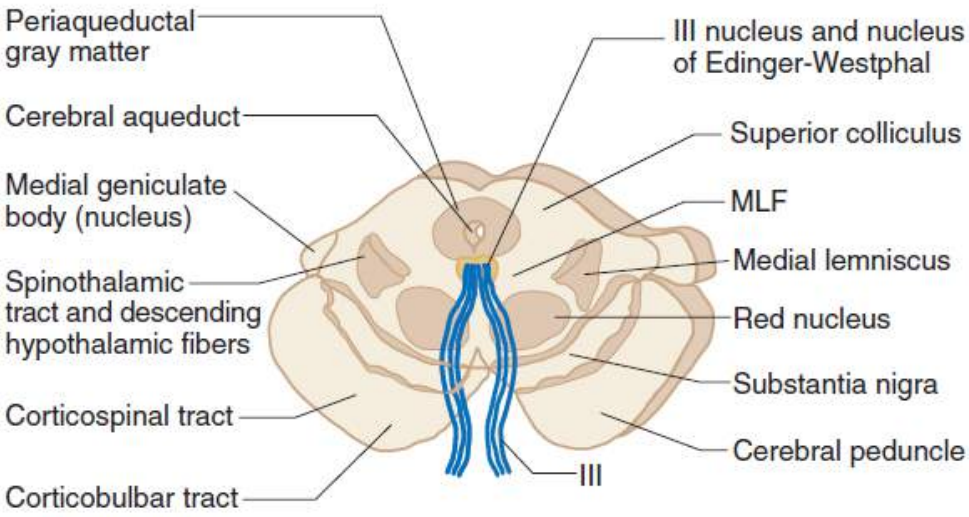


Figure III-5-4A. Upper Midbrain; Level of Nerve III

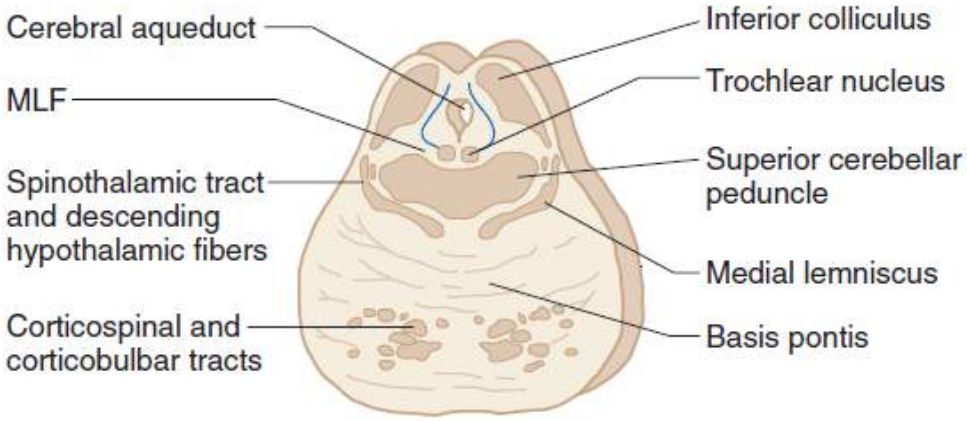


Figure III-5-4B. Lower Midbrain; Level of Nucleus CN IV

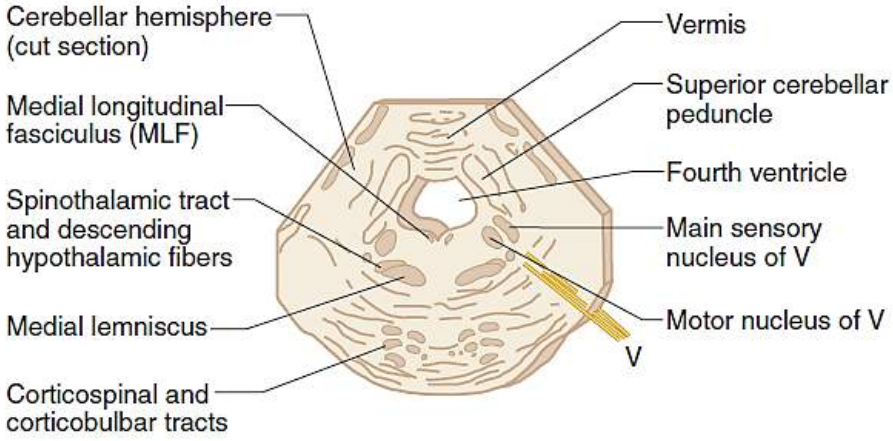


Figure III-5-4C. Middle Pons; Level of Nerve V

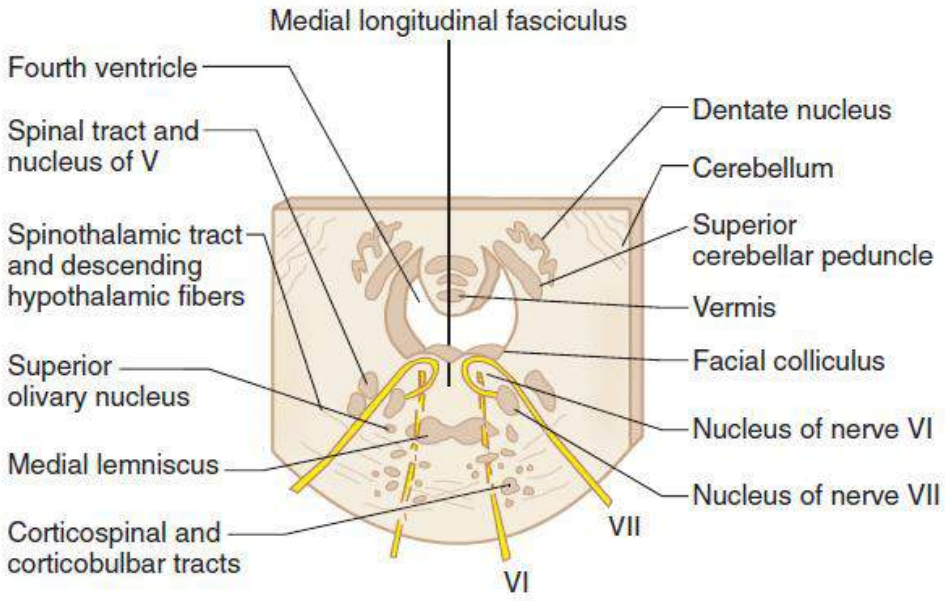


Figure III-5-4D. Lower Pons; Level of Nerves VI and VII

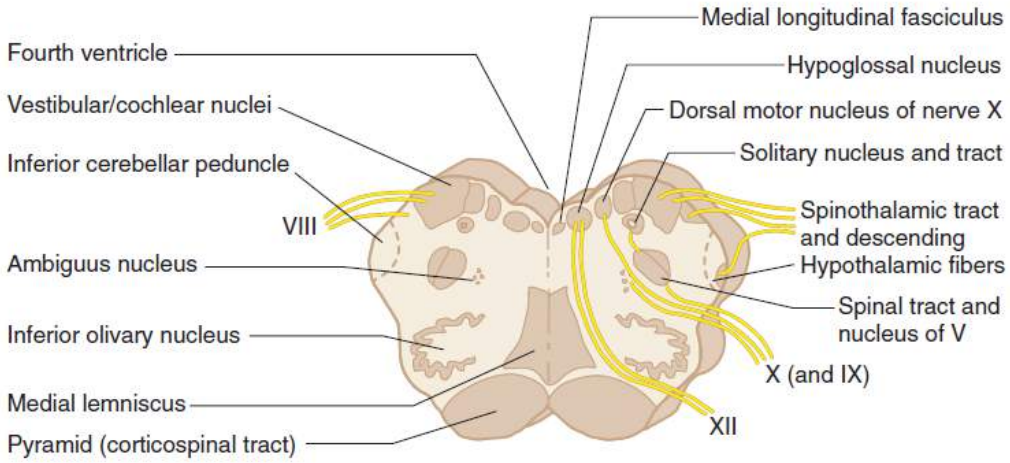


Figure III-5-4E. Open Medulla

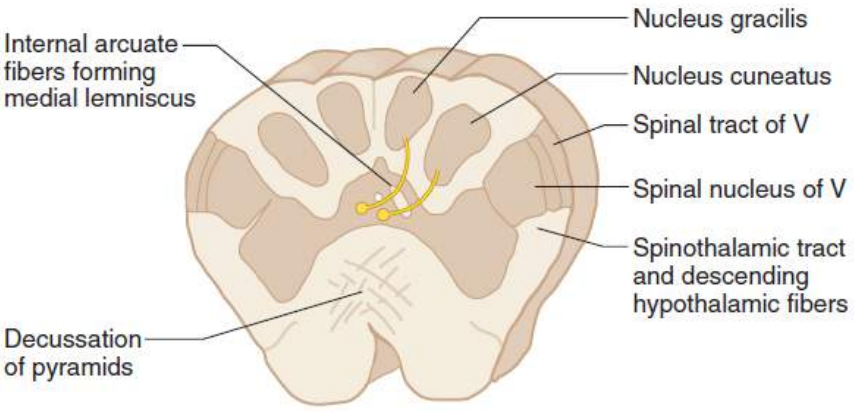


Figure III-5-4F. Closed Medulla

LATERAL MID-PONTINE LESIONS

- Lateral mid-pontine lesions affect the motor and principal sensory nuclei of the ipsilateral trigeminal nerve, causing weakness of the muscles of mastication, diminished jaw jerk reflex, and impaired tactile and position sensation over the face.

MEDIAL MID-PONTINE LESIONS

- Medial mid-pontine infarction presents with contralateral ataxia and hemiparesis of the face, trunk, and limbs (ie, ataxic hemiparesis). There is also variable loss of contralateral tactile and position sense.

LATERAL MEDULLARY SYNDROME (WALLENBERG SYNDROME)

- Due to occlusion or dissection of intracranial vertebral artery or PICA

Clinical features of Wallenberg syndrome	
Vestibulocerebellar symptoms	• **Vertigo**, falling to the side of the lesion • Difficulty sitting upright without support • Diplopia & **nystagmus** (horizontal & vertical) • Ipsilateral limb ataxia
Sensory symptoms	• Abnormal facial sensation or pain (early symptom) • Loss of pain & temperature in **ipsilateral** face & **contralateral** trunk & limbs
Ipsilateral bulbar muscle weakness	• Dysphagia & aspiration • Dysarthria, dysphonia & **hoarseness** (ipsilateral vocal cord paralysis)
Autonomic dysfunction	• Ipsilateral **Horner's syndrome** (miosis, ptosis & anhidrosis) • Intractable hiccups • Lack of automatic respiration (especially during sleep)

Signs of nucleus ambiguous are typical—loss of gag reflex

- Voluntary motor function of face and body usually intact
- Dx: made by MRI
- Rx: IV thrombolytics (eg tPA)

Table 11-1. Posterior Circulation Syndromes

	Ipsilateral	Contralateral
Weber	CN III	Hemiplegia
Benedikt	CN III	Ataxia
Wallenberg	Facial sensory loss	Body sensory loss

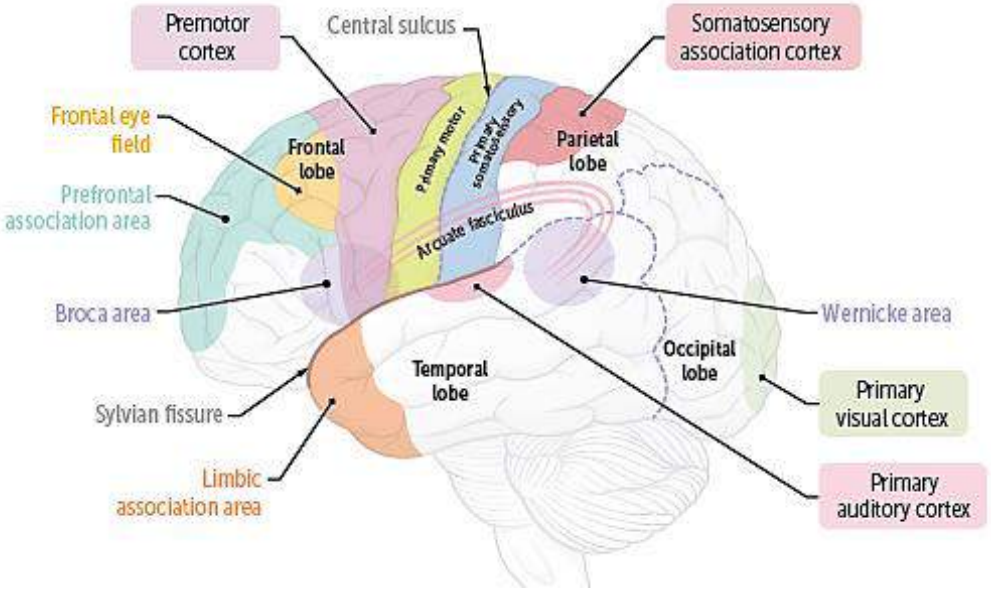
MEDIAL MEDULLARY SYNDROME

- (alternating hypoglossal hemiplegia)
- Due to branch occlusion of vertebral or anterior spinal artery

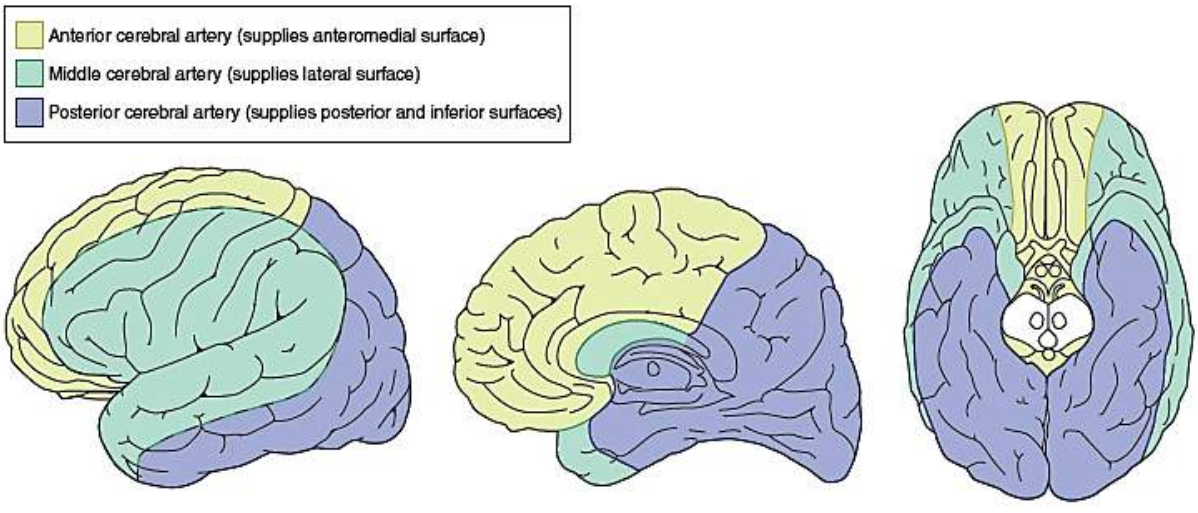
Medial medullary syndrome	
Structure	**Sign** present at the same time
Medullar pyramid	Contralateral hemiparesis
Medial lemniscus	Contralateral loss of tactile, vibratory & position sense
Hypoglossal nucleus/fibers	Ipsilateral tongue paralysis with deviation to side of lesion

BRAIN LESIONS

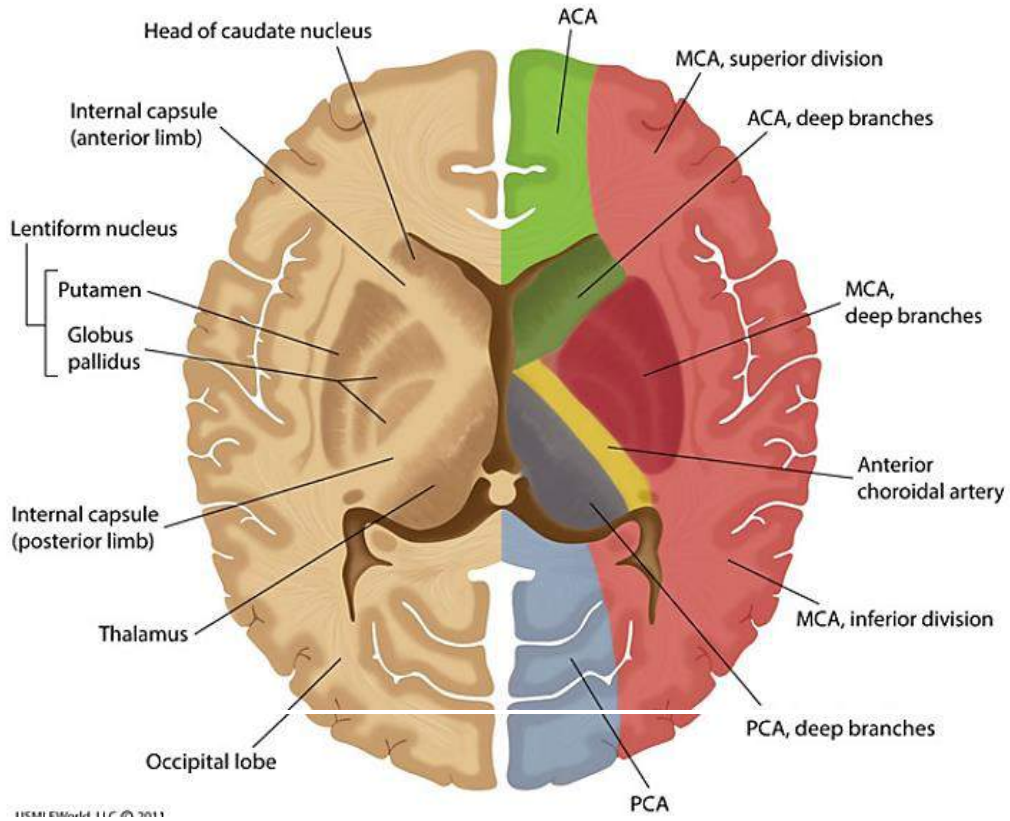
Cerebral cortex functions



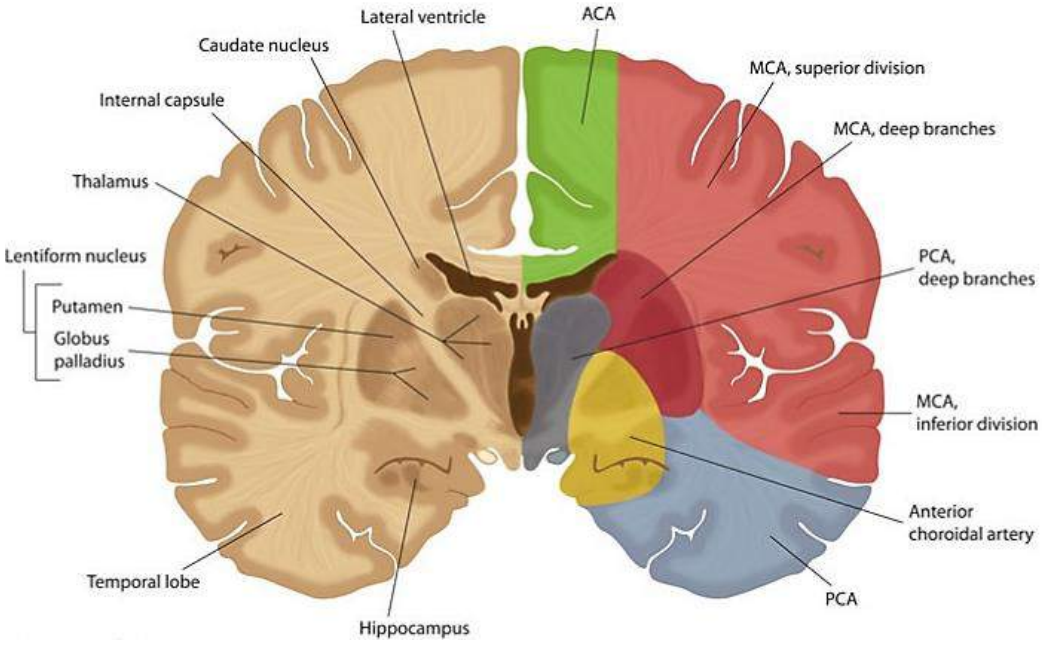
Cerebral arteries—cortical distribution



Blood supply to the Cerebral Hemispheres



Blood supply to the Cerebral Hemispheres



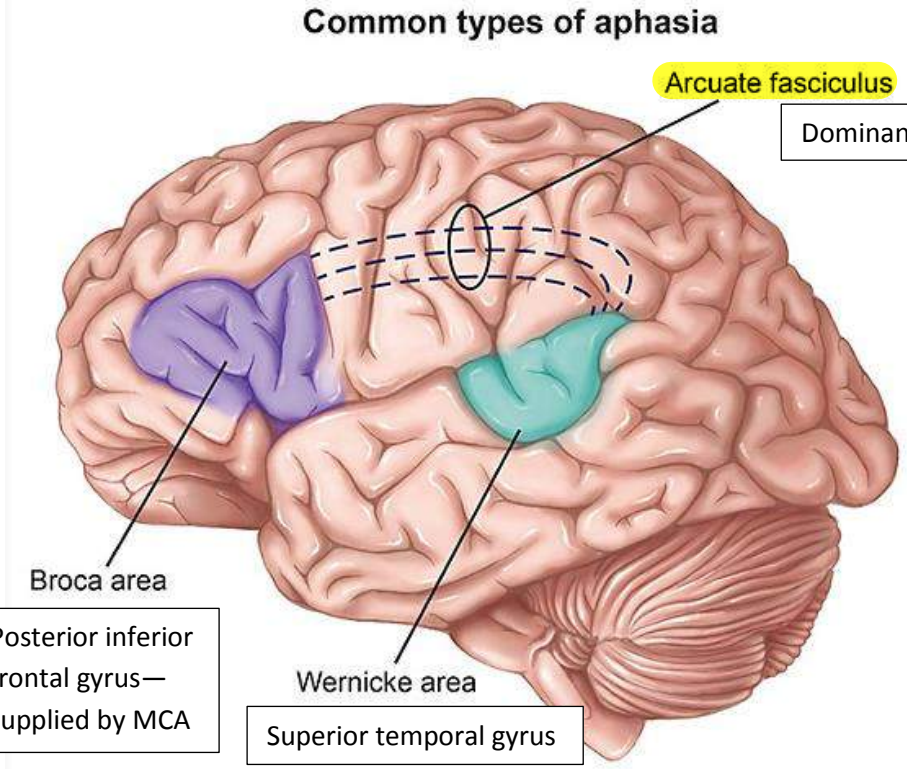
Brain lesions & clinical presentations	
Lesion	**Clinical presentation**
Posterior limb of internal capsule (lacunar infarct)	• Unilateral motor impairment • No sensory or cortical deficits • No visual field abnormalities
Middle cerebral artery occlusion	• **Contralateral** somatosensory **& motor deficit (face, arm & leg)** • Conjugate eye deviation toward side of infarct • Homonymous hemianopia • Aphasia (dominant hemisphere) • Hemineglect (nondominant hemisphere)
Anterior cerebral artery occlusion	• Contralateral somatosensory & motor deficit, predominantly in lower extremity • Abulia (lack of will or initiative) • Dyspraxia, emotional disturbances, urinary incontinence
Vertebrobasilar system lesion (supplying the brain stem)	• Alternate syndromes with contralateral hemiplegia & ipsilateral cranial nerve involvement • Possible ataxia

Urinary incontinence— from damage to cortical micturition centers of mesial frontal lobe

Primitive reflexes may also appear like Moro, grasp and tonic neck reflexes

Posterior cerebral artery stroke	Homonymous hemianopia, alexia without agraphia (dominant hemisphere), visual hallucinations (calcarine cortex), sensory symptoms (thalamus), third nerve palsy with paresis of vertical and horizontal eye movements, and contralateral motor deficits (cerebral peduncle, midbrain).

APHASIA



Aphasia syndrome	Spontaneous speech	Comprehension	Repetition	Associated features
Broca	Sparse & nonfluent	Relatively preserved	Impaired	Right hemiparesis (face & upper limb)
Wernicke	Fluent & voluminous but lacks meaning	Greatly diminished	Impaired	Right superior visual field defect
Conduction	Fluent with phonemic errors	Relatively preserved	Very poor	None

, contralateral apraxia due to involvement of supplementary motor cortex and conjugate gaze deviation to the side of lesion (contraversive frontal eye field)

Inability to speak nouns (anomic aphasia)—visual field defect due to inferior optic radiations (Meyer's loop)

(Check the table attached on page 460 of FA)

FRONTAL LOBE LESIONS

Dominant:

- As above

Non-dominant:

- Affect the way a person conveys emotion through speech (motor aprosodia), contralateral weakness, and apraxia

PARIETAL LOBE LESIONS

Dominant:

- Can present with contralateral sensory loss (eg, pain, vibration, agraphesthesia, astereognosis) and contralateral inferior homonymous quadrantanopsia due to superior optic radiations involvement.

Non-dominant (right):

- Responsible for spatial organization
- Hemi-neglect syndrome: pt neglects left side of body
- Typically cause anosognosia (denial of one's disabilities) and contralateral apraxia (inability to carry out learned purposeful movements).

TEMPORAL LOBE LESIONS

Dominant:

- As above

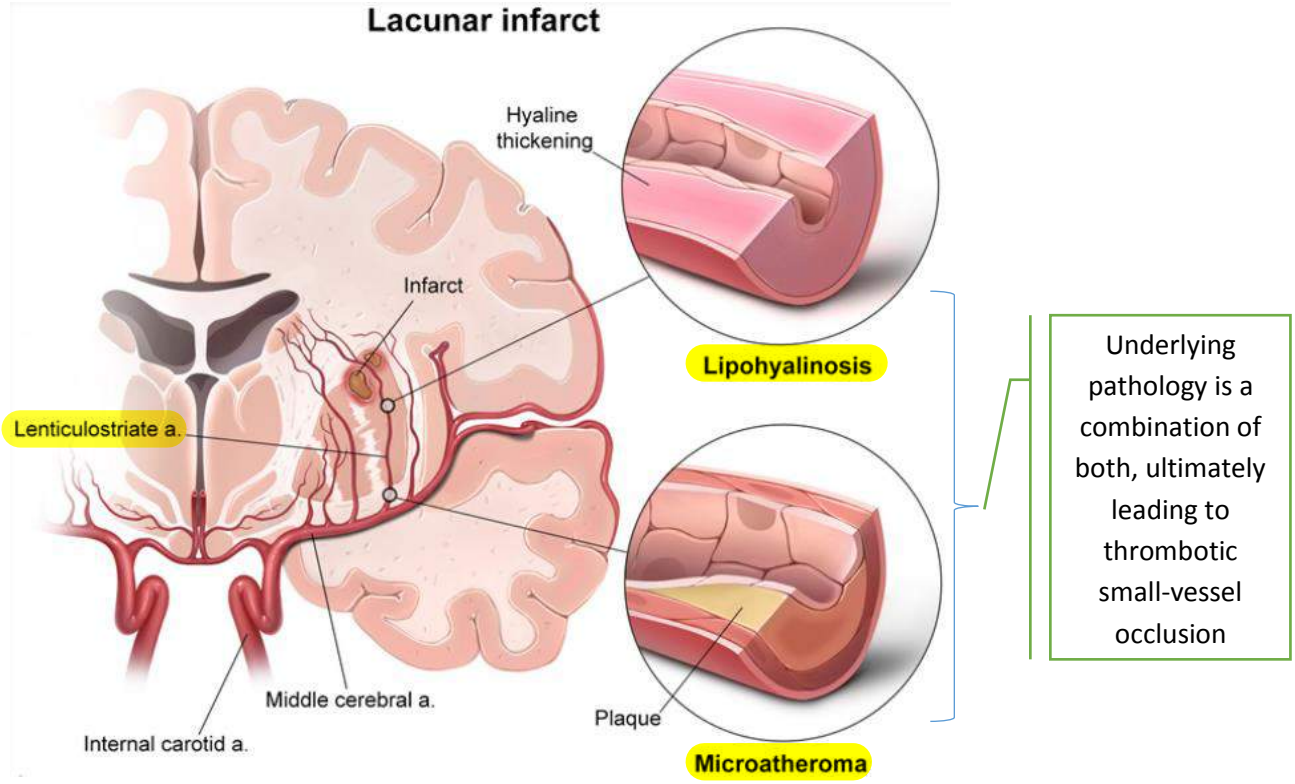
Non-dominant:

- Can impair ability to comprehend emotional gestures (sensory aprosodia). These patients can also develop a contralateral homonymous quadrantanopsia due to the inferior optic radiations involvement.

CEREBELLAR DYSFUNCTION

- Progressive gait dysfunction, truncal ataxia, nystagmus, intention tremor or dysmetria (limb-kinetic tremor when attempting to touch a target), and impaired rapid alternating movements (dysdiadochokinesia).
- Muscle hypotonia can also be present, leading to a pendular knee reflex - persistent swinging movements of the limb after eliciting the deep-tendon reflex (more than 4 swings is considered abnormal). Pendular reflexes are not brisk, unlike clonus which would suggest pyramidal tract disease
- Pyramidal tract signs, such as pronator drift, focal weakness, spasticity, hyperreflexia, and Babinski sign, are not observed with cerebellar lesions

LACUNAR STROKE



Lacunar stroke	
Etiology	• Small penetrating artery occlusion due to hypertensive arteriolar sclerosis
Affected areas	• Basal ganglia • Subcortical white matter (eg, internal capsule, corona radiata) • Pons
Risk factors	• **Hypertension** • Diabetes mellitus, advanced age, ↑LDL, smoking
Clinical features	• Absence of cortical signs (eg, aphasia, agnosia, neglect, apraxia, hemianopia), seizure, or mental status changes • Common syndromes: ◦ Pure motor hemiparesis (most frequent) ◦ Pure sensory stroke ◦ Ataxic hemiparesis ◦ Dysarthria-clumsy hand

- Due to their small size, lacunes are often not appreciated on non-contrast CT obtained shortly after the event
- Commonly occur in internal capsule→ can cause pure motor hemiparesis (corticospinal and corticobulbar fibers) of contralateral arm, leg and face

LACUNAR STROKE OF THALAMUS

Posteromedial thalamus

lateral

- Typically occurs due to atherothrombotic occlusion of the small, penetrating (thalamogeniculate) branches of the posterior cerebral artery.
- Ventral posterolateral and ventral posteromedial nuclei of the thalamus transmit sensory information from the contralateral side of the body and face, respectively.
- Thalamic stroke in this region→ sudden-onset contralateral sensory loss involving all sensory modalities (ie, **pure sensory stroke**). Symptoms can be accompanied by transient hemiparesis, athetosis, or ballistic movements due to disruption of neighboring basal ganglia structures and corticospinal fibers in the posterior limb of the internal capsule
- Several weeks to months following the stroke, sensory deficits can improve; however, some patients develop **thalamic pain syndrome (Dejerine-Roussy syndrome)**. This condition is characterized by severe paroxysmal burning pain over the affected area and is classically exacerbated by light touch (allodynia).

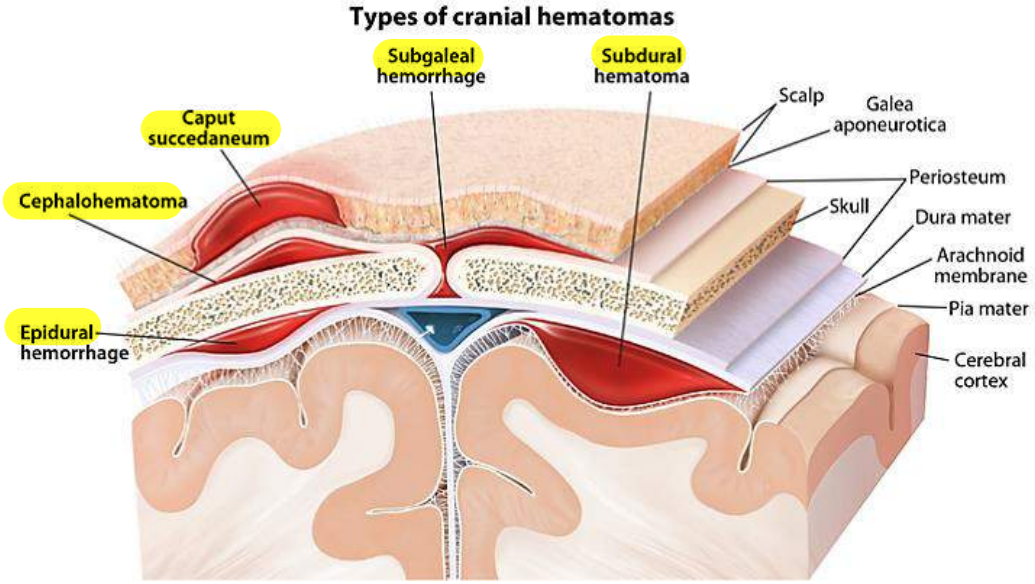
Lateral geniculate body

- The lateral geniculate nucleus is located in the thalamus and relays visual information to the ipsilateral primary visual cortex. Damage to this structure would result in a contralateral homonymous hemianopsia.

ARTERIAL DISSECTION

- Commonly affects vertebral or internal carotid artery→ cause cerebral ischemia due to thromboembolism or hypoperfusion
- Neurologic deficits preceded by head or neck pain
- **Carotid dissection**: commonly causes partial ipsilateral Horner syndrome (ptosis and miosis without anhidrosis) due to damage of postganglionic sympathetic fibers supplying the head.
- **Vertebral artery dissection**: lateral medullary syndrome, or Wallenberg syndrome (eg, vertigo, ipsilateral ataxia), due to damage of vestibular nuclei and the inferior cerebellar peduncle.

TYPES OF CRANIAL HEMATOMAS



EPIDURAL HEMATOMA

Epidural hematoma	
Pathogenesis	Trauma to sphenoid bone with tearing of middle meningeal artery
Clinical features	• Brief loss of consciousness followed by lucid interval • Hematoma expansion leads to ↓ consciousness & ↑ intracranial pressure (eg, headache, nausea/vomiting)
Diagnosis	Head CT: Biconvex (lens-shaped) hyper-density that does not cross suture lines
Treatment	Urgent surgical evacuation for symptomatic patients

- Failure to treat EDH emergently→ worsening intracranial hypertension and uncal herniation.
- On examination, patients with **uncal herniation** have dilation of the pupil on the ipsilateral side of the lesion (due to oculomotor nerve compression) along with ipsilateral hemiparesis (due to contralateral crus cerebri compression).
- Emergent craniotomy should be performed in patients with focal neurologic deficits to prevent brain herniation and death.

SUBDURAL HEMATOMA

Subdural hematoma	
Pathogenesis	Rupture of bridging veins (head trauma)
Risk factors	• Elderly & alcoholics (cerebral atrophy, ↑ fall risk) • Infants (thin-walled vessels) • Anticoagulant use

Clinical features	• Acute: Gradual onset 1-2 days after injury
	  ○ Impaired consciousness (eg, coma), confusion
	  ○ Headache, nausea, & vomiting (↑ intracranial pressure)
	• Chronic: Insidious onset weeks after injury
	  ○ Headache, somnolence, confusion, lightheadedness
	  ○ Focal neurologic deficits

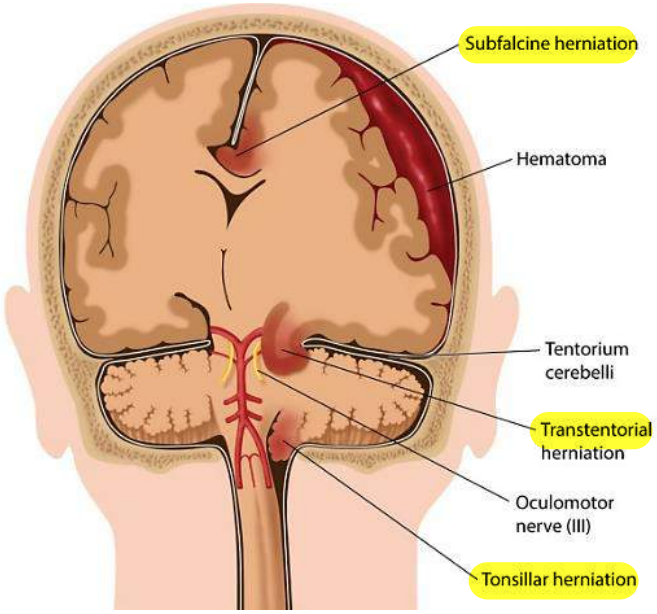
Diagnosis	Head CT: Crescent shaped hyperdensity (acute) or hypodensity (chronic) crossing suture lines
Treatment	• Reverse/discontinue anticoagulants • Surgical evacuation of symptomatic or large bleeds

- Small asymptomatic hematomas are managed conservatively

DIFFUSE AXONAL INJURY

- Most significant cause of morbidity in patients with traumatic brain injuries. It is frequently due to traumatic acceleration-deceleration injury and results in vegetative state
- Sudden acceleration-deceleration impact produces rotational forces that affect the brain areas where the density difference is the maximum, thus most of the diffuse axonal injury occur at gray white matter junction.
- **C/F:** out of proportion with the CT scan findings. Patient loses consciousness instantaneously and later develops persistent vegetative state.
- **CT scan** characteristically shows numerous minute punctate hemorrhages with blurring of grey white interface. However, MRI is more sensitive than CT scan for diagnosing diffuse axonal injury.

MAJOR HERNIATIONS OF BRAIN



TRANSTENTORIAL (UNCAL) HERNIATION

Transtentorial (Uncal) Herniation	
Lesion	**Neurologic Signs**
Compression of the contralateral crus cerebri against the tentorial edge	Ipsilateral hemiparesis
Compression of the ipsilateral oculomotor nerve (i.e., CN III) by the herniated uncus	Loss of parasympathetic innervation causes mydriasis (occurs early); loss of motor innervation causes ptosis and a down-and-out gaze of the ipsilateral pupil due to unopposed trochlear (i.e., CN IV) and abducent (i.e., CN VI) action (occurs late)
Compression of the ipsilateral posterior cerebral artery (i.e., ischemia of visual cortex)	Contralateral homonymous hemianopsia
Compression of the reticular formation	Altered level of consciousness; coma

POSTCONCUSSIVE SYNDROME

- Traumatic brain injury (TBI) of any severity can lead to (a few hours or days later) postconcussive syndrome
- Sx: headache, confusion, amnesia, difficulty concentrating or with multitasking, vertigo, mood alteration, sleep disturbance, and anxiety.
- Typically, these symptoms resolve with symptomatic treatment within a few weeks to months following TBI; however, some patients may have persistent symptoms lasting >/=6 months.

AMAUROSIS FUGAX

- Sudden, painless loss of vision from emboli
- Cholesterol particles (Hollenhorst bodies) may be seen in eye
- It is warning sign of impending stroke
- Underlying embolic disease is almost always present
- Most emboli occur from carotid bifurcation; hence, duplex USG of neck often done to identify any plaques which may be present

MAJOR STROKE SUBTYPES

Stroke type	Clinical characteristics of major stroke subtypes
Ischemic (thrombotic)	• Atherosclerotic risk factors (eg, uncontrolled hypertension, diabetes), ± history of transient ischemic attack • Local in-situ obstruction of an artery • Symptoms often fluctuate - stuttering progression with periods of improvement
Ischemic (embolic)	• History of cardiac disease (eg, atrial fibrillation, endocarditis) or carotid atherosclerosis (bruit) • Onset of symptoms is **abrupt** & **usually maximal at the start** • Multiple infarcts within different vascular territories
Intracerebral hemorrhage	• History of uncontrolled hypertension, coagulopathy, illicit drug use (eg, amphetamines, cocaine) • Symptoms progress over minutes to hours • Focal neurologic symptoms appear early, followed by features of increased intracranial pressure (eg, vomiting & headache, bradycardia, reduced alertness)
Spontaneous subarachnoid hemorrhage	• Rupture of an arterial saccular ("berry") aneurysm or from an arteriovenous malformation • Severe headache at onset of neurologic symptoms • Meningeal irritation (eg, neck stiffness) • Focal deficits uncommon

Usually lack of headache and impaired consciousness

More common than AV malformation

- HTN is the most important risk factor for stroke than any other risk factor. Hypertensive pts have 4 times risk of stroke than non-hypertensive pts

ISCHEMIC STROKE

Antiplatelet/antithrombotic therapy for ischemic stroke	
Clinical presentation	**Therapy**
Presentation within 3.5-4 hours of symptom onset & no contraindications	Intravenous alteplase
Stroke with no prior antiplatelet therapy	Aspirin
Stroke on aspirin therapy	Aspirin + dipyridamole OR clopidogrel
Stroke on aspirin therapy & patient with intracranial large artery atherosclerosis	Aspirin + clopidogrel
Stroke with evidence of atrial fibrillation	Long-term anticoagulation (eg, warfarin, dabigatran, rivaroxaban)

CRITERIA FOR GIVING THOMBOLYSIS (IV ALTEPLASE)

Criteria for thrombolytics in stroke	
Inclusion criteria	• Ischemic stroke with measurable neurodeficits • Symptom onset <3-4.5 hours before treatment initiation
Strict exclusion criteria	• Hemorrhage or multilobar infarct involving >33% of cerebral hemisphere on CT • Stroke/head trauma in past 3 months • History of intracranial hemorrhage, neoplasm, or vascular malformation • Recent intracranial/spinal surgery • Active bleeding or arterial puncture in past 7 days at noncompressible site • BP >185/110 mm Hg • Platelets <100,000 /mm^3 or glucose <50 mg/dL • Anticoagulant use with INR >1.7, PT >15 sec, or ↑ aPTT
Relative exclusion criteria	• Minor or rapidly improving neurodeficits • Major surgery/trauma in the past 14 days • MI in the past 3 months • GU or GI bleeding in the past 21 days • Seizure at stroke onset • Pregnancy

aPTT = activated partial thromboplastin time; BP = blood pressure; GI = gastrointestinal; GU = genitourinary; INR = International Normalized Ratio; MI = myocardial infarction; PT = prothrombin time.

- Blood pressure control is critical in patients undergoing fibrinolytic therapy, and should be kept below 185/110 during in the 24 hours after it is administered. Labetalol, an alpha-1 and beta adrenergic blocker, may be used for this purpose.
- In patients who do receive fibrinolytic therapy, aspirin should be held for 24 hours.

ASPIRIN

- Only antiplatelet agent that is effective in reducing the risk of early recurrence of ischemic stroke and given to those who are not candidates for fibrinolytic therapy
- Should be given as early as possible (within 24 hours of stroke onset) and continue it indefinitely to prevent future strokes.

CLOPIDOGREL

- Given to those who fail or intolerant to aspirin.

LONG TERM ANTICOAGULATION FOR STROKE PREVENTION

- For stroke prevention in patients with atrial fibrillation based on the CHADS2 criteria and stroke risk

	Risk criteria	Score
C	Congestive heart failure	1
H	Hypertension (blood pressure consistently above 140/90 mm Hg)	1
A	Age ≥75	1
D	Diabetes mellitus	1
S_2	Prior stroke or TIA	2

Anticoagulation in atrial fibrillation		
$CHADS_2$ score	Stroke risk	Antithrombotic therapy
0	Low	No anticoagulation (preferred) or Aspirin
1	Intermediate	Anticoagulation (preferred) or Aspirin
2-6	High	Anticoagulation

- Should be done with warfarin—start 2 wks after cardioembolic stroke to prevent recurrence

HEPRAIN

- Avoid unfractionated and LMWH in acute stroke due to risk of bleeding

INTRAPARENCHYMAL HEMORRHAGE

- **HTN** is more commonly associated with intracerebral or intraparenchymal hemorrhage than extra-axial hemorrhages
- **Amyloid angiopathy→ 2nd** most common cause of intracerebral hemorrhage→ typically lobar

- **AV malformation**→ can cause both intracerebral or SAH but aneurysm is more common cause of SAH. AVM is most common cause of intraparenchymal hemorrhage in children
- **Venous sinus thrombosis**→ intracerebral/intraparenchymal hemorrhages along the courses of major cerebral draining veins due to backup pressure. Progressively worsening headache over several days
- Common sites and presentation:

Site of hemorrhage	Neurologic findings
Basal ganglia Putamen	• Contralateral hemiparesis & hemisensory loss • Homonymous hemianopsia • Gaze palsy
Cerebellum	• Usually **NO** hemiparesis • Facial weakness • Ataxia & nystagmus • Occipital headache & neck stiffness
Thalamus	• Contralateral hemiparesis & hemisensory loss • Nonreactive miotic pupils • Upgaze palsy • Eyes deviate Towards hemiparesis
Cerebral lobe	• Contralateral hemiparesis (frontal lobe) • Contralateral hemisensory loss (parietal lobe) • Homonymous hemianopsia (occipital lobe) • Eyes deviate away from hemiparesis • High incidence of seizures
Pons	• Deep coma & total paralysis within minutes • Pinpoint reactive pupils

Early Dx with non-contrast CT is crucial as early surgical decompression is life-saving

Due to reticular activating system disruption

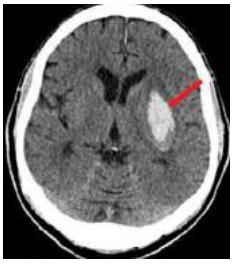
Corticospinal and corticobulbar tract. Decerebrate rigidity

Descending sympathetic tract

- Usually occur during routine activities but maybe precipitated by exertion
- Hypertensive hemorrhages→ usually involve same small, penetrating arteries that cause lacunar stroke (frequently involved locations in table)
- Chronic HTN→ Charcot-bouchard aneurysm→ rupture

PUTAMINAL HEMORRHAGE

- Almost always involve **adjacent internal capsule**→ cause of contralateral hemiparesis and hemisensory loss (due to disruption of corticospinal and somatosensory fibers in posterior limb of internal capsule)
- Conjugate gaze deviation towards side of lesion (due to damage of frontal eye field efferents in anterior limb) i.e. away from the paralytic side
- May lead to stupor and coma
- Supplied by lenticulostriate arteries (small vessel branches from MCA)

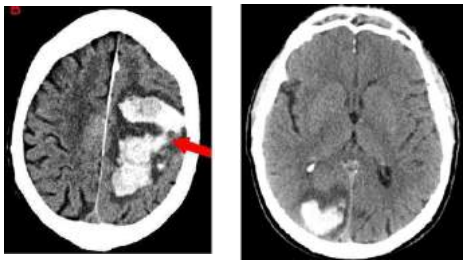


LOBAR HEMORRHAGES

- Lobar hemorrhages typically occur in adults age >60 due to amyloid angiopathy.
- Hemorrhage tends to be recurrent and most often involves the occipital or parietal lobes.
- Occipital lobe hemorrhage may cause homonymous hemianopsia, whereas parietal hemorrhage can cause contralateral hemisensory loss.

SUBARACHNOID HEMORRHAGE

- Cisterns are subarachnoid spaces that fill with blood in SAH
- Aneurysms 3-4% in general population but rarely rupture
- More commonly rupture when >7mm

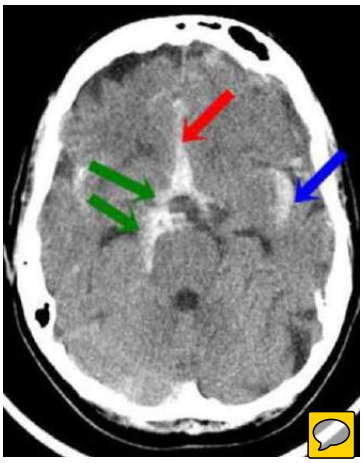


- Occur more in anterior circulation of circle of Willis
- **Dx:** CT without contrast→ negative→ LP—↑ opening pressure and unexplained xanthochromia—highly suggestive of SAH
- **Further evaluation in SAH:** cerebral angiography and treated with surgery (craniotomy with aneurysm clipping) or endovascular methods (coiling and/or stenting of the aneurysm)

Overview of subarachnoid hemorrhage	
Clinical features	• Most commonly due to ruptured arterial saccular ("berry") aneurysm • Severe headache at onset of neurologic symptoms • Meningeal irritation (eg, neck stiffness) • Focal deficits uncommon
Complications	• Rebleeding (first 24 hr) • Vasospasm (after 3 days) • Hydrocephalus/increased intracranial pressure • Seizures • Hyponatremia (usually from syndrome of inappropriate antidiuretic hormone secretion)
Diagnosis	• Noncontrast head CT scan is >90% sensitive • Lumbar puncture required to definitely rule out SAH • Xanthochromia in cerebrospinal fluid confirms diagnosis (usually seen 6 hr after onset) • Cerebral angiography to identify bleeding source
Treatment	• Angiographic procedure to stabilize aneurysm by coiling &/or stenting (endovascular therapy) • Nimodipine & hyperdynamic therapy to reduce vasospasm

Esp. 1st 6 hours of untreated SAH

From 3-10 days—CT angiography preferred for detecting vasospasm—occurs cox of narrowing of arteries at base of brain due to degradation of blood and its metabolites



HEADACHES

CLUSTER HEADACHE

- U/L retro-orbital pain and later spreads to hemicranium
- Occurs in clusters; sudden onset usually night, peaks rapidly, lasts for approx. 2 hours daily, for 6-8 wks and followed by remission up to a year. Associated with redness of eye, tearing, stuffed or runny nose, and ipsilateral Horner's syndrome
- The pathophysiology is related to alterations in the circadian pacemaker, which may be due to hypothalamic dysfunction
- Short but severe attacks, hence, prophylaxis is key to management
- **Prophylaxis:** verapamil, lithium (used for chronic form of cluster headaches), ergotamine, prednisone, methysergide, cyproheptadine and indomethacin
- **Rx acute attack:** inhalation of 100% oxygen and subcutaneous or nasal sumatriptan

MIGRAINE HEADACHE

- **Rx of acute migraine headache in children <12 years:** migraine can be bifrontal and of short duration in children as compared to adults. Rx is mainly supportive (e.g. lying in dark, quiet room

	Types of headache		
	Migraine	**Cluster**	**Tension**
Sex predilection	Female > male	Male > female	Female > male
Family history	Often present	No	No
Onset	Variable	During sleep	Under stress
Location	Often unilateral	Behind one eye	Band-like pattern around the head (bilateral)
Character	Pulsatile & throbbing	Excruciating, sharp & steady	Dull, tight & persistent
Duration	4-72 hours	15-90 minutes	30 minutes to 7 days
Associated symptoms	Auras, photophobia, phonophobia & nausea	Sweating, facial flushing, nasal congestion, lacrimation & pupillary changes	Muscle tenderness in the head, neck or shoulders

with cool cloth on forehead) and acetaminophen or NSAIDS like ibuprofen→ If not effective, oral, intranasal or IV triptans can be tried.

- **Rx of acute migraine headache in adults:** IV antiemetics (chlorpromazine, prochlorperazine or metoclopramide)—can be used as monotherapy or as adjuvant therapy in combination with NSAIDS or triptan
  - Antiemetics—given because of high tendency of vomiting
  - Triptan medications are an effective migraine treatment, but must be started early on in the course of the migraine before symptoms become severe in order to be of benefit.
- **Prophylaxis:** tricyclic antidepressants (e.g. amitriptyline), propranolol

INTRACRANIAL HYPERTENSION

- Skull contains: brain parenchyma, CSF and blood
- ↑ in any of these leads to ICH
- **Causes:** tumor, trauma, hydrocephalus, impaired CNS venous flow, and idiopathic (IIH)
- **C/F:** headache (worse at night), N/V, and mental status changes (e.g. ↓ level of consciousness, cognitive dysfunction). Focal neurologic symptoms (e.g. vision changes, unsteady gait) and seizures may also be present. Sx can worsen with maneuvers that ↑ intracranial pressure like bending forward, Valsalva, coughing etc
- **Sign:** papilledema and focal neurologic deficits. **Cushing reflex** (HTN, bradycardia, respiratory depression)—worrisome finding suggestive of brainstem compression and ↑ intracranial pressure

INTERVENTIONS FOR LOWERING INTRACRANIAL PRESSURE

Interventions for lowering ICP	
Intervention	**Mechanism**
Head elevation	Increased venous outflow from the brain
Sedation	Decreased metabolic demand & control of hypertension
Intravenous mannitol	Extraction of free water from brain tissue → osmotic diuresis
Hyperventilation	CO_2 washout → cerebral vasoconstriction
Removal of CSF	Reduction of CSF volume/pressure

IDIOPATHIC INTRACRANIAL HTN (IIH) OR PSEUDOTUMOR CEREBRI

Idiopathic intracranial hypertension	
Risk factors	• Overweight women of childbearing age • Possible link to certain medications • (eg, tetracyclines, hypervitaminosis A)
Symptoms	• Headache (92%) • Transient vision loss (72%) • Pulsatile tinnitus (60%) • Diplopia (38%)
Physical examination	• Papilledema • Peripheral visual field defect • CN VI palsy
Diagnosis	• MRI +/- MRV • Lumbar puncture (CSF pressure >250 mm H_2O with normal analysis)
Treatment	• Stop the offending medications • Weight loss & acetazolamide for idiopathic cases

Isotretinoin, growth hormone, OCPs, glucocorticoids

Holocranial headache worse with lying flat and improves with standing, visual changes like blurry vision, diplopia

Papilledema can lead to momentary vision loss that varies according to changes in head position→ urgent dx→ if persistent→ permanent vision loss

To rule out cerebral venous thrombosis

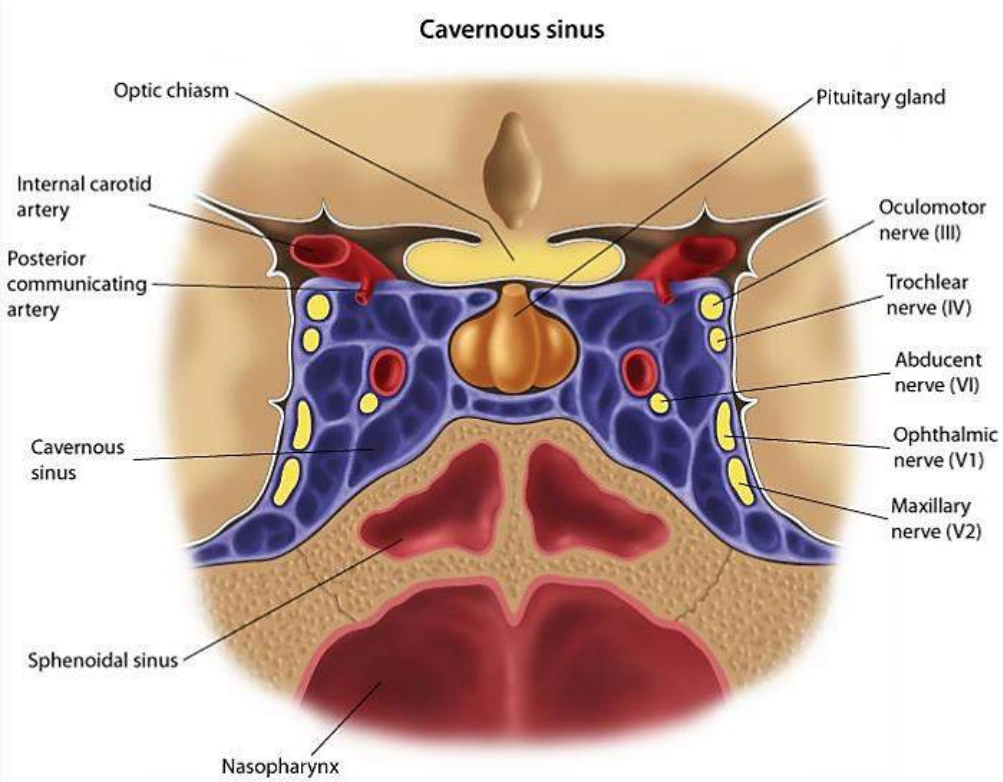
- **Pathology:** impaired absorption of CSF by arachnoid villi or ↑ production—slit like appearance of lateral ventricles
- Pain usually worse at night or lying flat—pain associated with ↑ ICP is usually worse in the morning (QID 4900)
- Empty sella present in 70% pts but is non-diagnostic
- **Rx goals:** prevent vision loss, ↓ ICP and symptomatic relief of headache
- Funduscopy and routine monitoring of visual acquity and visual fields to prevent vision loss
- **Rx:** Acetazolamide→ 1st line→ inhibit choroid plexus carbonic anhydrase→↓ CSF and IH. Add furosemide in pts with continued symptoms→ symptoms refractory to medical therapy or those with progressive vision loss→ surgical intervention with optic nerve sheath decompression or lumboperitoneal shunting is recommended. Short-term use of corticosteroids or serial lumbar puncture (LP) can serve as bridging therapy for patients awaiting definitive surgical treatment→ not recommended as primary intervention due to side effects
- Papilledema is not CI for LP unless there is evidence of non-communicating hydrocephalus, and/or space occupying lesion with/without mass effect or midline shift—performed in lateral decubitus position with legs extended

CAVERNOUS SINUS THROMBOSIS (CST)

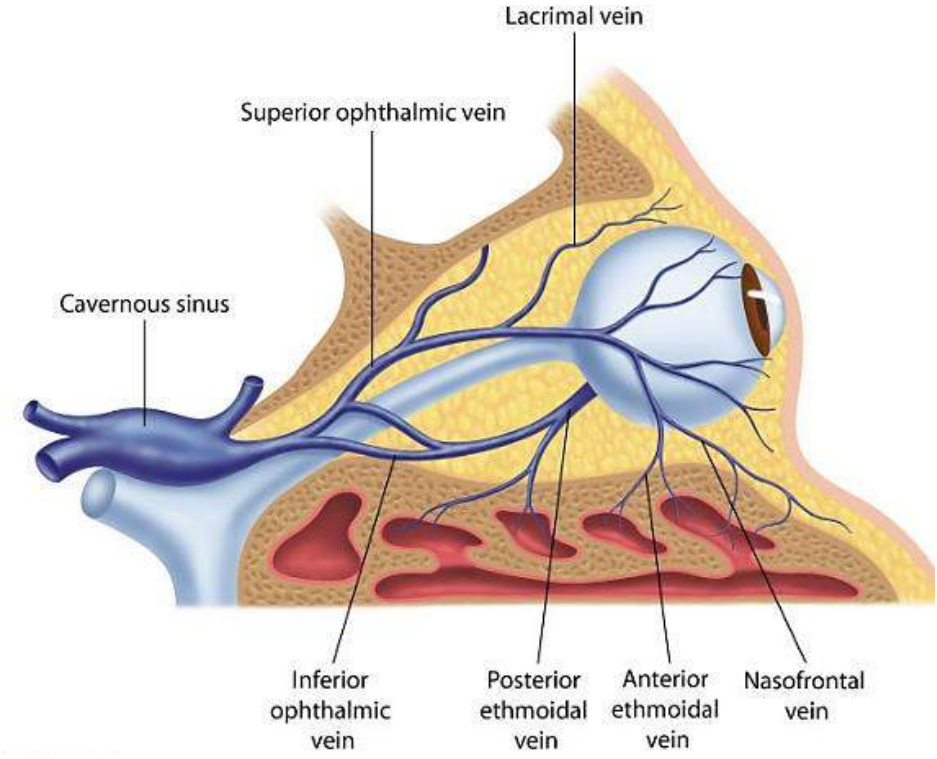
- It can be caused by infection
- Because the **facial/ophthalmic venous system is valveless**, uncontrolled infection of the skin, sinuses, and orbit→ spread to the cavernous sinus→inflammation of the cavernous sinus→ life-threatening CST and intracranial hypertension (ICH).
- **C/F**:
  - Headache—most common symptom and can become intolerable.

- A low-grade fever and periorbital edema usually occur several days later secondary to impaired venous flow in the orbital veins.
- ICH→ vomiting and papilledema on fundoscopy.
- Cranial nerves III, IV, V, and VI pass through the cavernous sinus, which has anastomoses crossing midline. As a result, unilateral symptoms (eg, **headache, binocular palsies, periorbital edema, hypoesthesia, or hyperesthesia in V1/V2 distribution**) can rapidly become bilateral.

- **Dx:** Magnetic resonance imaging with magnetic resonance venography is the imaging modality of choice for diagnosis of CST.
- **Rx:** broad-spectrum intravenous antibiotics and prevention or reversal of cerebral herniation



The valveless venous system:



CEREBRAL EDEMA

- Mannitol→ ↓ ICP associated with cerebral edema. Given IV and needs regular monitoring of renal function and electrolytes→ used in inpatient setting in pts with severely elevated ICP (obtunded pts)

WARFARIN ASSOCIATED INTRACEREBRAL BLEED

- OTC cold meds usually contain acetaminophen→ potentiate anticoagulant effect of warfarin. Also contains decongestants→ ↑ BP. Severe cough→ ↑ intracranial pressure→ ↑ risk of intracerebral haemorrhage
- **Rx:** reverse anticoagulation immediately→ vitamin K and prothrombin complex concentrate are given. If PCC not available→ give FFP. Vitamin K→ sustained effect over 12-24 hours. PCC→ contains vitamin K dependent clotting factors (II, VII, IX, X)→ provide rapid but short term reversal of symptoms. FFP takes longer to prepare/administer and require more volume infusion compared to PCC

TORTICOLLIS

- Focal dystonia of sternocleidomastoid
- Can be congenital, idiopathic, 2* to trauma or local inflammation or drug induced (metoclopramide, atypical antipsychotics, prochlorperazine)

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome	

Signs/ symptoms	• Fever sometimes >40 C
	• Mental status changes
	• Muscle rigidity (generalized)
	• Autonomic instability
	  ○ Tachycardia/dysrhythmias
	  ○ Labile blood pressure
	  ○ Tachypnea
	  ○ Diaphoresis

Precipitating factors	• Antipsychotics (typical & atypical) • Antiemetics (eg, promethazine, metoclopramide) • Antiparkinson (dopamine agonists) medication withdrawal • Infection • Surgery
Treatment	• Stop neuroleptics or restart dopamine agents • Supportive care (hydration, cooling) • Dantrolene or bromocriptine

In contrast, hyperreflexia and myoclonus are typical of serotonin syndrome

- Rigidity in NMS→ muscle necrosis→ ↑ CPK
- Leukocytosis and electrolyte abnormalities
- Begin within 2 wks of initiation of causative drug→ mortality 10-20%
- Type of **Type B drug reaction**: unexpected, dose independent (eg. Steven Johnson syndrome with lamotrigene)
- **Type A drug reactions:** dose-dependent increases in normal pharmacologic action (eg. Respiratory depression with opioids)

METOCLOPRAMIDE-INDUCED DYSTONIC REACTION

- Dopamine antagonist
- Used to treat nausea, vomiting and gastroparesis
- Significant prokinetic effect→ promote peristalsis, ↑ strength of gastric contractions, and relaxation of pyloric sphincter
- **S/E:** agitation and loose stools. Extrapyramidal symptoms (tardive dyskinesia, dystonic reactions and Parkinsonism) occur less frequently. Neuroleptic malignant syndrome may occur rarely
- **Rx of dystonic reaction:** discontinuation of medication, and administration of benztropine, or diphenhydramine

CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

- Causative agents: Vinca alkaloids (e.g. vincristine), platinum based meds (e.g. cisplatin) and taxanes (e.g. paclitaxel)
- Starts weeks after treatment initiation
- **C/F:** symmetrical paresthesia in fingers and toes spreading proximally in stocking-glove pattern, early loss of ankle jerk reflex and loss of pain and temperature sensation. Occasionally there can motor neuropathy resulting in weakness and B/L foot drops

STIFF PERSON SYNDROME

- Rare, autoimmune disorder
- Rigidity, stiffness, muscle spasms involving axial skeleton
- Autonomic instability can occur but mental status changes are typically not seen

PARANEOPLASTIC SYNDROMES

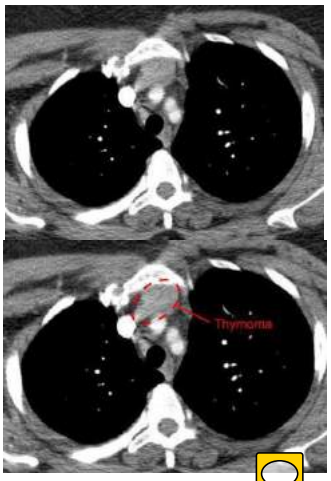
Paraneoplastic syndrome	Involved site	Clinical features
Myasthenia gravis	Acetylcholine receptor in postsynaptic membrane	Fluctuating muscle weakness • Ocular (ptosis, diplopia) • Bulbar (dysphagia, dysarthria) • Facial, neck & limb muscles
Lambert-Eaton syndrome	Presynaptic membrane voltage-gated calcium channels	• Proximal muscle weakness • Autonomic dysfunction (eg, dry mouth) • Cranial nerve involvement (eg, ptosis) • **Diminished or absent deep-tendon reflexes**
Dermatomyositis/ polymyositis	Muscle fiber injury	• Symmetrical & more proximal muscle weakness • Interstitial lung disease, esophageal dysmotility, Raynaud phenomenon • Polyarthritis • Esophageal dysmotility • **Skin findings** (eg, Gottron papules, heliotrope rash) in dermatomyositis

Symmetric

Reflexes preserved

MYASTHENIA GRAVIS

Myasthenia gravis	
Epidemiology	• Women: Second to third decade • Men: Sixth to eighth decade
Symptoms/signs	• Fluctuating & fatigable proximal muscle weakness; worse later in the day o Ocular (eg, diplopia, ptosis) o Bulbar (eg, dysphagia, dysarthria) o Respiratory muscles (myasthenic crisis)
Diagnosis	• Bedside: Edrophonium ("Tensilon") test, ice pack test • Acetylcholine receptor antibodies (highly specific) • CT scan of chest to evaluate for thymoma
Treatment	• Acetylcholinesterase inhibitors (eg, pyridostigmine) • +/− Immunotherapy (eg, corticosteroids, azathioprine) • Thymectomy



- Can also cause **symmetric** proximal muscle weakness involving neck and upper extremities (e.g difficulty holding neck and difficulty combing hair)

- C/F highly suggestive of MG (positive icepack test—icepack placed on eyes for several minutes improves symptoms i.e. cold temp inhibit breakdown of acetylcholine in NMJ) → perform acetylcholine receptor antibodies test→ negative→ check muscle-specific tyrosine kinase antibodies→ unclear diagnosis→ electrophysiologic studies (eg repetitive nerve stimulation, single-fiber electromyography) may be helpful→ diagnosis established→ Chest CT or MRI as thymectomy can lead to long-term improvement

MYASTHENIC CRISIS

Myasthenic crisis	
Precipitating factors	• Infection or surgery • Pregnancy or childbirth • Tapering immunosuppressive drugs • Medications (eg, aminoglycosides, beta blockers)
Signs/symptoms	• ↑ Generalized & oropharyngeal weakness • Respiratory insufficiency/dyspnea
Treatment	• Intubation for deteriorating respiratory status • Plasmapheresis or IVIG, & corticosteroids

IVIG = intravenous immunoglobulin.

Azithromycin

Given after pt is stabilized

Preferred over IVIG

- Following intubation, acetylcholinesterase inhibitors (eg pyridostigmine) used in daily management of MG are temporarily held to reduce excess airway secretions and risk of aspiration.
- Other immunomodulatory therapy (eg, mycophenolate mofetil or azathioprine) can be considered, especially if corticosteroid therapy is ineffective, but usually requires several weeks to reach clinical efficacy.

LAMBERT EATON SYNDROME

- ↓ acetylcholine release from pre-synaptic terminal
- Approx. 50% cases have underlying malignancy—most common being small cell lung cancer
- Examples: Difficulty standing from chair, combing hair, placing dishes overhead. Vigorous activity can improve muscle strength and reflexes temporarily
- **Dx:** checking autoantibodies and electrophyiologic studies
- **Rx:** Symptomatic therapy includes guanidine or 3,4-diaminopyridine to increase presynaptic acetylcholine levels.
- Refractory symptoms may respond to immunologic therapy with IVIG or oral immunosuppressants (e.g. corticosteroids, azathioprine)

MULTIPLE SCLEROSIS

Clinical features of multiple sclerosis	
Features suggesting multiple sclerosis	• Onset at age 15-50 • Optic neuritis • Lhermitte's sign • Internuclear ophthalmoplegia • Fatigue • Uhthoff's phenomenon (heat sensitivity) • Sensory symptoms (numbness & paresthesia) • Motor symptoms (paraparesis & spasticity) • Bowel/bladder dysfunction
Disease pattern	• Relapsing-remitting (majority) • Primary progressive • Secondary progressive • Progressive relapsing
Diagnosis	• T2 MRI lesions disseminated in time & space (periventricular, juxtacortical, infratentorial, or spinal cord) • Oligoclonal IgG bands on cerebrospinal fluid analysis

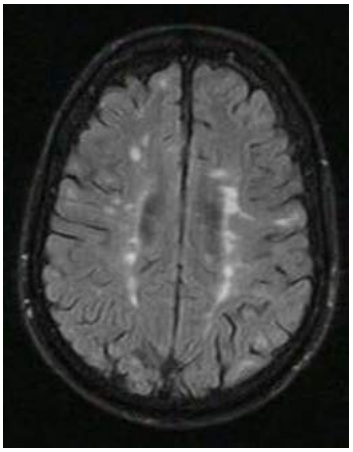
Electric shock-like sensation down the spine or limbs on flexion of neck

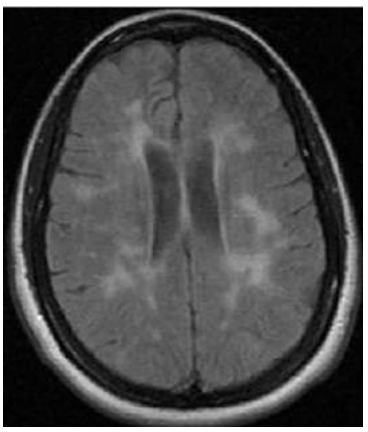
Gradual progression from initial onset without acute relapse

Steady deterioration after initial relapsing remitting stage

Progressive disease between relapses

- Neuropsychiatric disturbance
- Hypo/hyperintense lesions are seen on MRI—periventricular, juxtacortical and infratentorial regions. Spinal cord may also be involved
- IgM and IgA may also be increased. Immunoglobulins can be ↑ed in other conditions like neuropathies, chronic CNS infection or viral syndromes→ hence, oligoclonal bands are non-diagnostic.
- **CSF:** Normal pressure, total cell count and total protein conc. Predominant cell type: T lymphocytes
- **Rx:**
  - **Acute relapse**: high-dose intravenous glucocorticoids (methylprednisolone). Corticotropin injection gel, a purified from of adrenocorticotrophic hormone, can be used as alternate therapy. Plasma exchange is also reserved for those who do not respond to high-dose glucocorticoids.
  - **Long-term disease modifying therapy**: Glatiramer, interferon, mitoxantrone, cyclophosphamide, methotrexate, and cladribine





DIFFERENTIAL DIAGNOSIS OF FLACCID PARALYSIS

Differential diagnosis of flaccid paralysis			
Diagnosis	**Infant botulism**	**Foodborne botulism**	**Guillain-Barré syndrome**
Pathogenesis	Ingestion of *Clostridium botulinum* spores from environmental dust	Ingestion of preformed *C botulinum* toxin	Autoimmune peripheral nerve demyelination
Presentation	Descending flaccid paralysis	Descending flaccid paralysis	Ascending flaccid paralysis
Treatment	Human-derived botulism immune globulin	Equine-derived botulism antitoxin	Pooled human immune globulin

+ Respiratory support + NG tube feeding

INFANT BOTULISM

- Raw honey ingestion is also a risk factor
- Highest incidence: California, Pennsylvania and Utah—greatest conc. Of soil botulism spores
- Environmental dust (eg construction site)→ ingestion of spores→ C. botulinum colonize colon→ produce and release toxin→ block Ach release at presynaptic NMJ
- Suspect diagnosis: infants with **bilateral bulbar palsies** (eg, ptosis, sluggish pupillary response to light, poor suck and gag reflexes) followed **by symmetric descending flaccid paralysis** (hypotonia). **Constipation and drooling** due to autonomic dysfunction also occur.
- Botulism immune globulin should be administered as soon as possible, even before diagnostic confirmation of stool spores or toxin.

FOODBORNE BOTULISM

Foodborne botulism	
Pathogenesis	*Clostridium botulinum* toxin inhibits presynaptic acetylcholine release at neuromuscular junction
Sources	• Improperly canned foods (eg, fruits, vegetables) • Aged seafood (eg, cured fish)
Clinical features	Acute onset within 36 hours of ingestion: • Bilateral cranial neuropathies o Blurred vision, diplopia o Facial weakness, dysarthria, dysphagia • Symmetric descending muscle weakness • Diaphragmatic weakness with respiratory failure
Diagnosis	Serum analysis for toxin
Treatment	Equine serum heptavalent botulinum antitoxin

For adults and children >1year—this antitoxin is horse derived. Supportive care is also needed

- Prodromal symptoms: GI discomfort, dry mouth and sore throat
- The presentation differs from infant botulism in that the descending flaccid paralysis is preceded by a prodrome of nausea, vomiting, abdominal pain, and diarrhea.

GUILLAIN BARRE SYNDROME

Guillain-Barré syndrome	
Risk factors	• Antecedent respiratory or gastrointestinal infection (eg, ***Campylobacter jejuni***) • Probable association with certain vaccines (eg,influenza)
Clinical features	• Symmetric ascending muscle weakness with absent or depressed deep-tendon reflexes • Bulbar symptoms (dysarthria & dysphasia) • Facial nerve palsy • Respiratory compromise • Mild sensory symptoms • Autonomic dysfunction (arrhythmias, orthostatic hypotension, urinary retention, ileus & lack of sweating) • Back & extremity pain
Diagnosis	• Lumbar puncture with elevated cerebrospinal fluid protein & normal white blood cell count (<10 mm^3) • Electrodiagnostic findings consistent with GBS
Treatment	• Monitor autonomic & respiratory functions • Intravenous immunoglobulin **OR** plasmapheresis

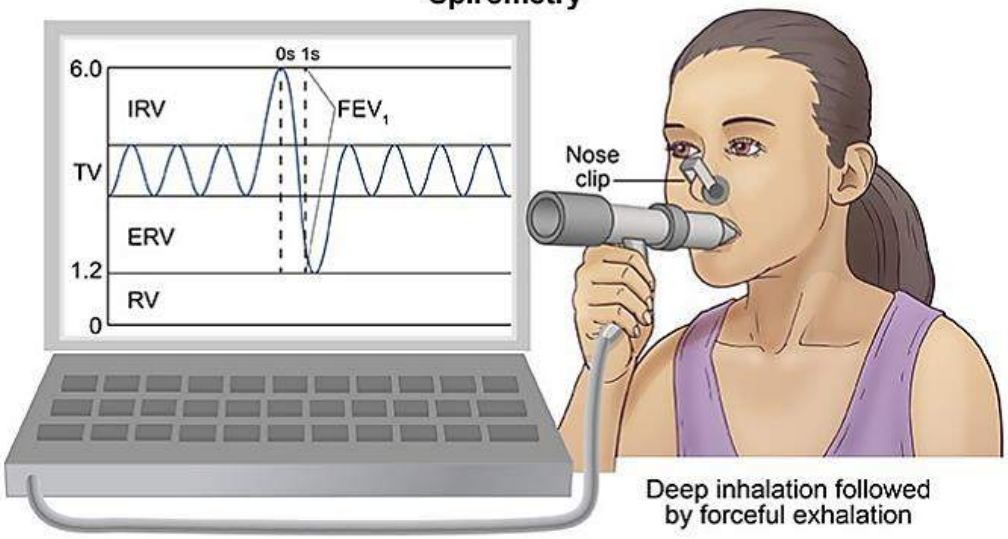
Albuminocytologic dissociation

Both are equally effective and choice depends on pt-specific risk factors and availability

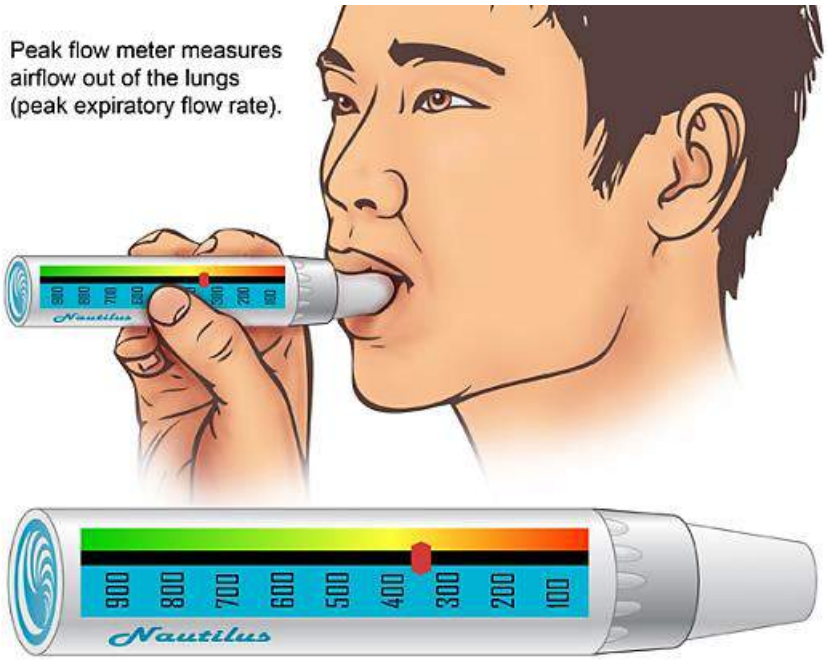
- The final stage is flaccid paralysis with absent deep-tendon reflexes and nerve conduction velocities.
- Glucocorticoids are not beneficial
- Campylobacter jejuni most frequently associated. Other organisms: Herpes virus, Mycoplasma and H. influenza also associated. Recent HIV infection and recent immunization
- More common in pts with sarcoidosis, SLE, and lymphoma.
- Recovery follows the inverse order of the initial disease progression
- Neuromuscular respiratory failure is the most life-threating complication→ once Dx of GBS confirmed→ assess pulmonary function **by serial spirometry**— FVC is the gold standard for assessing ventilation—if <20mL/kg→indicate impending respiratory arrest→ endotracheal intubation
- If spirometry not readily available or difficult in unstable pt→ peak flow meter is performed but less accurate

Diagnostic pulmonary tests		
Test	**Indications**	**Disadvantages**
Spirometry	Gold standard in evaluating pulmonary function (eg, FVC, forced expiratory volume in 1 second)	May be difficult to perform in unstable patients
Peak flow meter	Assessment of airflow out of the lungs (peak expiratory flow rate)	Less accurate than spirometry
Chest x-ray	First-line imaging of tracheal position, lung fields, bones & heart size with relatively low radiation	Insensitive for small tumors & pulmonary embolus; no information about lung function
Chest CT	Rapid & detailed visualization of tracheal position, lung fields, bones & heart size	Significant radiation exposure; no information about lung function
Pulse oximeter	Rapid assessment of oxygenation at fingertip, earlobe, or foot (infant)	Inaccurate if the extremity is cold, calloused, or moving; cannot assess ventilation
Arterial blood gas	Quantitative measurement of arterial pH, oxygen/carbon dioxide/ bicarbonate levels & base deficit	Slight risk of bleeding, infection & radial artery thrombosis

Spirometry



Functional Residual Capacity **(FRC) = RV + ERV**; Vital Capacity **(VC) = IRV + TV + ERV**; Forced expiratory volume (FEV_1); Inspiratory reserve volume (IRV); Expiratory reserve volume (ERV); Tidal volume (TV); Residual volume (RV)



TREMORS

Tremor	Clinical features
Essential	• Bilateral action tremor of the hands, usually without leg involvement • Possible isolated head tremor without dystonia • Usually no other neurologic signs • Relieved with alcohol in many cases
Parkinson's disease	• Resting tremor (4-6 Hz) that decreases with voluntary movement • Usually involves legs & hands • Facial involvement less common
Cerebellar	• Usually associated with ataxia, dysmetria, or gait disorder • Tremor increases steadily as the hand reaches its target
Physiologic	• Low amplitude (10-12 Hz) not visible under normal conditions • Acute onset with increased sympathetic activity (eg, drugs, hyperthyroidism, anxiety, caffeine) • Usually worse with movement & can involve the face & extremities

Action or postural tremor

Low frequency 3-4 Hz. Postural/action /intention tremor

Postural tremor (eg holding hand outstretched), infrequently occur with action

ESSENTIAL TREMORS

- May follow autosomal dominant pattern of inheritance
- May affect any part of body—can involve head, chin, voice and tongue
- Esp. apparent when arms are out-stretched.

- ↑ in amplitude at very end of goal directed activity, esp. fine motor movement. Can be present at rest as well
- Rx: beta blocker propranolol (not given if pt is bradycardic or has severe COPD) or primidone or topiramate. Benzos can also ↓symptoms but avoid them
- **Primidone:** anticonvulsant medication. Converts into phenylethylmelonamide and phenobarbital→ S/E: may precipitate acute intermittent porphyria→ abdominal pain, neurologic and psychiatric abnormalities (confusion, headaches, hallucinations, dizziness)→ diagnosed by checking urine porphobilinogen

ORTHOSTATIC TREMOR

- A postural tremor considered to be a variant of essential tremor.
- Orthostatic tremor occurs in the legs immediately on standing and is relieved by sitting down. It is usually high frequency (14-18 Hz) without other clinical signs or symptoms.

PARKINSON'S TREMORS

- Resting tremors—usually start in one hand and later in other hand→ rest of the body→ lower leg—"pill rolling"—4-6Hz. Can involve jaw, face, tongue and lips. Associated with rigidity. Often presenting symptom of Parkinson disease
- Anticholinergics (eg benztropine, trihexphenidyl)—treatment of choice. Trihexphenidyl—typically used in younger pts where tremor is predominant symptom

HUNTINGTON'S CHOREA

- Haloperidol is used for Huntington's chorea

HUNTINGTON DISEASE
- Autosomal dominant // CAG triplets repeat.
- characterized by choreiform movements, cognitive decline, mood dysfunction.
- number of CAG repeats may increase with subsequent generations (**anticipation**).
- begins between ages 30-50
- Atrophy of the **caudate** nucleus is a characteristic feature.
- Chorea: sudden, jerky and irregular movements of the extremities. (facial grimacing, ataxia, dystonia, tongue protrusion, writhing movements of extremities).

PARKINSON DISEASE

- Presence of any two of these three suggest clinical diagnosis→ further confirm by physical exam:
  1. Rigidity—uniform→leadpipe, or oscillating→cogwheel),
  2. Bradykinesia—narrow-base, hypokinetic, shuffling gait (festinating gait) and
  3. Tremor

Drug	Action	Side effects
Levodopa plus carbidopa	Dopamine precursor	• Somnolence, confusion, hallucinations (older patients) • Dyskinesia
Trihexyphenidyl or benztropine	Anticholinergic	• Dry mouth, blurred vision, constipation, nausea & urinary retention
Amantadine	Unclear mechanism	• Ankle edema & livedo reticularis
Apomorphine, bromocriptine, pramipexole, or ropinirole	Dopamine agonist	• Somnolence, hypotension & confusion • Hallucinations (older patients)
Entacapone or tolcapone	COMT inhibitor	• Dyskinesia, hallucinations, confusion, nausea & orthostatic hypotension
Selegiline	MAO B inhibitor	• Insomnia & confusion (elderly patients)

Agitation, dizziness nausea—these are initial symptoms.

Involuntary movements (dystonia, dyskinesia)—begin after 5-10 years of therapy in 50% pts. As a result, imp. To find initial therapeutic dose and closely monitor pt

- Dyskinesia is earlier finding with COMT inhibitors
- Anticholinergics do not improve bradykinesia but improves tremors and rigidity

Tremor:

- A resting 4 to 6 Hz tremor with a "pill rolling" quality
- Frequently first manifests in one hand, and may then slowly generalize to involve the other side of the body and the lower extremities

Rigidity:

- Baseline increased resistance to passive movement about a joint which may be uniform (lead pipe) or oscillating (cogwheel)

Bradykinesia:

- Difficulty initiating movements, as when starting to walk or rising from a chair
- Narrow-based, shuffling gait with short strides and without arm swing (festinating gait)
- Micrographia (small handwriting)
- Hypomimia (decreased facial expression)
- Hypophonia (soft speech)

Postural instability:

- Flexed axial posture
- Loss of balance during turning or stopping
- Loss of balance when pushed slightly from a stationary bipedal stance
- Frequent falls

Parkinson psychosis: **UW**:12152
- visual hallucinations and paranoid delusions.
- First step is antiparkinson medication adjustments → fail → anti-psychotic (**quetiapine,** clozapine,or pimavanserin).

RESTLESS LEG SYNDROME

Restless legs syndrome	

Diagnostic criteria	**Urge to move the legs and**
	• Unpleasant sensations in the legs or other body parts (eg, arms) that begin/worsen during inactivity (lying down, sitting)
	• Unpleasant sensations in the legs that:
	  ○ Are relieved by movement (walking, stretching)
	  ○ Worsen or occur only in the evening/night
	• Symptoms not explained by another disorder

Secondary causes	• Iron deficiency anemia • Uremia (end-stage renal disease, chronic kidney disease) • Diabetes mellitus • Multiple sclerosis, Parkinson disease • Pregnancy • Drugs (eg, antidepressants, metoclopramide)
Treatment	**Mild/intermittent symptoms** • Supplement iron when serum ferritin ≤75 µg/L • Use supportive measures (eg, leg massage, heating pads, exercise) • Avoid aggravating factors (eg, sleep deprivation, medications) **Persistent/moderate to severe symptoms** • **First-line:** Dopamine agonists (pramipexole) • **Alternate:** Alpha-2-delta calcium channel ligands (gabapentin enacarbil)

- Evaluation should include exclusion of secondary causes and diseases that may present similarly
- Pts with comorbid insomnia, chronic pain syndrome or anxiety may benefit from alpha-2-delta calcium channel ligands over dopaminergic agents→ gabapentin is similar to GABA but targets voltage gated calcium channel
- Pts with refractory symptoms after this treatment may benefit for opioids

DEMENTIA

- MMSE score <24 is suggestive of dementia. Maximum score is 30.
- By definition, social functioning must be impaired in order to diagnose dementia

DIFFERENCE BETWEEN DEMENTIA AND NORMAL AGING

NORMAL AGING	DEMENTIA
Independence in activities of daily living (ADLs) preserved	Person becomes dependent on others for ADL
Person complains of memory loss but can provide details about incidents of forgetfulness	May complain of memory problems only if asked; unable to remember specific instances where memory loss was noticed by others
Patient is more concerned about memory loss	Close family members are more concerned about memory loss
Recent memory for important events and conversations intact	Notable decline in memory for recent important events and conversations
Occasional word-finding difficulties (expressive aphasia)	Frequent word-finding difficulty and substitutions; also some receptive aphasia
Does not get lost in familiar territory; may have to pause briefly to reorient	Can get lost for hours in familiar territory while walking or driving
Able to operate common appliances	Becomes unable to operate common appliances
Maintains previous interpersonal social skills	Shows loss of interest in social activities and inappropriate behavior
Normal performance on mental status examination	Abnormal mental status exam

- Expressive aphasia in normal adults is most likely because of some age-related impairment of dominant frontal lobe

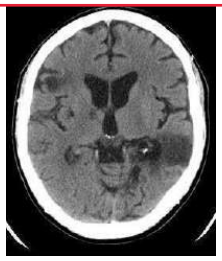
1. **MMSE** normal = ≥ 24/30

2. **Montreal cognitive assessment** normal = ≥ 26/30.

DIFFERENTIAL DIAGNOSIS OF DEMENTIA SUBTYPES

Differential diagnosis of dementia subtypes	
Alzheimer disease	• **Early, insidious short-term memory loss** • Language deficits & spatial disorientation • Later personality changes
Vascular dementia	• **Stepwise** decline • Early executive dysfunction • **Cerebral infarction** &/or deep white matter changes on neuroimaging
Frontotemporal dementia	• **Early personality changes** • Apathy, disinhibition & compulsive behavior • **Frontotemporal atrophy** on neuroimaging
Lewy body dementia	• **Visual hallucinations** • Spontaneous **parkinsonism** • Fluctuating cognition
Normal pressure hydrocephalus	• **Ataxia** early in disease • Urinary **incontinence** • **Dilated ventricles** on neuroimaging
Prion disease	• Behavioral changes • **Rapidly progressive** • **Myoclonus** &/or seizures

Vascular dementia presents as a **sudden** or **stepwise** decline in executive function after stroke, which **interferes with activities of daily living**. Patients typically have abnormal neurologic findings on examination (eg, **hemiparesis, pronator drift, Romberg sign**).



Fecal incontinence may develop in advanced disease

ALZHEIMER'S DISEASE

almost exclusively occurs in individuals over the age of 60

Clinical features of Alzheimer's disease	
Early findings	• Anterograde memory loss (immediate recall affected, distant memories preserved) • Visuospatial deficits (eg, lost in own neighborhood) • Language difficulties (eg, difficulty finding words) • Cognitive impairment with progressive decline
Late findings	• Neuropsychiatric (eg, hallucinations, wandering) • Dyspraxia (eg, difficulty performing learned motor tasks) • Lack of insight regarding deficits • Noncognitive neurologic deficits (eg, pyramidal & extrapyramidal motor, myoclonus, seizures) • Urinary incontinence

The associated risk factors include:
age, **female** gender, positive family history, head trauma and **Down's** syndrome.

Later findings usually include personality and behavioral changes (eg, apathy, agitation), confusion, disorientation

- Difficult to distinguish from pseudodementia as depression can occur as comorbid condition.
- Selective loss of cholinergic neurons

- Findings suggestive of Alzheimer's: presence of more symptoms, such as apraxia, agnosia, aphasia and disturbance in executive functioning
- Life span 3-8 years after diagnosis
- CT scan to exclude other causes→ normal initially→ later cortical and sub-cortical atrophy (only minimally more than normal controls of same age). Parietal and temporal lobes more commonly affected esp. hippocampus
- **Diagnosis:**
  - MMSE, neuropsychological testing and following diagnostic criteria:
    - Two or more areas of cognitive deficits
    - Progressively worsening memory and other cognitive function
    - No disturbance of consciousness
    - Onset after age 60 and risk ↑es with age
    - Absence of other systemic or neurologic disorder causing progressive cognitive defects
- **Rx:** psychosocial intervention and pharmacological intervention
  - **Acetylcholinesterase inhibitors**: donepezil (Aricept), galantamine (Razadyne), galantamine ER (Razadyne ER), and rivastigmine (Exelon)—for **mild-to-moderate dementia**—improve quality of life and cognitive functions, including memory, language, thought, and reasoning. Donepezil is approved for all stages
  - **N-methyl-D-aspartate receptor antagonist i.e.** Memantine**:** for **moderate to severe dementia**

PICK'S DISEASE/FRONTO-TEMPORAL DEMENTIA

- Early onset—40-60 years. 40% have positive family history
- Similar to Alzheimer but disease progression is different
- Personality change (euphoria, disinhibition and apathy), loss of social restraints, compulsive behaviour (eg. peculiar eating habits), hyperorality→ disorientation and memory loss→ mute, immobile and incontinent. Visuo-spatial functions usually remain intact
- CT: frontal and temporal lobes atrophy

LEWY BODY DEMENTIA

- Cause of 10-20% of dementias in the United States.
- **Characterized by**: alterations in consciousness, disorganized speech, visual hallucinations, extrapyramidal symptoms, and relatively early compromise of executive functions. Visuospatial decline before memory deficits (opposite of AD). Prominent or persistent memory impairment may not occur early but usually evident with progression
- **Autopsy findings**: "Lewy bodies," or eosinophilic intracytoplasmic inclusions→ represent accumulations of alpha-synuclein protein—seen in neurons of the substantia nigra, locus ceruleus, dorsal raphe, and substantia innominata.
- **Treatment of motor and psychiatric symptoms:** acetylcholinesterase inhibitors like rivastigmine. For hallucinations refractory to acetylcholinesterase inhibitors→ atypical anti-psychotics may benefit. Poor response to dopaminergic agonists and worsening of features with neuroleptic drugs
- Lewy bodies are also present in Parkinson's disease. The key distinction between these two: early appearance of dementia in Lewy body disease and of motor symptoms in Parkinson's disease.

Diagnostic features of Lewy body dementia	
Central (required)	• Progressive cognitive decline, dementia
Core	• Fluctuating cognition • Visual hallucinations (detailed, recurrent) • Spontaneous parkinsonism features
Suggestive	• REM sleep disorder (eg, vivid dreams) • Severe neuroleptic sensitivity • SPECT or PET showing low dopamine transporter uptake in basal ganglia
Supportive	• Repeated falls • Syncope or near-syncope • Severe autonomic dysfunction • Hallucinations or delusions • Depression
Conflicting (make LBD less likely)	• Neuroimaging showing cerebrovascular disease • Parkinsonism appearing first with dementia later • Other physical or brain condition that explains clinical presentation

With pronounced variation in attention and alertness

LBD = Lewy body dementia; PET = positron emission tomography;
REM = rapid eye movement; SPECT = single-photon emission computed tomography.

- Two of the core features are essential for probable diagnosis and 1 for possible diagnosis

PSEUDODEMENTIA/ REVERSIBLE COGNITIVE IMPAIREMENT

- Elderly pt with major depression may present with pseudodementia
- Dementia and pseudodementia may present similarly and CT findings may be normal in Alzheimer's disease as well— although dementia will be associated with other findings too
- No single test to distinguish between dementia and pseudodementia—however, dexamethasone suppression test (DST) is abnormal in 50% of pseudodementia pts and may help physician to detect endogenous depression
- Can also have slow movements due to psychomotor retardation
- An interesting difference between pseudodementia and dementia of Alzheimer's origin is that patients with pseudodementia tend to be "overly concerned" about their memory loss and often seek help. On the other hand, patients with Alzheimer's tend to be indifferent to their memory loss and are usually brought in by their families
- **Rx:** anti-depressants→ improvement in depression but not cognitive symptoms→ consider Alzheimer and give donepezil (acetylcholinesterase inhibitors)

CREUTZFELDT-JAKOB DISEASE

- Spongiform encephalopathy caused by prion
- Features other than table: insomnia, apathy, behaviour abnormality, and sharp, bi- or tri-phasic, synchronous discharges on EEG. Ultimately pt loses ability to speak and move and become comatose
- Most pts die within 1 year of onset of symptoms
- Key features of this disease include a long incubation period, characteristic spongiform changes, and lack of inflammatory response. Most cases are sporadic (85%), with the remainder being hereditary or iatrogenic (due to contaminated transplants or surgical instruments).
- Rx: supportive

Creutzfeldt-Jakob disease

Probable diagnosis:

- Rapidly progressive dementia
- 2 out of 4 clinical features:
  - Myoclonus
  - Akinetic mutism
  - Cerebellar or visual disturbance
  - Pyramidal/extrapyramidal dysfunction (hypokinesia)
- Periodic sharp wave complexes on EEG &/OR
- Positive 14-3-3 CSF assay

Definitive diagnosis includes above features in combination with

- Brain biopsy findings (gold standard) OR
- Demonstrated *PRNP* gene mutations

HIV-associated dementia "HAD"

- untreated HIV patients with a **CD4+ cell count of < 200** and in patients with **long-standing HIV** disease.

1. Onset is typically subacute and characterized by increasing apathy and impaired attention

2. Subcortical Sx: slowed movement and difficulty with smooth limb movement. (happens EARLY in the disease)

3. memory decline.

- Adherence to **antiretroviral therapy** decreases the chance of developing HAD, and resuming treatment may improve HAD symptoms.

UW = **11954**

NEUROSYPHILIS

- Neurosyphilis appears in 15-20% of late syphilis cases.
- There are four types.
- In general paresis type, there is general involvement of the cerebral cortex. There is usually a decrease in concentrating power, memory loss, dysarthria, tremors of fingers and lips, irritability, and mild headaches. In addition, there are also characteristic personality changes, with the patient becoming slovenly, irresponsible, confused and psychotic.

MULTIPLE SYSTEM ATROPHY/ SHY-DRAGER SYNDROME

- Degenerative disease characterized by:
  1. Parkinsonism
  2. Autonomic dysfunction (postural hypotension, abnormal sweating eg dry skin, disturbance of bowel or bladder control, abnormal salivation or lacrimation eg dry eyes or dry mouth, impotence, gastroparesis, etc.)
  3. Widespread neurological signs (cerebellar, pyramidal or lower motor neuron)
- Accompanying bulbar dysfunction and laryngeal stridor may be fatal
- **Rx:** anti-Parkinsonism drugs—not effective. Treatment aimed at: intravascular volume expansion with fludrocortisone, salt supplementation, alpha-adrenergic agonists and application of constrictive garments to lower body

RILEY DAY SYNDROME OR FAMILIAL DYSAUTONOMIA

- Autosomal-recessive disease seen predominantly in children of Ashkenazi Jewish ancestry.
- Characterized by: gross dysfunction of the autonomic nervous system with severe orthostatic hypotension

DELIRIUM

Causes of delirium	
Predisposing risk factors	• Dementia • Parkinson's disease • Prior stroke • Advanced age • Sensory impairment
Precipitating factors	• **Drugs** (eg, narcotics, sedatives, antihistamines, muscle relaxers, polypharmacy) • **Infections** (eg, pneumonia, urinary tract infection, meningitis) • **Electrolyte disturbances** (eg, hyponatremia, hypercalcemia) • **Metabolic derangements** (eg, volume depletion, vitamin B12 deficiency, hyperglycemia) • **Systemic illness** (eg, congestive heart failure, hepatic failure, malignancy) • **Central nervous system** (eg, seizure, stroke, head injury, subdural hematoma)

- Waxing and waning levels of consciousness
- Initial evaluation should include a focused history and physical evaluation (including pulse oximetry), review of all medications, complete blood count, serum electrolytes, and urinalysis and possible imaging
- Infection identified→ treat ASAP
- **Rx:** Regardless of cause, treatment of agitation in elderly: **low dose haloperidol.** Atypical antipsychotics (risperidone, quetiapine) may also be used. Usage of typical and atypical antipsychotics is safe in acute setting, but prolonged use ↑ mortality in elderly
- Typical antipsychotics should not be used in Lewy body dementia, who may exhibit neuroleptic hypersensitivity (severe parkinsonism and impaired consciousness with neuroleptic administration)

Delirium	
Risk factors	• Advanced **age** • Neurologic disorder (eg, **dementia**, stroke) • Sensory impairment (eg, hearing loss)
Precipitating causes	• Central nervous system insult (eg, seizure, stroke) • **Infection** (eg, pneumonia, urinary tract) • **Medications** (eg, sedatives) • **Metabolic disturbances** (eg, electrolytes, uremia)
Clinical features	• Acute-onset, **fluctuating** mental status changes • Disturbance in attention • Sleep-wake changes (eg, sundowning)
Management	• Avoid polypharmacy, physical restraints • Maintain normal sleep-wake cycle • Provide frequent reorientation • **Treat underlying cause** (eg, antibiotics)

HEAT STROKE

Exertional heat stroke	
Risk factors	• Strenuous activity during **hot & humid weather** • Dehydration • Poor acclimatization • Lack of physical fitness • Obesity • Medications: Anticholinergics, antihistamines, phenothiazines, tricyclics
Clinical manifestations	• Core temperature >40 C (104 F) immediately after **collapse** **AND** • Central nervous system dysfunction: Altered mental status, confusion, irritability, seizure • Additional organ or tissue damage: Renal/hepatic failure, disseminated intravascular coagulation, acute respiratory distress syndrome Rhabdomyolysis
Management	• Rapid cooling: Ice water immersion preferred; can consider: high-flow cool water dousing, ice/wet towel rotation, evaporative cooling • Fluid resuscitation • Electrolyte correction • Management of end-organ complications • No role for antipyretic therapy

- EHS exists on the same spectrum as heat exhaustion with a body temperature >40 C (104 F) but is characterized in addition by central nervous system (CNS) dysfunction (eg, confusion, irritability, seizures).
- Main mechanism of heat dissipation: evaporation of sweat. If humidity >75% → sweating overwhelmed→ exertional heat illness
- Other C/F: include dry or sweaty skin, hypotension, tachycardia, hyperventilation, diarrhea, cramps, and ataxia.
- Mortality rate 20%

NONEXERTIONAL OR CLASSIC HEAT STROKE

- Evaporative cooling (ie, spraying the naked patient with lukewarm water and running fans to circulate air),is preferred for nonexertional or classic heat stroke (seen in elderly patients with underlying comorbidities that limit their ability to cope with excessive heat) as ice water immersion is associated with higher morbidity and mortality in these patients.

SEIZURES AND SYNCOPE

Comparison of syncope & seizures		
	Seizures	**Syncope (typically vasovagal)**
Circumstances	• Sleep loss • Emotions • Alcohol withdrawal • Flashing light	• Upright position • Emotions • Heat • Crowded places
Clinical clues	• Aura (eg, olfactory hallucinations) • Can occur with sleeping/sitting position • Head movements • Tongue biting • Rapid, strong pulses	• Symptoms of presyncope (eg, lightheadedness) • Unlikely to occur with sleeping/sitting position (except in cardiac arrhythmia) • Rarely, several clonic jerks can occur with prolonged cerebral hypoperfusion • Pallor & diaphoresis • Weak, slow pulses
Sequelae	• Delayed return to baseline • Usually sleepy & confused afterward (postictal state)	• Immediate spontaneous return

WORK-UP FOR FIRST TIME SEIZURE

- Initial diagnostic evaluation of a **first time seizure** in an **adult** is aimed at excluding metabolic (e.g. hypoglycaemia, electrolyte disturbances) and toxic causes (amphetamine use and alcohol/benzo withdrawal).
  1. **Basic lab tests:** serum electrolytes, glucose, calcium, magnesium, CBC, RFTs, LFTs, and toxicology screen
  2. **ECG** in pts with LOC to rule out arrhythmia
  3. **Imaging:** once metabolic and toxic causes ruled out→ neuroimaging performed (eg brain MRI or CT—CT without contrast in emergency situation as it can be performed in unstable pt & needed to rule out intracranial bleed and MRI in non-emergency and elective situations due to better visualization) to evaluate structural brain abnormalities (e.g. tumor, stroke, cerebral infarction, mesial temporal sclerosis, infections, cortical dysplasia, vascular malformations, traumatic brain injury)
  4. **Lumber puncture** after imaging has ruled out space occupying lesion (reserved for suspected meningitis)
  5. **Routine EEG—**risk-stratifying patients after a first-time seizure once metabolic and toxic etiologies have been excluded. The presence of epileptiform activity on an EEG indicates a higher risk of seizure recurrence and therefore may justify the need to start anti-epileptic therapy.

STATUS EPILEPTICUS

- **Definition:**
  - **Historical:** a single seizure lasting > 30min
  - **Latest:** any single seizure lasting > 5min or a cluster of seizures with pt not recovering a normal mental status in between
- Occur in 30% pts with epilepsy esp. those non-compliant with medication
- Recent studies suggest that a brain that has seized for > 5 min is at ↑ risk of developing permanent injury to excitatory cytotoxicity
- Cortical laminar necrosis is the hallmark of prolonged seizures and can lead to persistent neurologic deficits and recurrent seizures
- MRI of the brain will generally show evidence of cortical hyperintensity on diffusion-weighted imaging suggesting infarction.

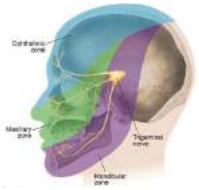
SYNCOPE

Syncope	
Likely etiology	**Clinical clues to diagnosis**
Vasovagal or neurally mediated syncope	• Triggers: Prolonged standing or emotional distress, painful stimuli • Prodromal symptoms: Nausea, warmth, diaphoresis
Situational syncope	• Triggers: Cough, micturition, defecation
Orthostatic hypotension	• Postural changes in heart rate/blood pressure after standing suddenly
Aortic stenosis, hypertrophic cardiomyopathy, anomalous coronary arteries	• Syncope with exertion or during exercise
Ventricular arrhythmias	• Prior history of coronary artery disease, myocardial infarction, cardiomyopathy, or reduced ejection fraction
Sick sinus syndrome, bradyarrhythmias, atrioventricular block	• Sinus pauses on monitor, prolonged PR interval or QRS duration
Torsades de pointes (acquired long QT syndrome)	• Hypokalemia, hypomagnesemia, medications causing prolonged QT interval
Congenital long QT syndrome	• Family history of sudden death, prolonged QT interval on ECG, syncope with triggers (exercise, swimming, sudden noise, during sleep)

ECG = electrocardiogram.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

- Carbamazepine—treatment of atypical bipolar depression and trigeminal neuralgia—effective in 80% cases
  - S/E: Aplastic anemia can occur with prolonged use; therefore, routine CBC is included in follow-up
- If medication fails to control pain→ surgical gangliolysis or suboccipital craniectomy for decompression of trigeminal nerve are options



- Trigeminal neuralgia is characterized by recurrent and sudden-onset severe, stabbing pain along the **V2** (maxillary) and **V3** (mandibular) branches of the trigeminal nerve.

- **Multiple sclerosis** should be suspected when trigeminal neuralgia presents **bilaterally.**

CAROTIDYNIA

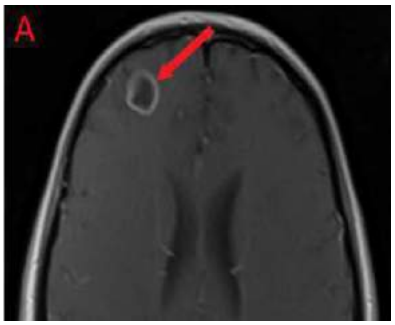
- Neurological condition caused by inflammation of the carotids and the vagus.
- The pain is sharp and localized to the carotid artery distribution in the neck. Usually, the intensity of pain is much less.
- The diagnosis is clinical, although an MRI is sometimes required.

BURNING MOUTH SYNDROME

- Rare cause of facial pain.
- It is caused by a virus and the individual has reddened mucosa and has significant pain. The condition is aggravated by dryness.
- It is treated by supportive care.

BRAIN ABSCESS

Risk factors for brain abscess		
Predisposing problem	**Pathogenesis**	**Affected area(s)**
Otitis media, mastoiditis	Direct spread	Temporal lobe, cerebellum
Frontal or ethmoid sinusitis	Direct spread	Frontal lobe
Dental infection	Direct spread	Frontal lobe
Bacteremia from other sites of infection, cyanotic heart disease	Hematogenous spread	Multiple abscesses along distribution of middle cerebral artery (gray-white matter junction)



Brain abscess	
Microbiology	• Anaerobic organisms (eg, viridans streptococci) • *Staphylococcus aureus* • Gram-negative organisms
Pathogenesis	Bacterial invasion due to: Direct extension from contiguous infection (eg, sinusitis, mastoiditis, otitis media) OR Hematogenous spread from distant infection (eg, endocarditis, osteomyelitis)
Clinical manifestations	• Headache, mental status changes • Focal neurologic deficits, seizure • Fever
Treatment	• Surgical drainage or aspiration • Prolonged antibiotic therapy

50% due to direct extension—most common flora recovered: Viridans (eg S. mitis, S. intermedius, S. oralis, S. mutans) and other anaerobes (eg Prevotella, Peptostreptococcus, Bacteroides

25% result from hematogenous spread—gram –ve organisms and S. aureus are implicated. Rarely, due to direct inoculation from trauma or neurosurgery—S. aureus implicated

4-8wks

- Classic triad of headache, focal neurologic deficit and fever— <20%. Fever is present in only 50% cases. ↑ ICP—depicted by morning or nocturnal headache and vomiting is usually the most prominent sign.
- ~~CT with contrast (superior for depicting bone, fast) or MRI (superior for soft-tissue details, does not use ionizing radiations, more sensitive for early cerebritis and is better at delineating the extent of ring enhancement and differentiating between edema and necrosis)~~ showing ring-enhancing lesion (uniform contrast enhancement) is highly specific but should be confirmed by culture of aspirated or resected material

SPINAL EPIDURAL ABSCESS

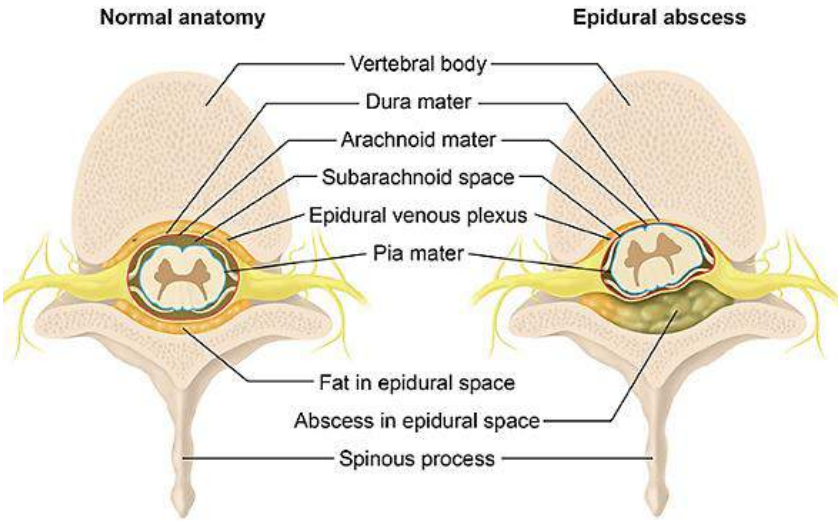
Spinal epidural abscess	

Epidemiology	• ***Staphylococcus aureus*** (65%)
	• Inoculating sources
	  ○ Distant infection (eg, cellulitis, joint/bone)
	  ○ Spinal procedure (eg, epidural catheter)
	  ○ Injection drug use

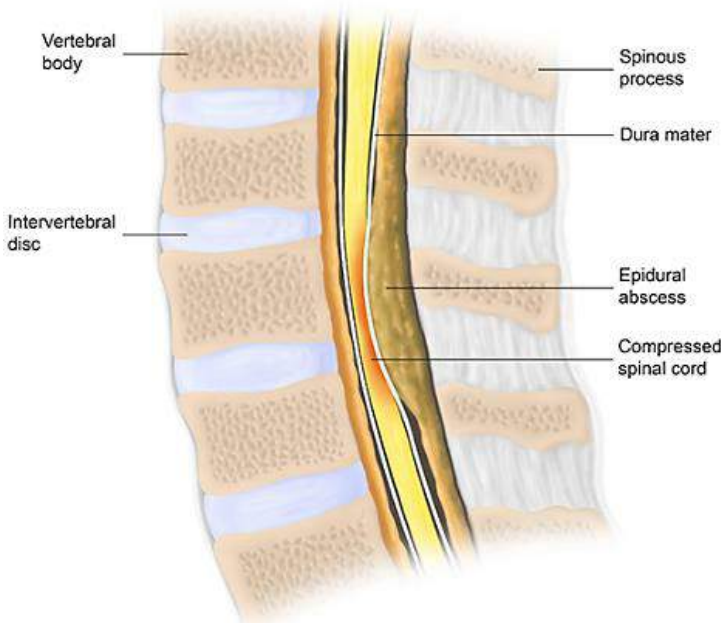
Manifestations	• Classic triad
	  ○ Fever (~50%)
	  ○ **Focal/severe back pain**
	  ○ **Neurologic findings** (eg, motor/sensory change, bowel/bladder dysfunction, paralysis)

Diagnosis	• ↑ ESR • Blood & aspirate cultures • **MRI of the spine**
Treatment	• Broad-spectrum antibiotics (eg, vancomycin plus ceftriaxone) • Aspiration/surgical decompression

Spinal epidural abscess



Epidural abscess: lateral view



CSF FINDINGS

Cerebrospinal fluid analysis			
Diagnosis	**WBC count (cells/μL)**	**Glucose (mg/dL)**	**Protein (mg/dL)**
Normal	0–5	40–70	<40
Bacterial meningitis	>1000	<40	>250
Tuberculosis meningitis	5–1000	<10	>250
Viral meningitis	100–1000	40–70	<100
Guillain-Barré	0–5	40–70	45–1000

HERPES ENCEPHALITIS

- Most common cause of fatal sporadic encephalitis in US; beyond neonatal period, HSV-1 is the most common cause
- **C/F:** it presents with acute onset (<1wk duration) of
  - Focal neurological findings (altered mentation, focal cranial nerve deficits, ataxia, hyperreflexia, or focal seizures)
  - Fever in 90% pts
  - Behavioural changes can be seen, and behavioural syndromes like hypomania, Kluver-Bucy syndrome (hyperphagia, hypersexuality) and amnesia have been reported
- **CSF findings:**
  - Lymphocytic pleocytosis
  - ↑ no. of RBCs (hemorrhagic destruction of temporal lobes)
  - ↑ proteins
  - ↓ glucose generally not seen
  - PCR analysis of HSV DNA in CSF (highly sensitive and specific)—gold standard of diagnosis (replacing brain biopsy)
- **Brain imaging:**
  - Temporal lobe lesions—MRI preferred over CT which is normal in 50% cases
- **Focal EEG findings:**
  - Prominent intermittent high amplitude slow waves—in >70-80% cases and can be used in some cases as corroborative evidence
- **Rx:** IV acyclovir—treatment of choice

TICK BORNE PARALYSIS

- Progressive ascending paralysis over hours to days
- May be localized or more pronounced in one leg or arm
- Fever typically not present; h/o fever or prodromal illness makes the diagnosis unlikely
- Normal sensations

- Normal autonomic system (unlike Guillain-Barre syndrome)
- CSF normal
- **Etiology:** tick needs 4-7 days for the release of neurotoxin→ paralysis
- **Rx:** meticulous search for tick usually reveals a tick→ removal leads to improvement within an hour and complete recovery after several days

PRIMARY CNS LYMPHOMA IN HIV PATIENT

- Altered mental status, EBV DNA in CSF and solitary weakly ring-enhancing periventricular mass on MRI
- **D/D:** Toxoplasmosis: multiple, ring-enhancing, spherical lesions in basal ganglia, uncommon in pt taking TMP-SMX. Positive serology is common in US and non-diagnostic

ACOUSTIC NEUROMA 

- Best diagnosed by MRI with gadolinium staining—preferred over CT. Audiometry is the best initial screening laboratory test for acoustic neuroma
- Young age, multiple café-au-lait spots, usually b/l→ neurofibromatosis type II
- Usually u/l in sporadic cases but arises after 40 years
- **Neurofibromatosis type 2:**
  - Autosomal dominant—caused by a mutation in tumor suppressor gene on chromosome 22
  - Severe variant: Wishart—caused by frameshift or nonsense mutation
  - Milder variant: Gardner—result from splice site or missense mutation

CNS TUMORS

GLIOBLASTOMA MULTIFORME

- Personality change and strange behaviour→ localizes lesion to frontal lobe
- CT/MRI: Butterfly lesion with central necrosis is classic and heterogeneous, serpiginous contrast enhancement is typical of high grade astrocytoma

MENINGIOMA

- Benign primary brain tumor
- Common in middle aged and elderly women
- Extra-axial, well-circumscribed, dural based mass, round homogenously enhancing on MRI—usually undergo partial calcification
- Can cause focal neurologic symptoms
- Dx: confirmed intraoperatively
- Rx: complete surgical resection in symptomatic cases→ cures in most cases. Focused tumor radiation (stereotactic radiosurgery) can be considered in partially resected or unresectable tumors

SELLAR MASSES

Clinical features of sellar masses	
Causes	**Benign tumors** • Pituitary adenoma (most common) • Craniopharyngioma (50% age >20) • Meningioma • Pituicytoma (low-grade glioma) **Malignant tumors** • Primary (eg, germ cell tumors, chordoma, lymphoma) • Metastatic (eg, breast, lung)
Clinical presentation	• Diplopia, bitemporal hemianopsia, vision loss • Headache • Hormonal deficiencies • Can be found incidentally on brain imaging

CRANIOPHARYNGIOMA

- Arise from Rathke's pouch
- 50% cases > 20 years esp. between 55 to 65
- Grow gradually and can cause slowly progressive symptoms
- Dx: CT or MRI
- Rx: surgery and/or radiation

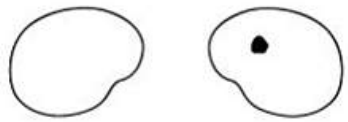
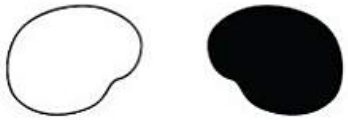
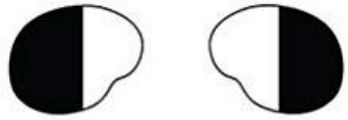
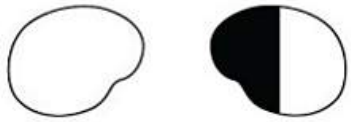
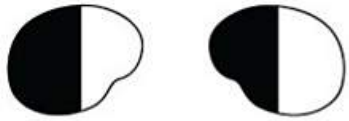
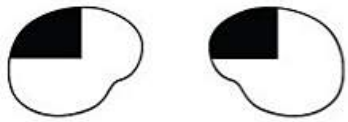
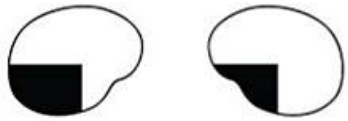
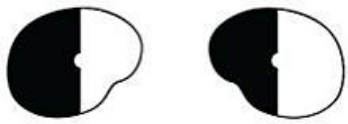
METASTATIC BRAIN TUMOR

- Most common type of intracranial brain tumor
- Can be: solitary or multiple
- Location: usually grey-white matter junction

Clinical features of metastatic brain cancer	
Incidence	Order of increased metastatic brain frequency: Lung > Breast > Unknown primary > Melanoma > Colon
Primarily solitary brain metastases	• Breast • Colon • Renal cell carcinoma
Multiple brain metastases	• Lung cancer • Malignant melanoma
Rare brain metastases	• Prostate cancer • Esophageal cancer • Oropharyngeal cancer • Hepatocellular carcinoma • Non-melanoma skin cancers

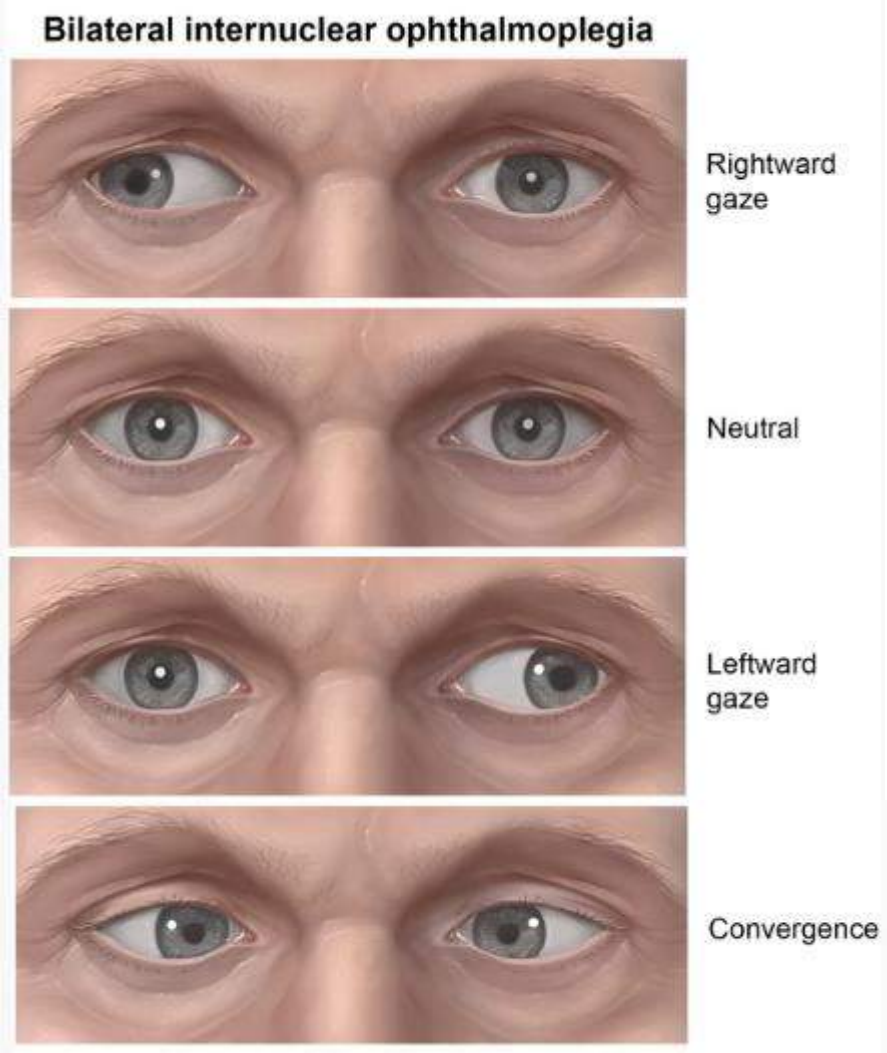
- Frequently seen in pts with non-small cell lung cancer (NSCLC)—approx. 80% metastatic brain tumors are lung cancers
- Favourable survival outcomes after diagnosis of brain mets: age <65, good functional performance, and stable extracranial disease
- Aggressive treatment is generally required to improve survival and control CNS disease
- **Single brain metastasis** in surgically accessible location and good performance status→ surgical resection is best therapeutic option. This is typically followed by stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT) to tumor bed
- **Pts who are not surgical candidates, have surgically inaccessible lesion or smaller mets (<3cm)**→ SRS
- **Multiple brain mets or poor performance status**→ WBRT or supportive care is typically recommended
- **Brachytherapy:** implantation of a radioactive source directly into an intracerebral mass or surgical cavity, allowing higher radiation doses to be delivered directly into the brain without affecting other organs. It is typically used in conjunction with surgery, or after recurrence following WBRT or surgery.
- Chemotherapy might be used in case of brain metastasis from chemosensitive tumors (eg, small cell lung cancer, lymphoma, choriocarcinoma).

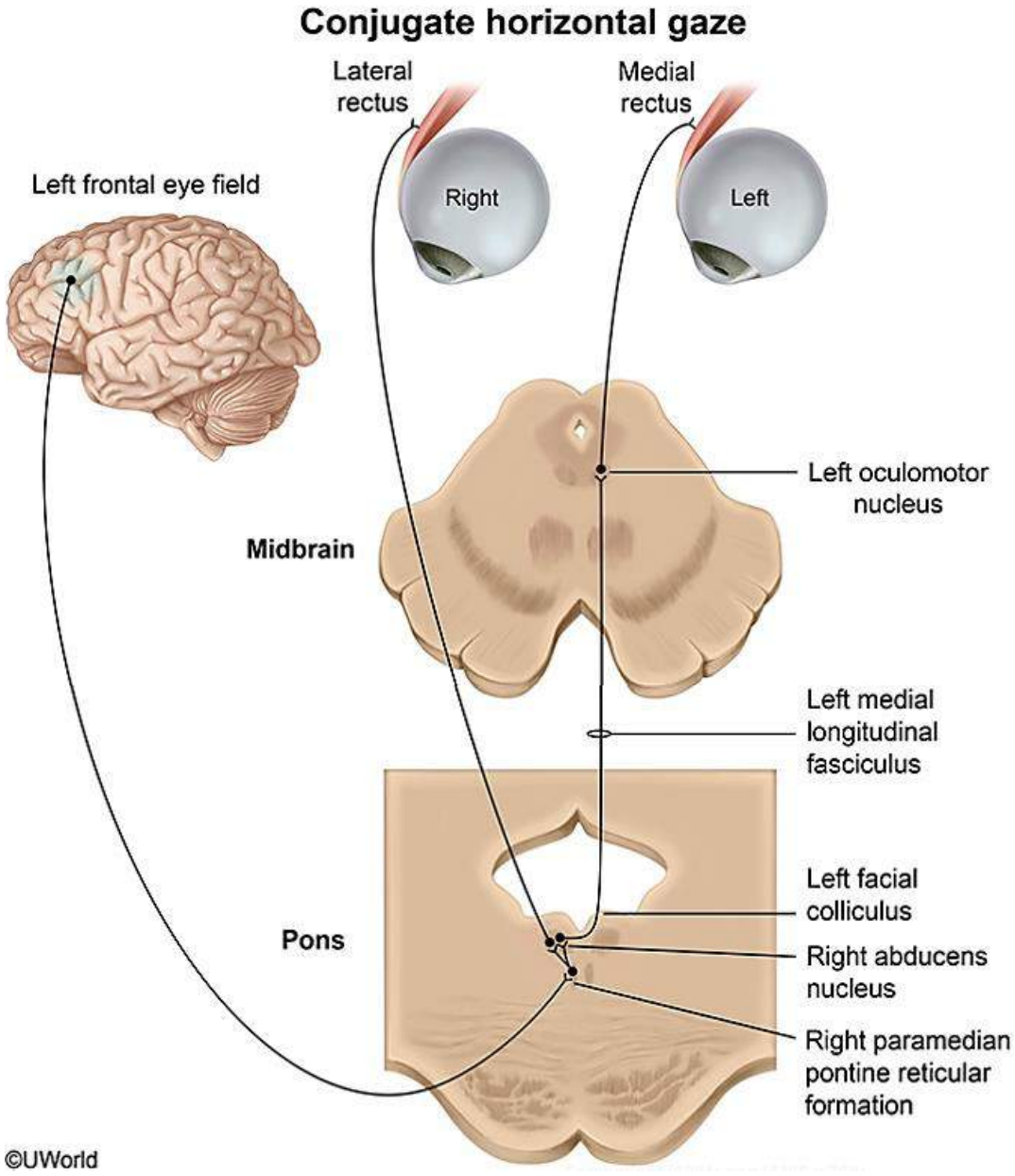
VISUAL FIELD DEFECTS

Visual field defect	Location of lesion	Possible causes
A. Monocular scotoma 	Partial lesion in the retina, optic disc, optic nerve	Macular degeneration, optic neuritis
B. Right anopia 	Right optic nerve	Retinal artery or central retinal vein occlusion
C. Bitemporal hemianopia 	Optic chiasm	Pressure exerted by a pituitary tumor, craniopharyngioma, aneurysm of anterior communicating artery
D. Right nasal hemianopia 	Right peri-chiasmal lesion	Calcification or aneurysm of the internal carotid artery impinging on uncrossed, lateral retinal fibers
E. Left homonymous hemianopia 	Right optic tract or optic radiation	Optic tract: occlusion of anterior choroidal artery Optic radiation: occlusion of a middle cerebral artery branch or lesion involving posterior limb of internal capsule
F. Left homonymous superior quadrantanopia ("pie in the sky") 	Right temporal lobe (Meyer's loop)	Lesion or stroke involving temporal lobe
G. Left homonymous inferior quadrantanopia ("pie on the floor") 	Right parietal lobe (dorsal optic radiation)	Lesion or stroke involving parietal lobe
H. Left homonymous hemianopia with macular sparing 	Right primary visual cortex (occipital lobe)	Occlusion of posterior cerebral artery. Macula is spared due to collateral blood from the middle cerebral artery

INTERNUCLEAR OPHTHALMOPLEGIA

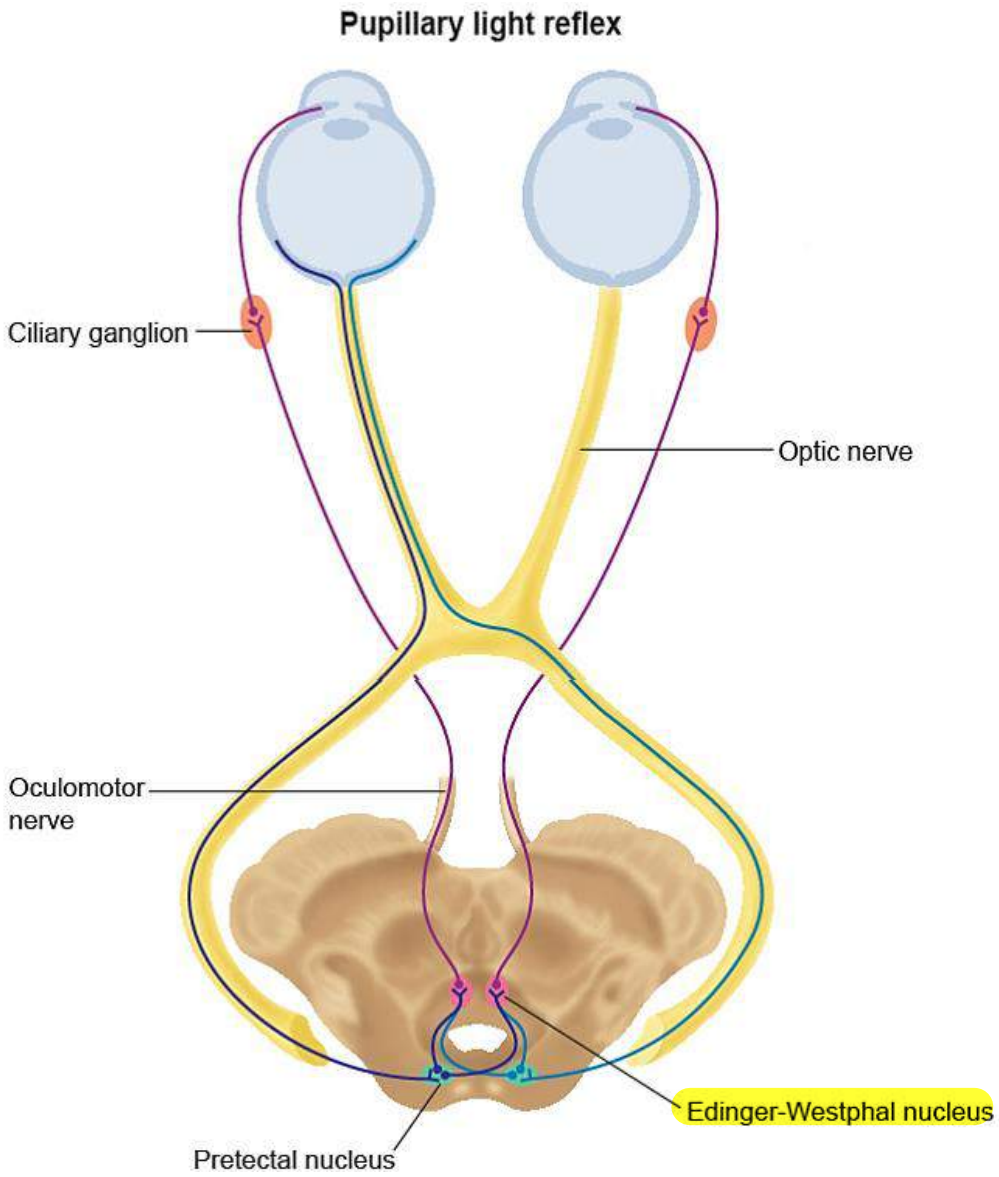
- A disorder of conjugate horizontal gaze in which the affected eye (ipsilateral to the lesion) is unable to adduct and the contralateral eye abducts with nystagmus. Convergence and the pupillary light reflex are preserved.
- Internuclear ophthalmoplegia results from damage to the heavily myelinated fibers of the medial longitudinal fasciculus (MLF). The MLF is a paired neural tract that mediates communication between CN III (oculomotor) and CN VI (abducens) nuclei, allowing for coordinated horizontal eye movements.
- **Unilateral MLF** lesions can occur with lacunar stroke in the pontine artery distribution;
- **Bilateral lesions** are classically seen in multiple sclerosis





EDINGER WESTPHAL NUCLEUS INJURY

- The Edinger-Westphal nucleus provides preganglionic parasympathetic outflow to the eye. Damage to this structure would result in an ipsilateral fixed and dilated pupil that is nonreactive to light or accommodation



CRANIAL NERVE III (OCULOMOTOR NERVE) NEUROPATHY

- Somatic and parasympathetic fibers of CN III have different nerve supplies.
- Can be due to ischemia or compression

ISCHEMIC NEUROPATHY

- Occurs in diabetes
- Only affects somatic fibers→ ptosis, down and out gaze. Accommodation and pupil's response to light remains intact

COMPRESSION NEUROPATHY

- Due to transtentorial (uncal) herniation or aneurysm of posterior communicating artery
- Both somatic and parasympathetic fibers affected→ ptosis, down and out gaze and fixed, dilated pupil and no accommodation reflex

CRANIAL NERVE IV (TROCHLEAR) NEUROPATHY

- Traumatic or idiopathic
- Presents with vertical diplopia that worsens when the affected eye looks down and toward the nose (eg, walking downstairs, reading).

- Patients may compensate by tucking the chin and tilting the head away from the affected eye

CORNEAL ABRASION

Clinical features of corneal abrasion	
Etiology	• Trauma (eg, fingernails, paws) or foreign body (eg, wood, glass, paper) lodging under the lid • Contact lens use leading to defects in corneal epithelium • Spontaneous (no obvious foreign body or injury)
Clinical presentation	• Severe eye pain due to trigeminal nerve sensory innervation (except in patients with trigeminal nerve dysfunction due to tumor, trauma, or prior zoster infection) • Possible sensation of foreign body in the eye • Photophobia with reluctance to open the eye
Evaluation	• Penlight test to document pupillary function & inspect for foreign body • Visual acuity with ophthalmology referral if decreased • Fluorescein examination **after** above tests to show corneal staining defect

- Indications for ophthalmology referral include ulceration, pus, drop in visual acuity (the potential cause of blurry vision in this patient), or lack of healing within 3-4 days

ACUTE ANGLE CLOSURE GLAUCOMA

- Usually occur in individuals >60 years
- Due to sudden narrowing or closure of anterior chamber angle.
- In pts with ACG, lens is located more forward and rests against the iris→ partially covers anterior chamber angle and prevent normal flow of aqueous humor (through pupil and into anterior chamber)→ ↑ intraocular pressure
- **Causes of Acute ACG:** sudden angle closure in response pupillary dilation from medications (e.g. anticholinergics like tolterodine, sympathomimetics, and decongestants) or other stimuli (e.g. dim light)
- **Risk factors:** more common in women (especially age >40), Asian and Inuit populations, and individuals with farsightedness.
- **C/F:** rapid onset severe eye pain, halos around eye, eye appear injected and pupils will be ~~mid-~~ dilated and poorly responsive to light, tearing and headache with N/V as intraocular pressure increases
- **Untreated acute ACG:** can lead to severe and permanent vision loss within 2-5 hours of symptom onset

OPTIC NEURITIS

- Optic neuritis (acute vision loss, pain, afferent pupillary defect) most commonly occurs in women age <50 and is often an initial presentation of multiple sclerosis. Optic neuritis is rarely associated with nausea/vomiting

HEARING LOSS

Classification & features of hearing loss		
Type	**Sensorineural**	**Conductive**
Cause	Disorder involving inner ear, cochlea, or auditory nerve	Any cause that limits sound from gaining access to the inner ear
Examples	• Presbycusis • Meniere disease • Barotrauma • Acoustic neuroma • Cerebrovascular ischemia	• Otitis externa or media • Cholesteatoma • Trauma • Cerumen • Tympanic membrane perforation

PRESBYCUSIS

- Progressive bilaterally symmetric and predominantly high-frequency sensorineural hearing loss that occurs over many years
- Affects >50% of adults > 75 years
- **Pathogenesis:** Due to degenerative changes of inner ear or cochlear portion of eighth cranial nerve
- **C/F:** usually hear well in one-to-one conversation in a quiet room but hearing significantly ↓es with even small amount of competing noise. Subjective bilateral **tinnitus** can develop as the hearing loss progresses and is typically described as a steady or continuous ringing or rushing sound.
- **Consider other diagnosis if:** U/L tinnitus, pulsatile tinnitus or tinnitus associated with other U/L otologic features is present

MENIERE DISEASE

- Meniere disease (excessive accumulation of endolymph in the membranous labyrinth) is characterized by recurrent episodes of vertigo as well as unilateral aural fullness, tinnitus, and sensorineural hearing loss.

CHOLESTEATOMA

- Erosive and expansile growth consisting of keratinizing squamous epithelium, which can cause destruction of the bones of the middle ear (ossicles) and sensorineural structures of the inner ear
- May have conductive and/or sensorineural hearing loss associated with intermittent ear discharge, tinnitus, and balance problems.
- Otoscopic examination typically shows a discrete white plaque on the tympanic membrane with or without perforation or retraction.

OTOSCLEROSIS

- Development of sclerotic changes within the ossicles of the middle ear→ progressive conductive hearing loss with a normal otoscopic examination

VERTIGO

Common causes of vertigo	
Ménière disease	• Recurrent episodes • Unilateral **hearing loss & tinnitus** • Feeling of fullness in the ear
BPPV	• Brief episodes triggered by head movement • Dix-Hallpike maneuver causes nystagmus
Vestibular neuritis	• Acute, **single episode** that can last days • Often follows viral syndrome • Abnormal head thrust test
Migraine	• Vertigo associated with headache or other migrainous phenomenon (eg, visual aura) • Symptoms resolve completely between episodes
Brainstem/ cerebellar stroke	• Sudden-onset, persistent vertigo • Usually other neurologic symptoms

BPPV = benign paroxysmal positional vertigo.

- Other causes: vestibular nerve impairment due to medications (e.g. aminoglycosides), or tumor (e.g. schwannoma), regional infections (e.g. otitis media, labrynthitis)

BENIGN PAROXYSMAL POSITIONAL VERTIGO

- Crystalline deposits **(canaliths)** in semi-circular canals → disrupt normal flow of fluid in vestibular system → **contradictory signalling** from corresponding canals on each side→ interpreted as spinning/vertigo sensation
- **Dix-Hallpike maneuver:** diagnose BPPV; vertigo and nystagmus are triggered as pt quickly lies back into supine position with head rotated 45 degrees
- Resolve spontaneously in most cases but can recur months or years later
- **Rx:** symptoms can be relieved by **canalith repositioning maneuver (Epley maneuver)**

AMINOGLYCOSIDE TOXICITY

- Aminoglycosides can cause **ototoxicity** (hearing loss) by damaging the cochlear cells.
- Some aminoglycosides (especially gentamicin) can also damage the **motion-sensitive hair cells** in the inner ear to cause selective **vestibular injury (vestibulopathy)** with or without significant ototoxicity.
- Because both vestibular end organs are equally affected, patients usually do not experience significant vertigo as there is no left or right imbalance in vestibular input to the central nervous system.
- Patients can experience **oscillopsia**, a sensation of objects moving around in the visual field when looking in any direction. This deficient vestibule-ocular reflex can lead to gait disturbances.
- An abnormal **head thrust test** can help detect vestibular dysfunction due to gentamicin. The patient is asked to look at a fixed target. Rapid head movement away from the target normally causes the eyes to remain fixed on the target. However, patients with vestibulopathy are unable to maintain their eyes on the target. The eyes move away and then return back to the target with a horizontal

saccade. Patients with aminoglycoside toxicity occasionally have severe bilateral vestibulopathy, which can lead to chronic symptoms.

PAIN MANAGEMENT

- Patients with acute, severe pain should receive the same standard of pain management regardless of drug history (current or past opioid abuse).
- IV morphine is appropriate treatment for acute, severe pain.
- Never undertreat pain, even if there is a risk of abuse, as it leads to dissatisfaction, longer hospital stay and higher risk of relapse
- In the case of concern for abuse, frequent reassessment, outpatient follow-up, and referral to a pain specialist is appropriate.

BRAIN DEATH

- Irreversible cessation of brain activities—it is a clinical diagnosis
- Criteria of brain death is not uniform in different countries, but common things are:
  - Evaluating cortical and brainstem functions—pupillary light reaction and oculovestibular reaction are absent→ reflecting global brainstem unresponsiveness
  - Proving irreversibility of brain activity loss (eg sufficient observation length, no hypothermia etc)
- Spinal cord may still be functioning; therefore, DTRs may still be present
- Isoelectric EEG may be used as confirmatory test, but is not absolutely necessary

- An apnea test shows no spontaneous respiration at Pco2 values of 50 mmHg and more

- heart rate fails to accelerate after atropine injection because vagal control of the heart is lost

Hemorrhagic transformation

- Patients with large or embolic ischemic strokes and those treated with thrombolytics are at high risk for **hemorrhagic transformation**.
- usually occurs **within 48 hours** of the stroke and often manifests with deteriorating mental status.
- Diagnosis requires **non-contrast CT scan** of the head. **Qid**:12214

Normal pressure hydrocephalus (NPH)

- Path: Decreased CSF absorption
- Triad of gait disturbance, dementia,and urinary incontinence. (WET,WACKY,WOBBLY)
- slow, **broad**-based, **shuffling** gait.
- CT or MRI shows dilated ventricles.
- CSF opening pressure is normal.
- Tx: serial LP , VP shunt (best).

Contents

DEVELOPMENTAL MILESTONES DURING TODDLERHOOD

Developmental milestones during toddlerhood				
Age	**Gross motor**	**Fine motor**	**Language**	**Social/Cognitive**
12 months	• Stands well • Walks first steps independently • Throws ball	• 2-finger pincer grasp	• Says first words (other than "mama" & "dada")	• Separation anxiety • Follows 1-step command with gesture
18 months	• Runs • Kicks ball	• Builds tower of 2-4 cubes • Removes clothing	• 10-25 word vocabulary • Identifies ≥1 body part	• Understands "mine" • Begins pretend play
2 years	• Walks up/down stairs with both feet on each step • Jumps	• Builds 6-cube tower • Copies a line • Turn pages	• 50+ word vocabulary • 2-word phrases	• Follows 2-step command • Parallel play • Begins toilet-training
3 years	• Walks up/down stairs with alternating feet • Rides tricycle	• Copies a circle • Uses utensils	• 3-word sentences • Speech 75% intelligible	• Knows age/gender • Imaginative play
4 years	• Balances & hops on 1 foot	• Copies a square	• Identifies colors • Speech 100% intelligible	• Cooperative play
5 years	• Skips • Walks backward	• Copies a triangle • Ties shoelaces • Independent dressing/bathing • Prints letters	• Counts to 10 • 5-word sentences	• Has friends • Completes toilet-training

Can run, throw a ball overhand and kick a ball

- Audiologic testing should be performed in all children with language delay to assess for underlying hearing loss

COMPLICATIONS OF PREMATURITY

Complications of prematurity
• Respiratory distress syndrome • Patent ductus arteriosus • Bronchopulmonary dysplasia • Intraventricular hemorrhage • Necrotizing enterocolitis • Retinopathy of prematurity

INTRAVENTRICULAR HEMORRHAGE

- Common complication in neonates born at <30 weeks gestation or <1500 g (3.3 lb).
- **Pathophysiology**: capillary fragility of subependymal germinal matrix and immature autoregulation of cerebral blood flow.
- **Screening**: **serial head ultrasounds** is necessary— as 25%-50% of cases are asymptomatic.
- **Presentation**: lethargy, hypotonia, high-pitched cry, rapidly increasing head circumference, bulging fontanels—in severe hemorrhage
- **Complications:** Communicating (nonobstructive) hydrocephalus—one-third of cases—as accumulating blood irritates the arachnoid villi, impairing its ability to absorb cerebrospinal fluid.
- **Greatest risk of death in high grade bleeds**—those who survive often suffer from significant neurodevelopmental disabilities (eg, cerebral palsy)
- **Prevention:** prevention of pre-term labor and ante-natal administration of corticosteroids—only interventions that can ↓ risk of IVH

LESCH-NYHAN SYNDROME

- X-linked recessive disorder→ affects males only
- Deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT)—involved in purine metabolism
- Uric acid accumulates in peripheral tissues→ gouty arthritis, tophus and obstructive nephropathy→ suspect this syndrome if you see a boy with gout (normally present after 50)
- Presents at 6 months with hypotonia and persistent vomiting
- Clinical picture worsens thereafter with the progressive mental retardation, choreoathetosis, spasticity, dysarthric speech, dystonia and compulsive self-injury, especially biting of the upper extremities.
- **Rx:** Allopurinol→↓ uric acid level. Pts should be advised to take adequate fluid intake

PHENYLKETONURIA

Phenylketonuria	
Pathophysiology	• Autosomal recessive mutation in phenylalanine hydroxylase • Failure to convert phenylalanine into tyrosine results in hyperphenylalaninemia & neurologic injury
Clinical features	• Severe intellectual disability • Seizures • Musty body odor • Hypopigmentation involving skin, hair, eyes & brain nuclei
Diagnosis	• Newborn screening (tandem mass spectrometry) • Quantitative amino acid analysis (↑ phenylalanine levels)
Treatment	Dietary restriction of phenylalanine

If PKU is suspected later in life, then this test is done

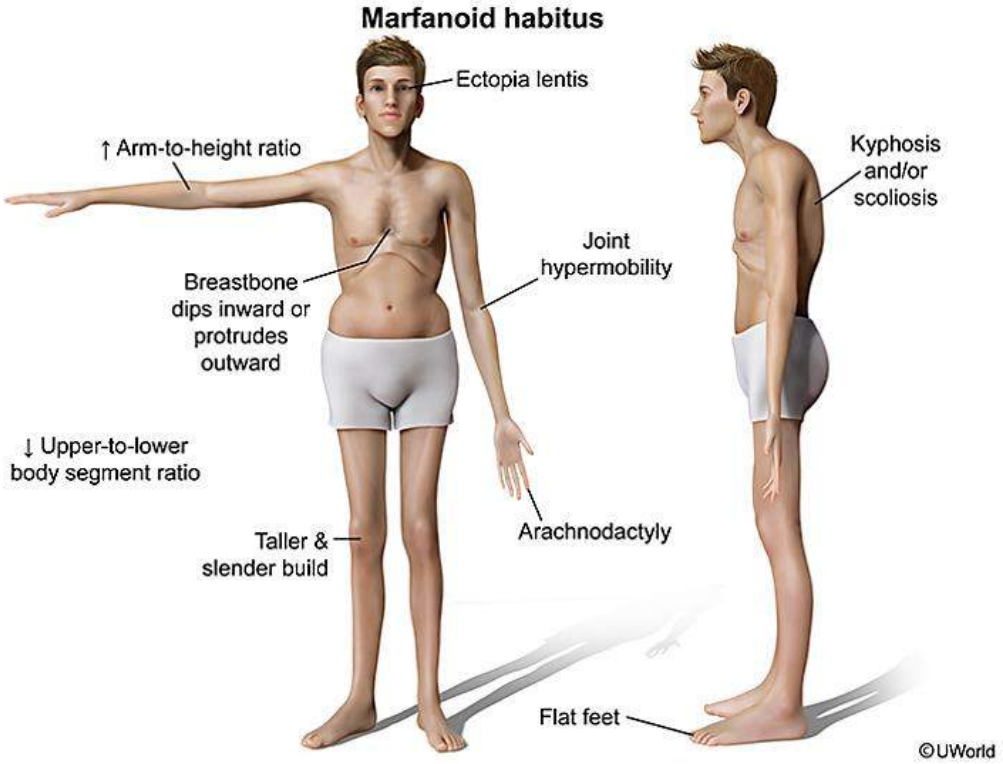
- **Tandem mass spectrometry** is done on dried blood spots to detect metabolic products of phenylalanine→ most cost effective screening
- **Phenylalanine** is essential a.a. and small amount is needed for growth and development→ hence, diet low on phenylalanine is given. Cereals, starches, fruits, vegetables and phenylalanine-free milk formulas are recommended. High protein foods should be avoided.
- **Prognosis:** early diagnosis and treatment→ most pts have normal mental development and normal life span

HOMOCYSTINURIA AND MARFANOID SYNDROME

Differential diagnosis of Marfanoid body habitus		
Diagnosis	**Overlapping features**	**Distinguishing features**

Marfan syndrome	• Pectus deformity
	• Tall stature
	  ◦ ↑ Arm : height ratio
	  ◦ ↓ Upper : lower segment ratio
	• Arachnodactyly
	• Joint hyperlaxity
	• Skin hyperelasticity
	• Scoliosis
		• Autosomal dominant
		• Normal intellect
		• **Aortic root dilation**
		• Upward lens dislocation

Homocystinuria		• Autosomal recessive • **Intellectual disability** • **Thrombosis** • Downward lens dislocation • Megaloblastic anemia • Fair complexion



HOMOCYSTINURIA

- Error in methionine metabolism due to deficiency of cystathionine synthase def.
- Thromboembolic event can occur at any age due to pathologic changes in vessel walls and ↑ adhesiveness of platelets—most commonly involve cerebral vessels
- **Dx**: ↑ homocysteine and methionine levels
- **Rx**: vitamin B6, folate and vitamin B12→ ↓ homocysteine levels. Also administer antiplatelet or anticoagulation to prevent stroke, coronary heart disease and venous thromboembolic disease

DISORDERS OF FRUCTOSE METABOLISM

ALDOLASE B DEFICIENCY

- Introduction of fruits and vegetables in diet→ fructose-1-phosphate accumulation
- Presentation: vomiting, poor feeding and lethargy. Seizures and encephalopathy may follow if fructose is not discontinues

DISORDERS OF GALACTOSE METABOLISM

GALACTOKINASE DEFICIENCY

- B/L cataracts only
- No other symptoms

GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY

- Present in newborns or infants with:
  - Failure to thrive/poor weight gain
  - Vomiting
  - B/L cataracts
  - Jaundice
  - Hepatosplenomegaly
  - Hepatic cirrhosis
  - Hypoglycemia

- Elevated levels of blood galactose
- Convulsions
- Aminoaciduria
- Mental retardation
- High risk of E. coli neonatal sepsis

- Early diagnosis and intervention is imp for better survival outcomes and to prevent liver cirrhosis and mental retardation
- **Rx**: early elimination of galactose from diet may reverse growth failure and other organ (e.g. renal and liver) dysfunction

URIDYL DISPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY

- Rare disorder as compared to uridyl transferase def.
- In addition to above symptoms, additional symptoms are:
  - Hypotonia
  - Nerve deafness

GLYCOGEN STORAGE DISEASE

VON-GIERKE DISEASE (TYPE-I GLYCOGEN STORAGE DISEASE)

- Deficiency: Glucose-6-phosphatase in liver, kidney and intestinal mucosa
- Hypoglycemia, lactic acidosis, hypertriglyceridemia, and hyperuricemia→ presents at 3-4 months of age. Normal liver transaminases
- Hypoglycemic seizure may also occur
- Characteristic features: doll-like face (i.e. flat cheeks), thin extremities, short stature, protuberant abdomen (due to enlarged liver and kidneys)
- Normal spleen and heart

POMPE DISEASE (TYPE-II GLYCOGEN STORAGE DISEASE)

- Deficiency: acid maltase (lysosomal α-1,4-glucosidase wit α-1,6-glucosidase deficiency)
- Presentation: in 1st few wks of life as **floppy baby** with feeding difficulties, macroglossia, and heart failure (due to progressive hypertrophic cardiomyopathy). Hepatomegaly +ve. Exercise intolerance. Early death
- "Pompe trashes the pump" i.e. heart, liver and muscles.

CORI DISEASE (TYPE-III GLYCOGEN STORAGE DISEASE)

- Deficiency: glycogen debranching enzyme (α-1,6-glucosidase)
- **Findings similar to von-Gierke**: hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation—may make it difficult to distinguish initially
- **Different lab values from von-Gierke**: elevated liver transaminase, fasting ketosis, normal blood lactate and uric acid conc. Other findings: Splenomegaly and normal kidneys.

AMYLOPECTINOSIS (TYPE-IV GLYCOGEN STORAGE DISEASE)

- Deficiency: branching enzyme
- Presentation: in 1st 18 months of life with HSM and failure to thrive. Progressive cirrhosis of liver

LIVER PHOSPHORYLASE DEFICIENCY

- Benign course
- Hepatomegaly and growth retardation early in childhood
- Mild hypoglycemia, hyperlipidemia and hyperketosis
- Normal lactic acid and uric acid levels.

LYSOSOMAL STORAGE DISEASES

SPHINGOLIPIDOSES

FABRY DISEASE

- α-galactosidase deficiency
- ceramide trihexoside accumulates
- X-linked recessive
- Characterized by: angiokeratomas, peripheral neuropathy, and asymptomatic corneal dystrophy. Patients may also develop renal and heart failure and are at risk for thromboembolic events.

GAUCHER DISEASE

- Glucocerebrosidase deficiency
- Glucocerebroside accumulates
- Presentation: anemia, thrombocytopenia, HSM, osteoporosis, aseptic necrosis of femur, bone crisis, Gaucher cells (lipid laden macrophages resembling crumpled tissue paper)
- Rx: recombinant glucocerebrosidase

NIEMANN PICK AND TAY SACH'S DISEASE

Niemann-Pick disease versus Tay-Sachs disease		
Diagnosis	**Niemann-Pick disease**	**Tay-Sachs disease**
Pathology	Sphingomyelinase deficiency	β-hexosaminidase A deficiency
Epidemiology	• Autosomal recessive inheritance • Ashkenazi Jewish heritage	
Onset	Age 2–6 months	
Clinical features	• Loss of motor milestones • Hypotonia • Feeding difficulties • "Cherry-red" macula • Hepatosplenomegaly • Areflexia	• Loss of motor milestones • Hypotonia • Feeding difficulties • "Cherry-red" macula • Hyperreflexia

NIEMANN PICK DISEASE

- 3 types: A, B and C
- Type A is most severe and type B and C are milder. A and B are caused by sphingomyelinase def.
- Sphingomyelin accumulates
- NPD type A: progressive. Foam cells "lipid laden macrophages". Protuberant abdomen. Almost universally fatal by age 3 years
- No treatment yet. Supportive treatment is the mainstay of treatment

TAY SACH'S DISEASE

- Lysosomes with onion skin
- GM2 ganglioside accumulates

- Intellectual disability
- Weakness
- Seizure

KRABBE DISEASE

- Galactocerebrosidase deficiency
- Galactocerebroside and psychosine accumulate
- Autosomal recessive
- Presents in early infancy with developmental regression, hypotonia and areflexia, peripheral neuropathy, optic atrophy and globoid cells
- Cherry red macula and organomegaly not present

MUCOPOLYSACCHARIDOSES

HURLER SYNDROME

- α-L-iduronidase deficiency (lysosomal hydrolase def.)
- Heparan sulfate and dermatan sulfate accumulation
- Present at 6mo to 2 years
- Coarse facial features, inguinal or umbilical hernia, corneal clouding and HSM

COMMON CAUSES OF INTELLECTUAL DISABILITY

Common causes of intellectual disability

Syndrome	Key physical findings
Fetal alcohol syndrome	Face • Smooth philtrum • Thin vermillion border • Small palpebral fissures • Microcephaly
Down syndrome	Face • Flat facial profile • Slanted palpebral fissures • Small low-set ears Body • Excessive skin at nape of the neck • Single transverse palmar crease • Clinodactyly • Large space between the first 2 toes
Fragile X syndrome	Face • Long narrow face • Prominent forehead & chin • Large ears • Macrocephaly Body • Macroorchidism

Low or normal IQ. Results from a full mutation in the FMR1 gene caused by an increased number of CGG trinucleotide repeats accompanied by aberrant methylation of the FMR 1 gene.

FETAL ALCOHOL SYNDROME

- May result in no apparent sequelae for some fetuses, others may suffer from FAS or be stillborn

- Advise pregnant women and those planning to conceive to completely abstain from alcohol as there is **no known safe amount of prenatal alcohol consumption**
- Cause birth defects and neurodevelopmental problems
- Height and/or weight growth compromised with percentiles </=10th for age and sex
- Cognitive and behavioral disorders
- The phenotypic range of neurodevelopmental problems is wide and includes intellectual disability, attention-deficit hyperactivity disorder**, social withdrawal, and delays in motor and language milestones.**
- Early diagnosis is critical for affected children to benefit from aggressive speech, physical, and occupational therapies.

SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome		
	Risk factors	**Prevention**
Maternal factors	• Smoking during or after pregnancy • Maternal age <20 • Inconsistent prenatal care	• Smoke avoidance during & after pregnancy • Routine prenatal care
Infant factors	• Prone/side sleep position • Soft sleep surface, loose bedding • Bed-sharing • Prematurity • Sibling with SIDS	• Supine sleep position • Firm sleep surface • Room-sharing • Pacifier use

SIDS = sudden infant death syndrome.

- To avoid suffocation: avoid loose bedding, crib bumpers and soft mattresses

CEREBRAL PALSY

Cerebral palsy	
Risk factors	• **Prematurity** Before 32 wks • Intrauterine growth restriction • Intrauterine infection • Antepartum hemorrhage • Placental pathology • Multiple gestation • Maternal alcohol consumption • Maternal tobacco use
Management	• Physical, occupational & speech therapies • Baclofen & botulinum toxin for spasticity
Comorbidities	• Intellectual disability 50% • Epilepsy • Strabismus • Scoliosis

- Cerebral palsy is a group of clinical syndromes characterized primarily by non-progressive motor dysfunction
- 3 primary subtypes: spastic, dyskinetic and ataxic—often multifactorial in etiology

- **Spastic diplegia—**form most commonly seen in premature infants. Characterized by:
  - Hypertonia and hyperreflexia that predominantly involve lower extremities with both feet pointing down and inwards (equinovarus deformity)
  - Resistance to passive muscle movement increases with more rapid movement of the affected extremity ("clasp-knife").
- Many pts suffer from vision, hearing, speech or other impairments

HYDROCEPHALUS

- Infants with hydrocephalus may present with following findings:

Symptoms	Physical Exam Findings
Poor feeding Irritability Decreased activity Vomiting	Tense and bulging fontanelle Prominent scalp veins Widely spaced cranial sutures Rapidly increasing head circumference

- **Evaluation:**
  - Symptomatic pt with rapidly ↑ing head circumference: CT scan is the best initial test→ reveals ventricular dilation and infant's anatomy
  - Stable and asymptomatic infant: sedated MRI to spare pt from radiations
  - Both CT and MRI would provide much greater detail than ultrasound, which requires a widely open anterior fontanelle and is most useful in infants under 6 months of age.
- **Rx:**
  - Shunt placed from ventricles to peritoneum, pleura or right atrium

ACUTE CAUSES OF HEMIPLEGIA IN CHILDREN

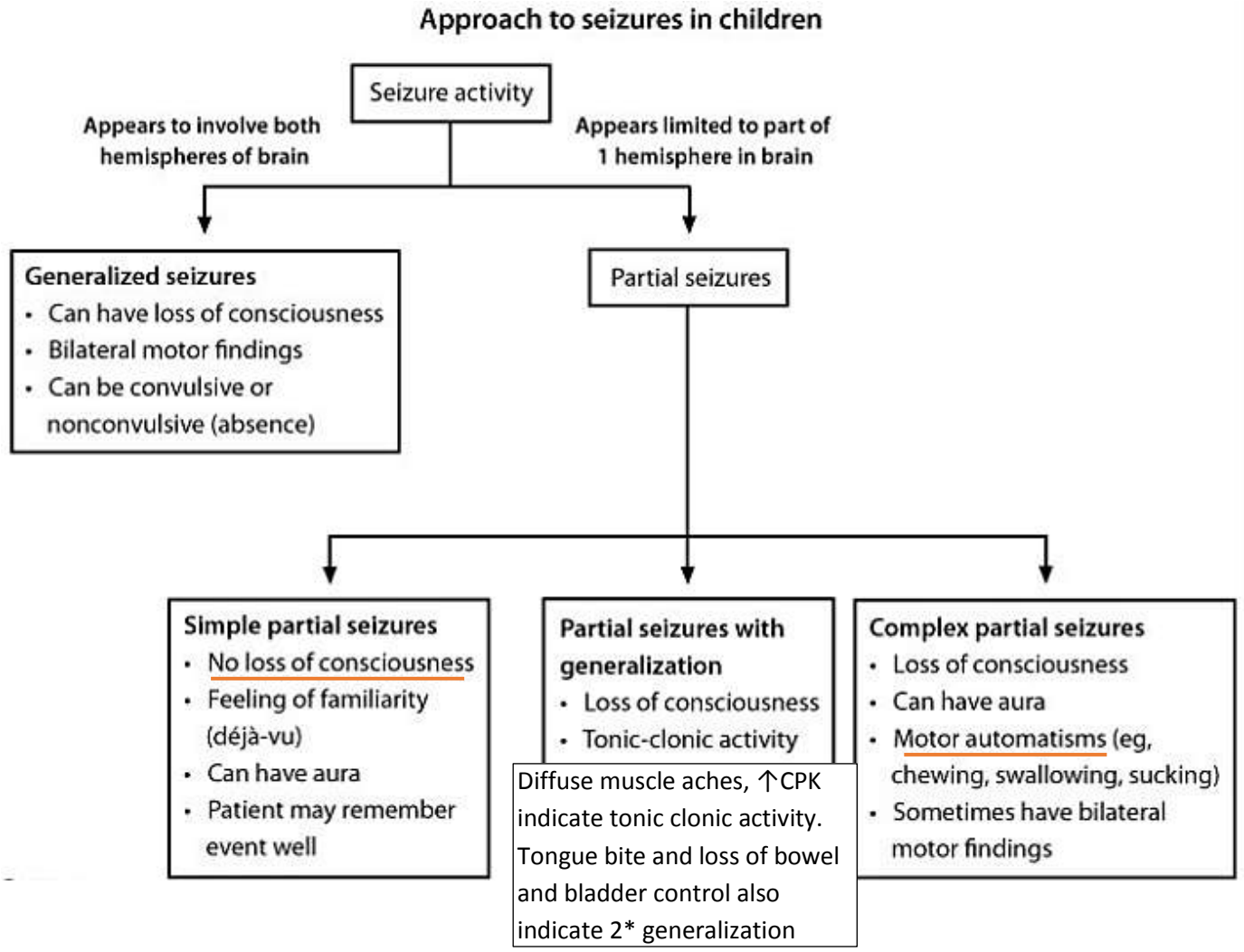
Acute causes of hemiplegia in children	
Cause	**Features**
Seizure	• History of generalized limb jerking or loss of consciousness • Presence of postictal confusion or Todd paralysis • Symptoms self-resolve
Intracranial hemorrhage	• History of trauma &/or bleeding disorder (eg, hemophilia) • Signs of increased intracranial pressure (eg, vomiting, bradycardia)
Ischemic stroke	• History of prothrombotic disorder (eg, antithrombin III deficiency) or cardiac disease (eg, patent foramen ovale) • Focal neurologic deficit (eg, hemiplegia, aphasia, ataxia)
Hemiplegic migraine	• Onset in adolescence & often positive family history • History of headache & visual aura • Symptoms self-resolve

TODD PARALYSIS

- Self-limited, focal weakness that occurs after a focal or generalized seizure.
- **Presents** in the postictal period with a partial or complete hemiplegia involving an ipsilateral upper and lower extremity, although one may be more affected than the other. Presenting signs can also include aphasia and visual defects
- **Pathophysiology:** unknown. It is hypothesized to involve neuronal exhaustion and/or inhibition in the postictal period.
- **Dx**: based on history alone. However, other causes of paralysis (eg embolism, intracranial bleed) should be ruled out with CT or MRI if no clear history of preceding seizure is present
- **Rx:** supportive as usually resolves within 36 hours

SEIZURES

- Classified as: focal or generalized (e.g. absence, tonic-clonic, myoclonic)—based on whether the abnormal neuronal discharges that cause the seizure originate from one or both cerebral hemispheres



Diffuse muscle aches, ↑CPK indicate tonic clonic activity. Tongue bite and loss of bowel and bladder control also indicate 2* generalization

FOCAL SEIZURES

Focal seizure	
Definition	• Originates from 1 cerebral hemisphere • +/- Loss of consciousness
Types	• Motor: Jacksonian march, turning of eyes/head/trunk • Sensory: Paresthesias, vertigo, visual phenomena • Autonomic: Sweating, epigastric "rising" sensation • Psychic: "Déjà vu," affective changes (eg, fear)

- Focal seizures arise from one hemisphere and may or may not subsequently involve both hemispheres
- Classified by: **presence or absence of impairment of consciousness**
- **Focal seizure with impairment of consciousness:** previously known as complex partial seizure—cannot respond to stimuli during the episode. Repetitive semi-purposeful movements (eg, chewing, sucking, swallowing) called **automatisms** involve both hemispheres and are seen in focal seizures with impairment of consciousness. School-aged children with such subtle presentation may also present with decline in school performance. Post ictal state lasting several hours can be seen in both complex partial seizure and partial seizure with 2* generalization. **EEG:** abnormal electrical activity that is sustained with a distinct start and stop different from pts background EEG.
- **Aura:** e.g. olfactory hallucination indicate origination from one hemisphere
- **Focal seizure without impairment of consciousness:** remain awake, alert and responsive
- Focal seizures are not provoked by hyperventilation
- Rx: phenytoin—DOC for partial seizures

GENERALIZED SEIZURES

ABSENCE (PETIT MAL) SEIZURES

Absence seizures	
Clinical features	• Sudden impairment of consciousness ("staring spells") • Preserved muscle tone • Unresponsive to tactile/verbal stimulation • Short duration (<20 seconds) • Simple automatisms frequently present • Easily provoked by hyperventilation
Diagnosis	EEG: 3-Hz spike-wave discharges during episodes
Comorbidities	• Attention deficit hyperactivity disorder • Anxiety
Treatment	Ethosuximide

EEG = electroencephalogram.

Valproic acid-2nd line—S/E: hair loss, tremor, thrombocytopenia

- Originate from both cerebral hemispheres
- Usually occur in children 4-10 years
- No memory of recent event

- Can occur infrequently or up to 100 times a day and without any trigger
- **Automatisms** (e.g. eye fluttering, lip smacking) may also be present—most consistent with absence seizure—but not more complex events—can be misdiagnosed as ADHD or normal childhood staring spells

Clinical features of absence seizures & inattentive staring spells	
Absence seizures	**Inattentive staring spells**
• Occurrence during all activities • Length <20 seconds • Lack of response to vocal or tactile stimulation • Presence of automatisms	• Occurrence primarily during "boring" activities • Variable length, often >1 minute • Response to vocal or tactile stimulation • Lack of automatisms

JUVENILE MYOCLONIC SEIZURE

- Presents with generalized seizures during adolescence, most commonly myoclonic jerks that are most prominent in the first hour after awakening. Absence seizures and generalized tonic-clonic seizures may also be seen.

➔ Lorazepam is first line for prolonged seizure and status epilepticus

FEBRILE SEIZURES

Febrile seizure	
Risk factors	• Fever from mild viral (eg, influenza, adenovirus, HHV-6) or bacterial infection • Immunizations (DTaP, MMR) • Family history
Diagnostic criteria	• Age 6 months-6 years • Temperature ≥38 C (100.4 F) • No history of previous afebrile seizures • No CNS infection • No acute systemic metabolic cause of seizure

Subtypes	• Simple:
	  ◦ Nonfocal (tonic-clonic or atonic)
	  ◦ 1 episode <15 minutes or multiple "episodes <30 minutes
	• Complex:
	  ◦ Focal
	  ◦ 1 episode >15 minutes or multiple "episodes >30 minutes

Management	• Abortive therapy if seizure ≥5 minutes • Reassurance/education
Prognosis	• Normal development/intelligence • ~30% risk of recurrence • <5% risk of epilepsy

DTaP = Diphtheria, tetanus, and pertussis; **CNS** = central nervous system;
HHV-6 = human herpesvirus 6; **MMR** = measles, mumps, rubella.

- Common and generally harmless cause of conculsion in children
- Most are short and **do not cause brain injury**

SIMPLE FEBRILE SEIZURE

- Multiple studies have shown that interventions such as imaging or lumbar puncture in the fully vaccinated child with a normal neurologic examination are low yield, unnecessarily invasive, and anxiety-provoking.
- Can be discharged home with education about seizure precautions and supportive care (eg, hydration) for the concurrent infection.
- Caregivers should be informed that antipyretics can make the child more comfortable, but there is no evidence that these will reduce the risk of future febrile seizures

COMPLEX FEBRILE SEIZURE

- Brain imaging should be considered in a child with a complex febrile seizure with a persistently abnormal neurologic examination, macrocephaly, or signs/symptoms of elevated intracranial pressure.

LENNOX GASTAUT SYNDROME

- Typically presents by age 5 with intellectual disability and severe seizures of varying types (eg, atypical absence, tonic). EEG demonstrates a slow spike-wave pattern.

FEATURES OF NON-ACCIDENTAL TRAUMA

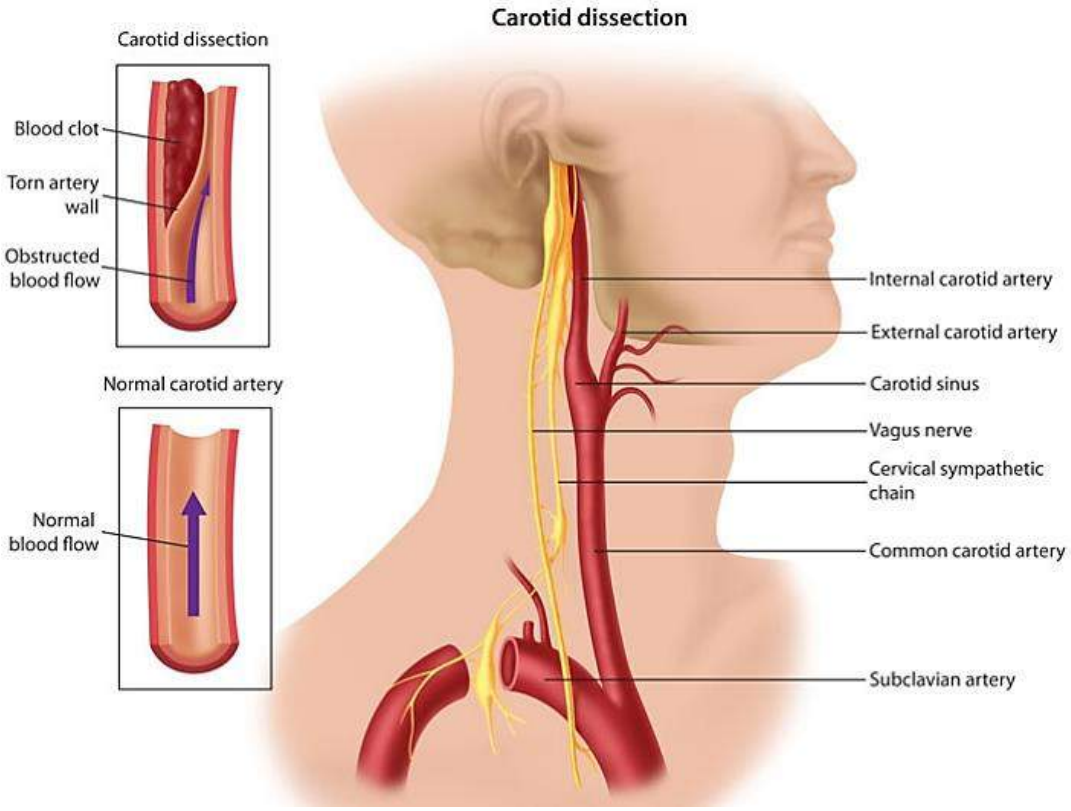
Features of non-accidental trauma	
History	• Vague or changing details • Injury inconsistent with child's developmental stage • Sibling described as responsible
Examination	• Injury inconsistent with history • Multiple fractures or bruises in different healing stages • Likely inflicted injuries (eg, cigarette burn) • Poorly kempt child • Bruises on neck, abdomen, or unusual sites • Injury to genitalia, hands, back, or buttocks
Caregiver behavior	• Argumentative or violent • Lack of emotional interaction with child • Inappropriate response to child's injury • Inappropriate delay in seeking medical care • Partial confession in causing injury

- Shaken baby syndrome is the most common form→ subdural bleeding due to rupture of bridging veins and retinal hemorrhages→ seizures, ↑ing head circumference, bulging ant. fontanelle and altered mental status→ non-contrast head CT and skeletal survey, admit to protect pt and inform child protective services

TRAUMATIC CAROTID INJURIES

Traumatic carotid injuries	
Mechanism	• Penetrating trauma • Fall with object in mouth (eg, toothbrush, pencil) • Neck manipulation (eg, yoga, sports)
Presentation	• Gradual-onset hemiplegia • Aphasia • Neck pain • "Thunderclap" headache
Diagnosis	• CT or MR angiography

- Injury to posterior pharynx can cause injury to cervical internal carotid artery which is located directly lateral and posterior to tonsillar pillars
- Intimal injury to internal carotid artery can cause dissection or thrombus formation within hours or days— can extend to MCA and ACA



HEAD TRAUMA IN CHILDREN 2-18 YEARS

Evaluation of head trauma in children age 2–18	
Clinical scenario	**Recommendation**
Any of the following: • Focal neurologic findings • Skull fracture, especially signs of basilar skull fracture • Seizure • Persistent altered mental status (eg, agitation, lethargy, slow response) • Prolonged loss of consciousness	Head CT without contrast
GCS = 15 with any of the following: • Vomiting • Headache • Questionable or brief loss of consciousness • Injury caused by high-risk mechanism of injury • Severe mechanism of injury*	Clinician preference: Observation for 4–6 hours OR Head CT without contrast
Minor head trauma (GCS = 15 with non-severe mechanism & no vomiting, headache, loss of consciousness, or signs of fracture)	No head CT

SEVERE TRAUMATIC BRAIN INJURY

MILD TRAUMATIC BRAIN INJURY

MINOR TRAUMATIC BRAIN INJURY

* Severe mechanism: car crash with patient ejection, passenger fatality, or rollover; pedestrian versus car; fall height >5 ft; or head hit by high-impact object

SEVERE TRAUMATIC BRAIN INJURY

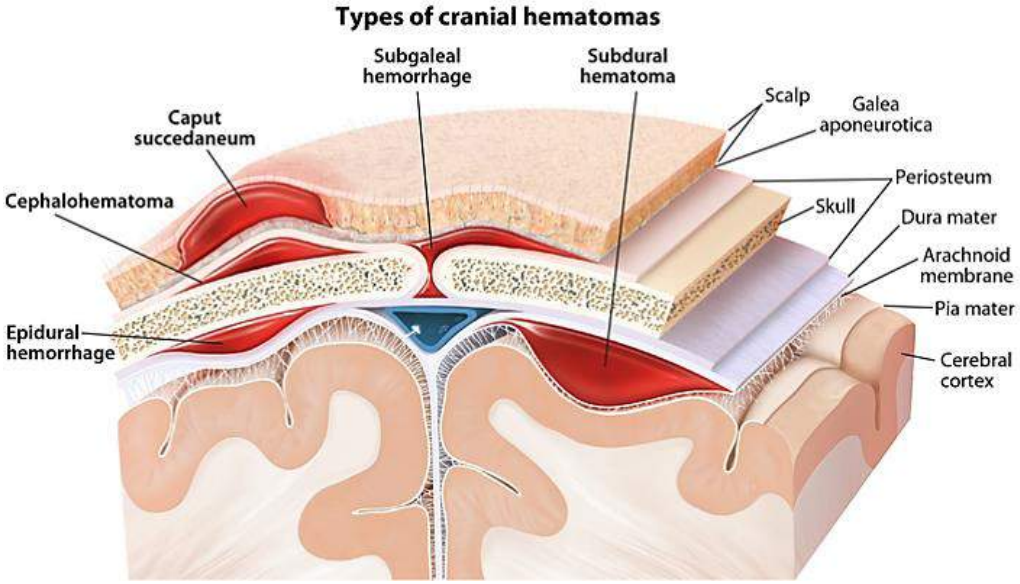
- Require neuroimaging, close inpatient monitoring (e.g. neurological examination every 2 hours) and neurosurgical consultation
- They typically have significant intracranial injury

MINOR TRAUMATIC BRAIN INJURY

- Example: concussion
- GCS 13-15
- Loss of consciousness < 5min
- Altered mental status at the time of injury
- Loss of memory (amnesia) before/after injury for <24 hours
- If clinician prefers to observe and symptoms deteriorate then CT should be performed
- Pt. can be discharged home with a reliable caretaker if CT scan is normal or there is improvement during observation. Clear written instructions with return precautions should be provided

➔ Potential risk of cancer from CT-scan associated radiation increases with decreasing age (e.g. 1 in 1500 at age 1 and 1 in 5000 at age 10)

TYPES OF CRANIAL HEMATOMAS



CAPUT SUCCEDANEUM

- Caput succedaneum is a diffuse, sometimes ecchymotic swelling of the scalp.
- Usually involves the portion of the head presenting during vertex delivery.
- It may extend across the midline and across suture lines.

CEPAHLOHEMATOMA

- Subperiosteal hemorrhage— always limited to one cranial bone
- No discoloration of overlying scalp
- Swelling usually not visible several hours after birth as subperiosteal bleeding is a slow process
- Most cases do not require any treatment and resolve spontaneously within 2 wks to 3 mo, depending on sign
- Rarely, phototherapy is needed to improve hyperbilirubinemia

MENINGITIS

The long-term neurologic sequelae associated with bacterial meningitis are:

1. Hearing loss
2. Loss of cognitive functions (due to the neuronal loss in the dentate gyrus of the hippocampus)

3. Seizures
4. Mental retardation
5. Spasticity or paresis

MUSCULAR DYSTROPHIES

Muscular dystrophies			
Diagnosis	**Duchenne**	**Becker**	**Myotonic**
Genetics	X-linked recessive deletion of dystrophin gene on chromosome Xp21		Autosomal dominant expansion of a CTG trinucleotide repeat in DMPK gene on chromosome 19q 13.3
Clinical presentation	• Onset: age 2-3 • Progressive weakness, Gower maneuver, calf pseudohypertrophy	• Onset: age 5-15 • Milder weakness compared to Duchenne muscular dystrophy	• Onset: age 12-30 • Facial weakness, hand grip myotonia, dysphagia
Comorbidities	• Scoliosis Cardiomyopathy	• Cardiomyopathy	• Arrhythmias • Cataracts • Balding • Testicular atrophy/ infertility
Prognosis	• Wheelchair-dependent by adolescence • Death by age 20-30 from respiratory or heart failure	Death by age 40-50 from heart failure	Death from respiratory or heart failure depending on age of onset

MYOTONIC MUSCULAR DYSTROPHY TYPE-1 (STEINERT DISEASE)

- Most common adolescent/adult onset muscular dystrophy, affecting ~1/8000 persons in US
- DMPK=dystrophia myotonica protein kinase gene
- Causes myotonia, weakness in skeletal, smooth and cardiac muscles; and problems in multiple other organs
- **Myotonia** (delayed muscle relaxation)—most notable when pt is unable to release hand after handshake (grip myotonia)
- **Skeletal muscle weakness** is prominent in face, forearms, hands and ankle dorsiflexors (e.g. B/L foot drop)
- **Smooth muscle weakness:** dysphagia—most dangerous manifestation→aspiration pneumonia
- **Insulin resistance**

- My Tonia, My Testicles (testicular atrophy), My Toupee (frontal balding), My Ticker (arrhythmia).

FRIEDREICH'S ATAXIA

- Autosomal recessive— excessive number of trinucleotide repeat sequences→ abnormality of a tocopherol transfer protein.
- Progressive and poor prognosis
- **CNS:** ↓ vibration and position in lower extremities, wide-based gait, high plantar arches, b/l absence of ankle jerks. Most pts are wheelchair bound by 25 and death occurs by 30-35 years. MRI of brain and spine: marked atrophy of cervical spine and cerebellar atrophy
- **Heart:** necrosis and degeneration of cardiac muscles→ myocarditis (causes T-wave inversion), myocardial fibrosis, and cardiomyopathy. Cardiac arrhythmia and CHF lead to significant no. of deaths [D/D of T-wave inversion: MI, myocarditis, old pericarditis, myocardial contusion and digoxin toxicity]
- In families with one affected child, genetic counselling is recommended for prenatal diagnosis

NEUROCUTANEOUS DISORDERS

STURGE WEBER SYNDROME

- **Presentation:**
  - Focal or generalized seizures—usual neurologic presentation and present at any age
  - Mental retardation
  - Port wine stain or nevus flammeus in the distribution of trigeminal nerve—represents congenital u/l cavernous hemangioma—does not blanch on pressure
  - Hemianopia
  - Hemiparesis
  - Hemisensory disturbance, and
  - Ipsilateral glaucoma
  - Skull x-rays, taken after the age of 2 years, reveal gyriform intracranial calcifications that resemble a tramline.
- **Rx**: aimed at controlling the seizures and reducing intraocular pressure. Argon laser therapy is successful in removing the skin lesions.

TUBEROUS SCLEROSIS

- Neurocutaneous genetic (TSC1 and TSC2 genes) syndrome
- Associated with intracranial tumors (eg, cortical tubers or hamartomas, subependymal giant cell astrocytomas, subependymal nodules)→ Initial presentation: seizure
- Cutaneous lesion called adenoma sebaceum appear at 5-10 years of age
- Additional characteristics include hypopigmented macules ("ash leaf spots"), facial angiofibromas, cardiac rhabdomyomas, renal angioleiomyomas, mental retardation

NEUROFIBROMATOSIS

Neurofibromatosis type 1 & type 2		
Diagnosis	NF1 (von Recklinghausen disease)	NF2 (central neurofibromatosis)
Gene mutation	NF1 tumor suppressor gene; codes the protein **neurofibromin**	NF2 tumor suppressor gene; codes the protein **merlin**
Location of mutated gene	Chromosome 17	Chromosome 22
Main clinical features	• Café-au-lait spots • Multiple neurofibromas • Lisch nodules	• Bilateral acoustic neuromas And cataracts

NEUROFIBROMATOSIS TYPE 1

- Café-au-lait spots—earliest manifestation—may occur in infancy
- ↑ing age→ axillary/inguinal freckles, Lisch nodules (iris hamartomas) and neurofibromas (benign nerve sheath tumors)
- Risk of intracranial tumors—**optic pathway gliomas:** most common type of intracranial lesion and typically manifests during toddlerhood
- Macrocephaly, feeding problems, short stature and learning disabilities
- MRI of the brain and orbits— best modality for a detailed evaluation of soft-tissue anatomy in any NF1 patient with concerning neurologic symptoms (eg, chronic headache, vision changes, early-morning vomiting)—preferred over CT

CAPILLARY HEMANGIOMA

- Presents at birth or appears by 6 months of age.
- Consists of small capillaries and presents as an irregular, raised lesion that blanches on pressure.
- Approximately 75% regress by age 7.

NEUROBLASTOMA (NBL)

- Most common extracranial solid tumor of childhood—3rd most common tumor in pediatric population after leukemia and CNS tumors
- Mean age of diagnosis: 2 years
- Arise from neural crest cells which also give rise to adrenal medulla and sympathetic chains—hence tumor can arise from adrenal medulla and paravertebral sympathetic chains (most common site: abdomen and retroperitoneal ganglia)
- Firm and nodular consistency
- Calcifications and hemorrhages seen on plain X-ray and CT scan
- 70% have metastasized by the time of diagnosis
- Common metastatic sites: long bones, skull, bone marrow, liver, lymph nodes and skin
- Labs: serum and urine catecholamines and their metabolites (i.e. HVA and VMA)—usually elevated but do not cause fainting spells, sweating, palpitations and HTN as in pheochromocytoma
- Prognosis: depends on clinical factors, tumor histology, and genetic characteristics (amplification of N-myc proto-oncogene and hyperdiploidy)

➔ Wilm's tumor—arise from metanephros—also precursor of renal parenchyma

➔ Mesonephros gives rise to: seminal vesicles, epididymis, ejaculatory ducts, and ductus deferens

➔ Paramesonephron→ fallopian tube, uterus and part of vagina

CNS TUMORS

PILOCYTIC (LOW GRADE) ASTROCYTOMA

- Usually present with seizures and longer duration of symptoms
- Contrast enhancement is less likely
- Most common posterior fossa and cerebral hemispheric tumor in children—more commonly in **lateral cerebellar hemisphere**

MEDULLOBLASTOMA

- Second most common posterior fossa tumor in children after cerebellar astrocytoma
- **Location:**
  - Majority in **cerebellar vermis—**responsible for gait and balance→ truncal or gait instability
  - Less common in **cerebellar hemisphere** – affects fine motor planning and cause dysmetria, intention tremor and dysdiadochokinesia
- Close to 4th ventricle and can cause **obstructive hydrocephalus→** signs of ↑ ICP
- Potential of leptomeningeal spread "drop mets"
- **Rx**: treat aggressively with surgery, craniospinal radiation and chemotherapy

CRANIOPHARYNGIOMA

Key features of craniopharyngioma

- Low-grade malignancy derived from remnants of Rathke pouch
- Optic chiasm compression → bitemporal hemianopsia
- Pituitary stalk compression → endocrinopathies (eg, growth hormone deficiency, diabetes insipidus)
- Suprasellar, calcified mass on imaging

- Bitemporal hemianopsia can cause pt. to run into the corners of walls and furniture
- Can present with headache 2* to compression of nearby structures or obstructive hydrocephalus

PARINAUD SYNDROME

- Results from pressure on the pretectal region of the midbrain.
- Findings: limitation of upward gaze with a downward gaze preference, bilateral eyelid retraction, and light-near dissociation. Pineal tumors are associated with Parinaud syndrome.

Contents

UPPER LIMB

ROTATOR CUFF TEAR

- Rotator cuff formed by tendons of: supraspinatus, infraspinatus, teres minor and subscapularis
- Supraspinatus most commonly injured due to repeated bouts of ischemia near its insertion on the humerus induced by compression between the humerus and the acromion.
- **Common cause**: fall on outstretched hand
- **C/F**: severe shoulder pain and edema and inability to abduct past 90*
- **Drop arm test**: is a maneuver that can help to diagnose a rotator cuff tear. Here, the patient's arm is abducted passively to greater than 90 degrees, and the patient is then asked to lower the arm slowly. With a complete rotator cuff tear, the patient will be unable to lower the arm smoothly and it will appear to drop rapidly from near the 90 degree position

ANTERIOR SHOULDER DISLOCATION

- **Cause**: Forceful abduction and external rotation of arm→ anterior dislocation of humeral head from glenoid fossa→ anterior capsule of glenohumeral joint often torn→ resists internal rotation of arm and supports weight of arm with other hand
- **Physical exam:** prominence of acromian with an abnormal subacromial space where humeral head normally resides. Fullness of anterior shoulder is noted on palpation
- **Warrants neurological exam of axillary nerve—**risk of injury due to anteroinferior dislocation→ paralysis of deltoid and teres minor + loss of sensation over upper lateral arm
- Can also damage axillary artery

RUPTURE OF LONG HEAD OF BICEPS

- Produces a positive "Popeye sign" where the biceps muscle belly becomes prominent in the mid upper arm.
- Weakness with supination is prominent, and forearm flexion is typically preserved

LONG THORACIC NERVE INJURY

- During axillary lymphadenectomy
- Serratus anterior palsy→ winged scapula

BRACHIAL PLEXUS INJURY

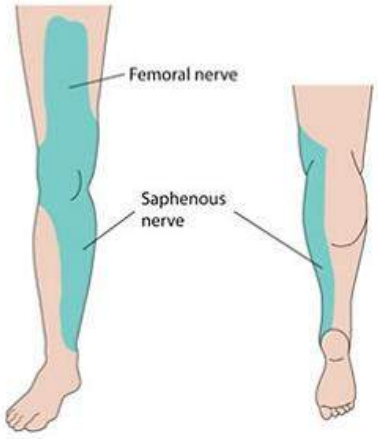
LOWER TRUNK OF BRACHIAL PLEXUS

- Originates from C8-T1 cervical roots
- Results from sudden upward pulling on the arm
- Leads to Klumpke's palasy
- Primarily affects muscles innervated by ulnar nerve, which supplies most of intrinsic muscles of hand→ weakness and atrophy of hypothenar and interosseous muscles and claw hand deformity may result

LOWER LIMB

FEMORAL NERVE

Nerve	Motor function	Region of sensory loss with neuropathy
Femoral nerve	Leg flexion at the hip, leg extension at the knee	



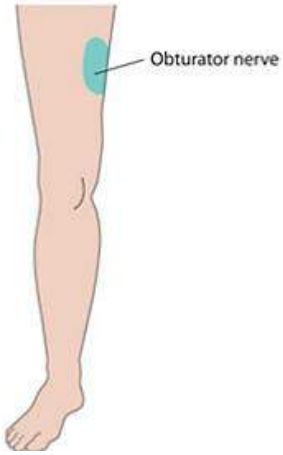
- **Motor:** innervates muscles of anterior compartment of thigh (i.e. quadriceps femoris, pectineus, sartorius)
- **Sensory:** anterior thigh and medial leg via saphenous branch

TIBIAL NERVE

- **Motor:** muscles of posterior compartment of thigh, posterior compartment of leg and plantar muscles of foot→ flexion of knee and digits and plantar flexion of foot
- **Sensory:** leg (except medial) and plantar foot

OBTURATOR NERVE

Nerve	Motor function	Region of sensory loss with neuropathy
Obturator nerve	Adduction of the thigh	

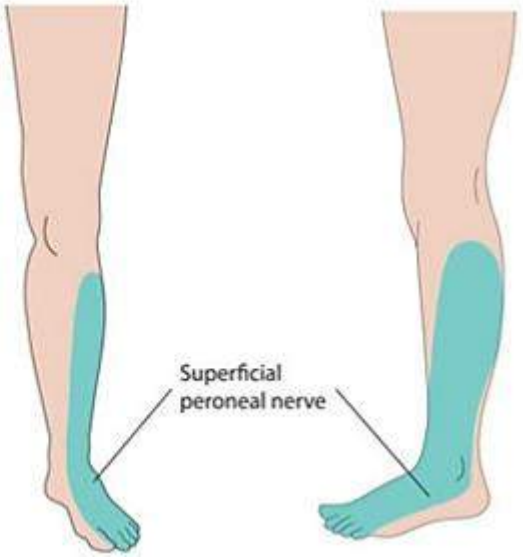


- **Motor:** medial compartment of the thigh (i.e., gracilis, adductor longus, adductor brevis, anterior portion of adductor magnus)
- **Sensory:** medial thigh

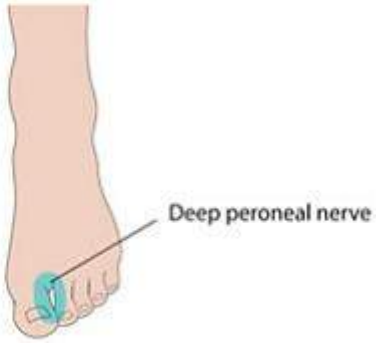
COMMON PERONEAL OR FIBULAR NERVE

- Gives rise to superficial and deep peroneal nerves.
- **Motor:** These two supply muscles of anterior and lateral leg
- **Sensory:** anterolateral leg and dorsum of foot

SUPERFICIAL PERONEAL NERVE

Nerve	Motor function	Region of sensory loss with neuropathy
Superficial peroneal nerve	Foot eversion	

DEEP PERONEAL NERVE

Nerve	Motor function	Region of sensory loss with neuropathy
Deep peroneal nerve	Foot dorsiflexion, toe extension	

FACIAL NERVE

- Extracranial part passes through substance of parotid gland and give motor innervation to muscles of facial expression
- Parotid gland tumor requiring deep lobe parotidectomy or if involves facial nerve→ excise nerve too→ can cause u/l facial droop

Contents

FETAL HYDANTOIN SYNDROME

- Due to exposure to many anticonvulsant medications during fetal development
- **Most commonly associated meds:** phenytoin and carbamazepine
- **C/F:** midfacial hypoplasia, microcephaly, cleft lip and palate, rib anomalies, digital hypoplasia, nail hypoplasia, hirsutism and developmental delay
- Pregnant women on phenytoin during their last trimester often receive prophylactic vitamin K to prevent neonatal bleeding as phenytoin may increase the rate of fetal vitamin K degradation.

CONGENITAL SYPHILIS

- **Signs present following birth**: rhinitis (snuffles), hepatosplenomegaly and skin lesions.
- **Later findings**: interstitial keratitis, Hutchinson teeth, saddle nose, saber shins, deafness and CNS involvement

Contents

UW acid base numbers

ACID-BASE BALANCE

- Normal pH: 7.35 to 7.45
- Normal pCO2: 33- 45 (40) mmHg
- Normal HCO3-:22-28 (24) mEq/L
- Major extracellular buffer in human blood is the carbon dioxide-bicarbonate buffer pair, which has a pK of 6.1
- Classically, the acid-base status of a buffer can be determined using the Henderson-Hasselbalch equation with its three variables, pH, [acid] and [conjugate base], as follows:

$$pH = pK + log\ ([conjugate\ base]/[acid])$$

- In carbon dioxide - bicarbonate buffer pair, where C02 is the acid and HC03- is the conjugate base, the equation is as follows:

$$pH = 6.1 + log\ ([HCO3-]/(0.03\ x\ PaCO2))$$

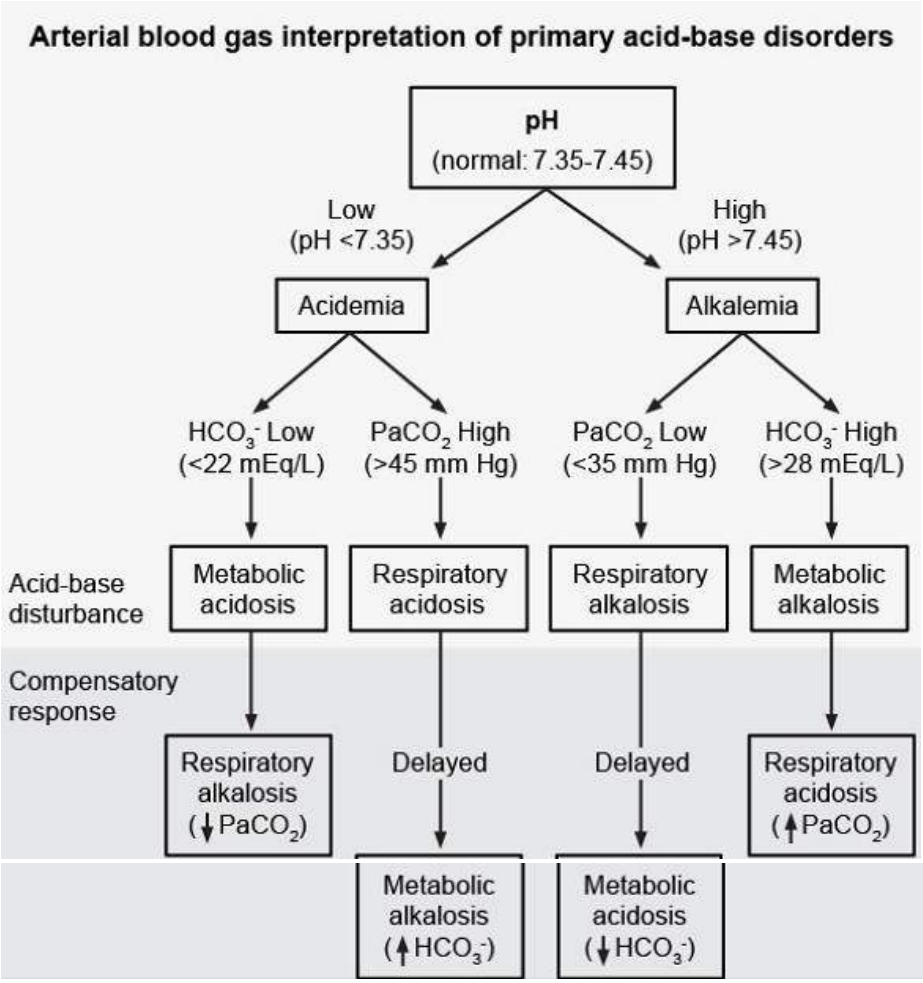
- Using the Henderson-Hasselbalch equation, any of the three variables can be calculated if the other two are given.

Acid-base disorders	
Primary disorder	**Appropriate compensation**
Metabolic acidosis	Arterial $PaCO_2$ = 1.5 (serum HCO_3) + 8 ± 2
Metabolic alkalosis	↑ Arterial $PaCO_2$ by 0.7 mm Hg for every 1 mEq/L rise in serum HCO_3
Acute respiratory acidosis	↑ Serum HCO_3 by 1 mEq/L for every 10 mm Hg rise in arterial $PaCO_2$
Acute respiratory alkalosis	↓ Serum HCO_3 by 2 mEq/L for every 10 mm Hg decrease in arterial $PaCO_2$

PaCO2= (0.9 x HCO3) +16+/-2

ΔPaC02 = 0.7 * Δ HCO3

ΔHCO3 = 0.1 * Δ PaC02



- Acidemia by itself does not cause CNS depression, but often underlying cause of academia results in lethargy and altered mental status e.g. CO2 retention due to COPD can cause **CO2 narcosis** (usually seen at PaCO2 >60mmHg) or anion gap metabolic acidosis due to AKI (due to unmeasured urea toxins retention). AKI can also cause non-anion gap metabolic acidosis which will not cause altered mental status. Whereas, ↑BUN (due to breakdown of blood proteins) due to GI bleeding will not cause AMS

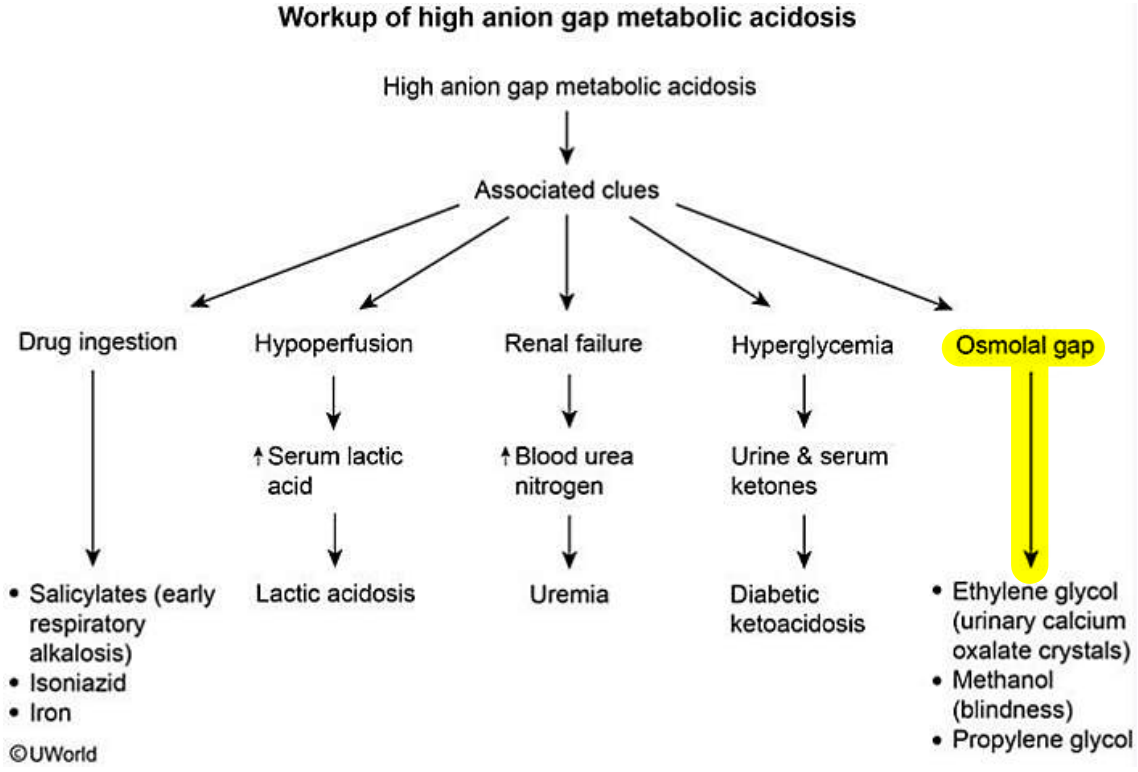
METABOLIC ACIDOSIS

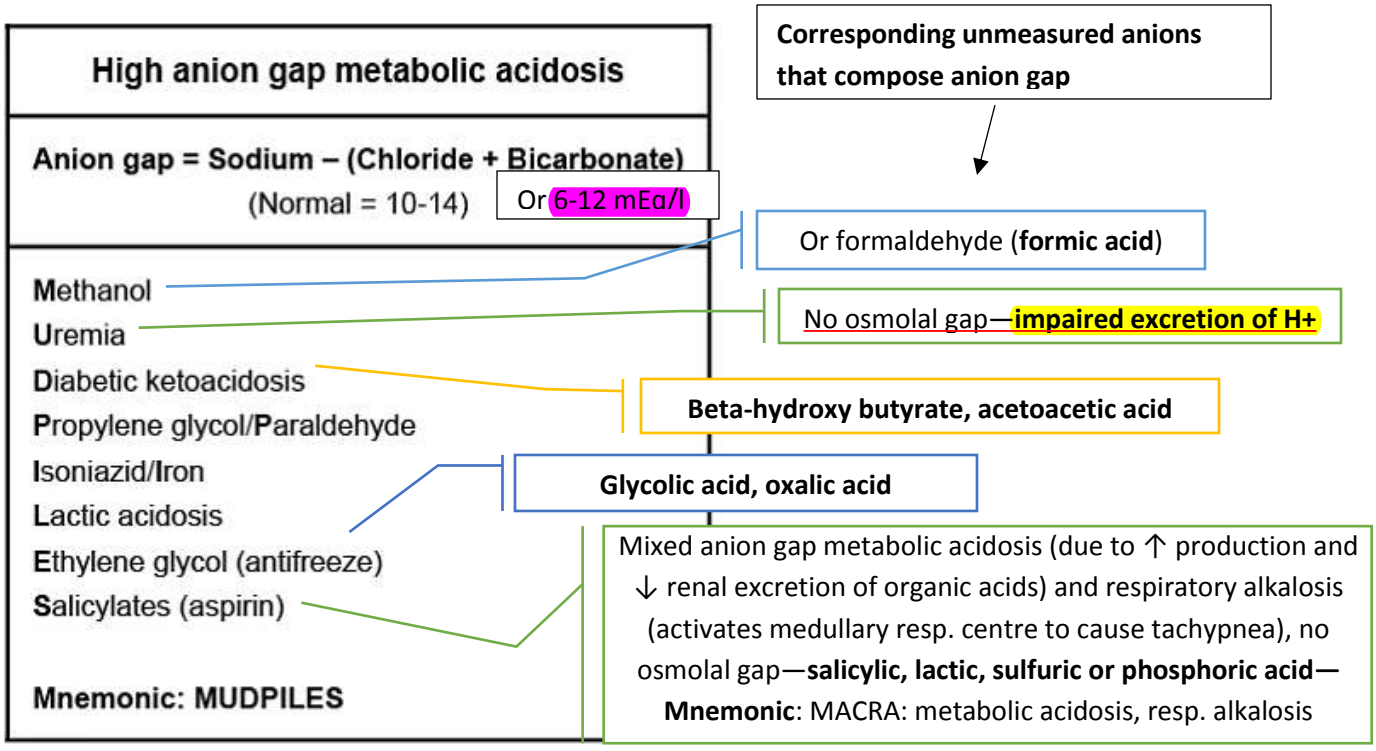
HIGH ANION GAP METABOLIC ACIDOSIS

- High anion gap indicate presence of non-chloride containing acids that contain inorganic (phosphate, sulfate), organic (ketoacids, lactate, uremic organic anions), exogenous (salicylate, or ingested toxins with organic acid production) or unidentified anions
- Seizure causes anion gap metabolic acidosis- usually due to ↑ lactic acid production in muscles and ↓ hepatic lactate uptake—usually resolve within 60-90 min→ so observe for 2 hours and repeat test → if not resolved→ look for other potential causes of metabolic acidosis

Postictal lactic acidosis commonly occurs following a tonic-clonic seizure (skeletal muscle hypoxia). It is a transient anion gap metabolic acidosis that resolves without treatment within 90 minutes following resolution of seizure activity.

Hypoventilation is a major cause of **respiratory acidosis** and may occur in the **post-ictal state**.





ETHYLENE GLYCOL POISONING (ANTIFREEZE)

- Metabolic acidosis (pH <7.35, primary decrease in HCO3-)
- Serum osmolality is often obtained in pts with anion gap metabolic acidosis and suspected ingestion→ ↑ed
- Combination of ↑ed anion gap and ↑osmolal gap: methanol, ethylene glycol or methanol poisoning
- **Osmolal gap:**

"$\boldsymbol{Osmolal\ gap = measured\ serum\ osmolality - calculated\ serum\ osmolality\ (NL < 10)}$"

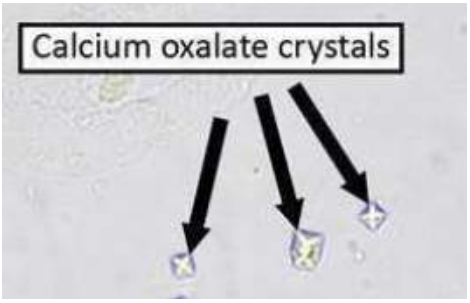
$$\boldsymbol{Calculated\ serum\ osmolality = (2 * sodium) + (glucose/18) + (BUN/2.8)}$$

- **Urinalysis:** rectangular, envelope-shaped calcium oxalate crystals
- **Complication:** acute renal failure
- The urine anion gap is calculated when there is a normal anion gap metabolic acidosis. The urine anion gap helps determine such acidosis is due to the renal or intestinal bicarbonate losses. Renal losses of bicarbonate occur in renal tubular acidosis or carbonic anhydrase inhibitor use. Gastrointestinal loss of bicarbonate occurs classically in diarrhea.

NON-ANION GAP METABOLIC ACIDOSIS

Causes of normal anion gap metabolic acidosis

- Diarrhea
- Fistulas (eg, pancreatic, ileocutaneous, etc.)
- Carbonic anhydrase inhibitors
- Renal tubular acidosis
- Ureteral diversion (e.g., ileal loop)
- Iatrogenic



METABOLIC ALKALOSIS

Differential diagnosis of metabolic alkalosis

Metabolic alkalosis
(arterial pH >7.45 & serum HCO_3^- >24 mEq/L)

Low urine chloride

High urine chloride

Hypovolemia/ euvolemia NO HTN

Hypervolemia HTN

↑ Aldosterone

- Vomiting/ nasogastric aspiration
- Prior diuretic use

- Current diuretic use

Saline-responsive

- Bartter & Gitelman syndromes

Excess mineralocorticoid activity
- Primary hyperaldosteronism
- Cushing disease
- Ectopic ACTH production

Excessive black liquorice ingestion

Saline-unresponsive

Clinical features of metabolic alkalosis	
Causes	**Saline-responsive** • Vomiting • Gastric suctioning • Diuretics • Laxative abuse • Decreased oral fluid intake (volume depletion) **Saline-resistant** • Primary hyperaldosteronism • Cushing's syndrome • Severe hypokalemia (<2 mEq/L)
Clinical presentation	• Volume depletion: Easy fatigability, postural dizziness, muscle cramps • Hypokalemia: Muscle weakness, arrhythmias • Urine chloride: <20 mEq/L (saline-responsive), >20 mEq/L (saline-resistant)
Treatment	• Treat underlying cause to reverse generation phase in all cases • Saline-responsive: Also give normal saline to correct maintenance phase

SALINE RESPONSIVE

- Recurrent vomiting/nasogastric suctioning→ loss of body acid "HCl", KCl, fluid, NaCl→ loss of Cl-, K+, lack of acidity→ ↓ excretion of bicarbonate from liver and pancreas→ metabolic alkalosis (generation phase)→ fluid depletion→ activation of renin-angiotensin-aldosterone system→ Na+, Cl- and H2O retention and K+ and H+ loss (contraction alkalosis-maintenance phase). ↓ serum Cl- also impairs HCO3- excretion, further worsening metabolic alkalosis. **Rx**: IV fluid (e.g. normal saline)→ fluid correction and diminishes RAAS affect. Also correct hypokalemia with potassium supplementation
- Saline responsive metabolic alkalosis usually respond to isotonic saline infusion alone and restore both, ECF volume and low serum Cl-

SALINE UN-RESPONSIVE

- ↑ aldosterone→ Na+ and H2O retention and K+ and H+ loss→ hypervolemia→ kidney detects→ Na+ and Cl- excretion→ hence, urinary chloride >20 mEq/L usually
- Usually do not respond to saline infusion alone and also require correction of underlying disorder

RESPIRATORY ALKALOSIS

- Causes: Hyperventilation due to pneumonia, high altitude or salicylate intoxication

The kidney compensates for respiratory alkalosis by preferentially excreting bicarbonate in the urine. The result is an alkalinized urine (**increased urine pH**). سؤال يوورلد

- Hypocapnia is a normal phenomenon of late pregnancy caused by direct stimulatory effect of progesterone on central respiratory center→ ↑ respiratory drive, relative hyperventilation and primary resp. alkalosis

RENAL TUBULAR ACIDOSIS

- Group of disorders characterized by non-anion gap metabolic acidosis in the presence of preserved kidney function.

Renal tubular acidosis			
Type	**1 (Distal)**	**2 (Proximal)**	**4** poorly controlled DM
Primary defect	Poor hydrogen secretion into urine	Poor bicarbonate resorption	Aldosterone resistance
Urine pH	≥5.5	<5.5	<5.5
Serum potassium	Low-normal	Low-normal	High
Causes	• Genetic disorders • Medication toxicity • Autoimmune disorders (eg, Sjögren syndrome, rheumatoid arthritis)	Fanconi syndrome (glucosuria, phosphaturia, aminoaciduria)	• Obstructive uropathy • Congenital adrenal hyperplasia

- Normal anion gap metabolic acidosis→ renal and GI abnormality more likely
- All result in growth failure due to poor cellular growth and division in acidic medium
- **Screening labs:** low serum bicarbonate and hyperchloremia→ normal anion gap metabolic acidosis
- Evaluation of urine pH and urine electrolytes can help distinguish different types of RTA

TYPE 1 (DISTAL) RTA

- ↓ H+ excretion in urine→ alkaline urine and no new bicarb generation→ metabolic acidosis
- Alkaline urine→ nephrolithiasis (calcium stones form in alkaline urine) and nephrocalcinosis
- Can occur in sickle cell trait
- **Dx**: give acid→ urine remains basic in it.
- **Rx**: oral bicarb to normalize bicarb level

TYPE 2 (PROXIMAL) RTA

- Inability to absorb HCO3- in proximal tubule→ ultimately all body bicarb is lost→ urine won't excrete more bicarb→ urine and serum acidic
- **Dx:** give bicarb→ urine remains basic instead of preserving bicarb
- **Rx:** oral bicarb replacement and diuretics to ↓ body volume

HYPERKALEMIC RTA OR TYPE 4 RTA

- Impaired function of cortical collecting tubule due to aldosterone def. or resistance to aldosterone→ retain H+ and K+

- Common in elderly pts with **poorly controlled DM** → damage juxtaglomerular apparatus → hyporeninemic hypoaldosteronism → mild hyperkalemia (5.2 to 6.0 mEq/L) and mild acidosis (HCO3 15-20 mEq/L) on a background of preserved or moderately ↓ GFR (20-50 mL/min)
- HTN may or may not be present—usually due to accompanying atherosclerosis

ELECTROLYTE IMBALANCE

HYPERKALEMIA

CAUSES

- Most often due to ↓ urinary potassium excretion. AKD or CKD
- Medications or disorders that impair renin angiotensin axis
- ↑ K+ movement out of cells (e.g. uncontrolled hyperglycemia, metabolic acidosis)
- ↑ tissue catabolism (e.g. trauma, tumor lysis syndrome)

Medications that can cause hyperkalemia	
Medication	**Mechanism**
Nonselective beta-adrenergic blockers	Interfere with beta-2-mediated intracellular potassium uptake
Angiotensin-converting-enzyme (ACE) inhibitors	Inhibition of angiotensin II formation with subsequent decrease in aldosterone secretion
Angiotensin II receptor blockers (ARBs)	Block the AT_1 receptor, thus decreasing aldosterone secretion
K^+-sparing diuretics	Block the epithelial sodium channel (ENaC) or aldosterone receptor
Cardiac glycosides (eg, digoxin)	Inhibition of the Na^+/K^+-ATPase pump
NSAIDs	Impaired local prostaglandin synthesis reduces renin and aldosterone secretion
Cyclosporine	Blocks aldosterone activity
Heparin	Blocks aldosterone production
NSAIDs	Decreases renal perfusion resulting in decreased K^+ delivery to the collecting ducts
Succinylcholine	Causes extracellular leakage of potassium through acetylcholine receptors

- **Trimethoprim:** can cause hyperkalemia by blocking epithelial sodium channel in collecting tubule (similar to K+ sparing diuretic amiloride)—more common in HIV infected pts being treated with high doses, but normal doses can also cause modest ↑ — serial monitoring required in those being treated with high doses to avoid serious complications. Also competitively inhibit renal tubular secretion of creatinine→ artificially ↑ing creatinine level although GFR remains unchanged

CLINICAL FEATURES

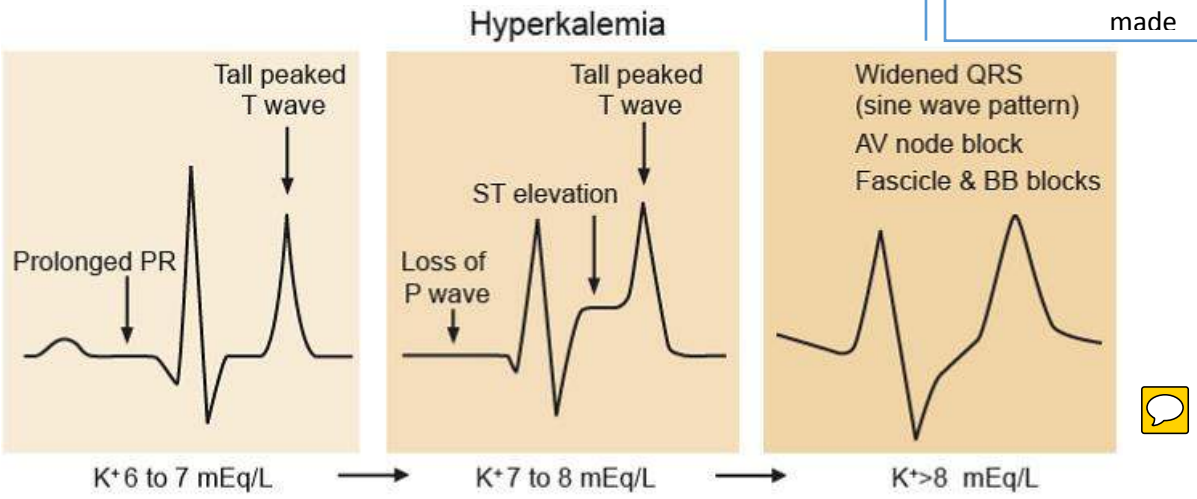
Clinical features of hyperkalemia	
Sequence of ECG changes	• Tall **peaked T waves** with shortened QT interval • **PR prolongation & QRS widening** • Disappearance of P wave • Conduction blocks, ectopy, or **sine wave** pattern
Cardiac membrane stabilization	• **Calcium** infusion
Rapidly acting treatment options	• Insulin with glucose • Beta-2 adrenergic agonists • Sodium bicarbonate
Removal of potassium from the body (slow-acting)	• Diuretics • Cation exchange resins • Hemodialysis

IV form—Calcium chloride or calcium gluconate→ stabilize cardiac memb., making it resistant to effect of ↑ K+

Inhaled form—use in coronary artery disease pts is dangerous as can cause tachycardia and precipitate angina

Diuretics contraindicated in dehydrated pts

Intracellular shift is usually transient, so efforts to ↓ total body K+ should still be made



- Pts with chronic hyperkalemia may be asymptomatic until K+ gradually rises >/=7.0 mEq/L.
- Acute can cause symptoms at lower level
- Pt may develop ascending muscle weakness with flaccid paralysis

MANAGEMENT

1. Initial evaluation with ECG

2. Exclude acute treatable causes of hyperkalemia (e.g. uncontrolled hyperglycemia, tumor lysis syndrome)
3. Review of recent or current meds
4. If none of above causes found, urinalysis for differentiating renal from non-renal causes of hyperkalemia
5. Evaluate for hypoaldosteronism with renin and aldosterone levels

INDICATIONS FOR EMERGENT TREATMENT OF HYPERKALEMIA

- Presence of hyperkalemia-related ECG changes or
- Marked elevation (>6.5 mEq/L) without characteristic ECG changes or
- Rapid rise in serum potassium level due to tissue breakdown

- Hemodialysis best for renal failure pts
- Diuretics delay excretion by approx. 30 min
- Sodium polystyrene sulfonate is a potassium-binding resin that decreases total body potassium content. Sodium is exchanged for potassium in the gut. Sodium polystyrene sulfonate takes at least 1-2 hours to take effect.

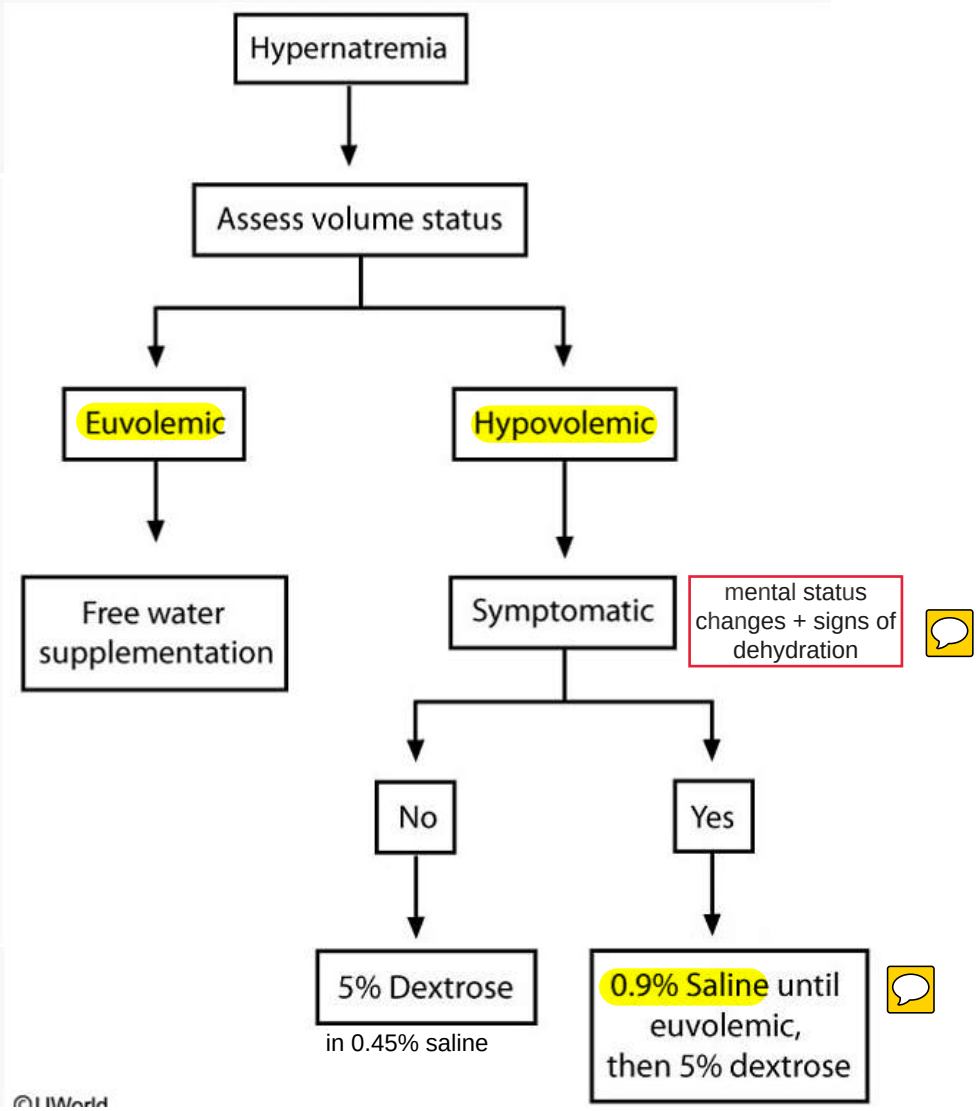
HYPOKALEMIA

CAUSES

1. ↑ K+ entry in to cells: **Beta adrenergic activity** (exogenous or endogenous) →stimulate Na-K ATPase pump and Na-K-2Cl cotransporter→ shift K+ into cells. Also promote **insulin** release→ further shift K+ in to cells. Hematopoiesis also shifts K+ in to cells
2. Renal K+ wasting: e.g. hyperaldosteronism, diuretics
3. GI losses: diarrhea because lower GI has ↑ K+ conc. And vomiting→ metabolic alkalosis→ renal K+ wasting
4. **Hypomagnesemia:** notorious for causing refractory hypokalemia. Chronic alcoholism causes ↓Mg, ↓K and ↓PO4. Mg is imp. cofactor for K+ uptake and maintenance of intracellular K+→ check and correct Mg in chronic alcoholics to correct hypokalemia. Another cause of hypomagnesemia is diuretics

Patients with chronic alcoholism often present with multiple electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypophosphatemia). Hypomagnesemia can lead to refractory hypokalemia that is difficult to correct with potassium replacement.

HYPERNATREMIA



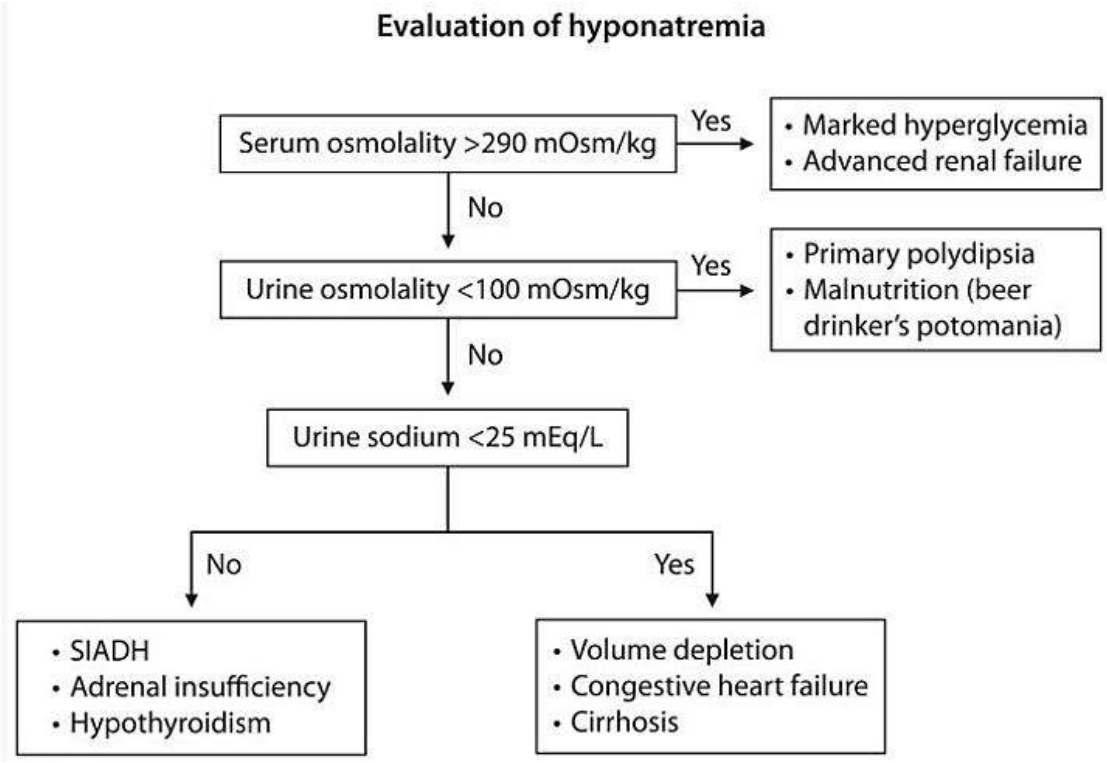
- Most common cause of hypernatremia is hypovolemia
- Causes of hypovolemia: ↑ hypotonic fluid loss and ↓ access to free water (usually in debilitated who do not have access to free water)
- **Management of mild hypovolemic hypernatremia:** 5% dextrose in 0.45% saline
- **Management of severe hypovolemic hypernatremia:** initially isotonic 0.9% saline→ gradually correct the hyperosmolality while normalizing the patient's volume status. Isotonic saline is usually hyposmolar in comparison to the hypernatremic plasma. Once the volume deficit has been restored, such patients are then switched to half-normal (0.45%) saline in order to better replace the free water deficit. The goal rate of plasma sodium correction is no more than 1 mEq/L/h (0.5 mEq/dl/hr) without exceeding 12 mEq/dl/24 hr. A greater rate of correction may result in cerebral edema (colloids are of no more benefit that normal saline and more expensive)
- **Management of euvolemic or hypervolemic hypernatremia:** 5% dextrose in water in treatment of choice
- **5% dextrose is preferred over 0.45% saline**

HYPONATREMIA

- i.e. serum sodium <130 mEq/L
- Can lead to seizure in case of severe hyponatremia

- Medical emergency and needs prompt correction with 3% saline however, correction or serum sodium should not exceed 0.5 mEq/L/hr to avoid causing irreversible damage to brain by osmotic demyelination or central pontine myelinolysis
- Rapid correction in hyponatremia→ fluid moves by osmosis from intracellular space (neurons and ganglia) to extracellular space→ disruption of cellular metabolic activity→ cell damage (osmotic demyelination)—opposite occurs in hypernatremia correction leading to cerebral edema

EVALUATION OF HYPONATREMIA



Patients with serum sodium
1. 130-135 mEq/L are usually asymptomatic
2. 120-130 mEq/L may be asymptomatic or display mild symptoms (lethargy,forgetfulness).
3. <120 mEq/L may have severe symptoms (eg, profound confusion, **seizures,** coma).

- Rapid hyper Na correctoin = cerebral edema
- Rapid Hypo Na correction = osmotic demyelination syndrome (old name: central pontine myelinolysis)

Serum osmolarity	Extracellular volume	Urine findings	Cause of hyponatremia
Normal	-	-	• Hyperproteinemia • Hyperlipidemia
High (> 295 mOsm/kg)	-	-	• Hyperglycemia • Exogenous solutes (radiocontrast, mannitol)

Low (< 280 mOsm/kg)	Hypovolemic	U_{Na} < 10 mEq/L	• Nonrenal salt loss
			  ◦ Dehydration
			  ◦ Vomiting
			  ◦ Diarrhea

		U_{Na} > 20 mEq/L	• Renal salt loss
			  ◦ Diuretics
			  ◦ ACE-inhibitor
			  ◦ Mineralocorticoid deficiency

	Euvolemic	U_{Na} > 20 mEq/L Uosm < 300	• Psychogenic polydipsia • Beer potomania
		UNa > 20 mEq/L Uosm > 300	• SIADH
	Hypervolemic	-	• CHF • Hepatic failure • Nephrotic syndrome

Tx: Diuretic

Causes of hyponatremia	
Hypovolemic hyponatremia	• Volume depletion (eg, acute blood loss) • Primary adrenal insufficiency • Gastrointestinal losses (eg, diarrhea, vomiting) • Renal losses (eg, diuretics)
Euvolemic hyponatremia	• Syndrome of inappropriate antidiuretic hormone (eg, due to drugs, malignancy) • Primary (psychogenic) polydipsia • Secondary adrenal insufficiency • Hypothyroidism
Hypervolemic hyponatremia	• Congestive heart failure • Cirrhosis • Chronic kidney disease or nephrotic syndrome

Hypovolemia→ ↑ renin-angiotensin-aldosterone and ↑ ADH→ corrects hypovolemia by ↑ing water absorption and causes hyponatremia until hypovolemia is corrected

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

- NSAIDS also cause SIADH by potentiating the action of ADH
- Before entertaining the Dx of SIADH, hypothyroidism and adrenal insufficiency should be ruled out. Then calculate plasma and urine osmolarity simultaneously to make final diagnosis
- Calculation of serum osmolarity

$$Serum\ osmolarity = (2 * Na) + (BUN/2.8) + (Glucose/18)$$

- Can occur in the presence of underlying lung cancer
- Findings seen in SIADH are as follows:
  - Serum osmolality <270 mOsm/kg (water retention from high ADH)
  - Urine osmolality >100 mOsm/kg (inappropriately elevated). U_{osm}>S_{osm}
  - Urine sodium >20 mEq/L
  - Absence of hypovolemia
  - Normal serum creatinine, potassium, and acid-base balance
  - Normal adrenal and thyroid function
  - No obvious surgical, traumatic or painful stimulus known to activate the neuroendocrine stress response, including ADH release
  - Absence of other known causes of hyponatremia
  - In addition, when a normal saline fluid bolus is given, the urine sodium excretion appears to increase while the serum sodium is relatively unaffected, indicating that the kidneys are continuing to inappropriately excrete sodium and retain water under the influence of ADH
  - Low serum uric acid level due to ↑ excretion in urine and hemodilution
- Usually asymptomatic or mild symptoms until serum sodium is <120mEq/L

Syndrome of inappropriate antidiuretic hormone	
Etiologies	• CNS disturbance (eg, stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Ectopic ADH secretion (eg, small cell lung cancer) • Pain &/or nausea
Clinical features	• Mild/moderate hyponatremia - nausea, forgetfulness • Severe hyponatremia - seizures, coma • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Serum osmolality <275 mOsm/kg H_2O (hypotonic) • Urine osmolality >100 mOsm/kg H_2O • Urine sodium >40 mEq/L
Management	• Fluid restriction ± salt tablets • Hypertonic (3%) saline for severe hyponatremia

Treatment of SIADH	
Asymptomatic or mild symptoms (forgetfulness, unstable gait)	• Fluid restriction (<800 mL/day) • Possible oral salt tablets • Loop diuretic if urine osmolality >2 times serum osmolality
Moderate symptoms (confusion, lethargy)	• Hypertonic saline in first 3-4 hours to ↑ sodium >120 mEq/L • Later treatment same as for mild hyponatremia
Severe symptoms (seizures, inability to communicate &/or coma)	• Bolus of hypertonic saline until symptom resolution • +/-Vasopressin receptor antagonists (conivaptan)

The serum sodium should then be gradually corrected (0.5-1 mEq/L/hr or 10 mEq/24 hr) to prevent osmotic demyelination syndrome.

This is given IV—renal ADH receptor antagonist→ selective water diuresis. Can be given alone in combo with bolus hypertonic saline

- Hypertonic saline is 3% and has an electrolyte concentration of 1025 mOsm/kg
- Normal saline is 0.9% and has electrolyte conc. Of 300 mOsm/kg and leads to NaCl excretion→worsens condition as effective management of SIADH requires the infused fluid to have a higher electrolyte concentration than the urine (not just that of the plasma).

HYPERCALCEMIA

- Hypercalcemia and ↑ed or inappropriately normal PTH→ either primary hyperparathyroidism or familial hypocalciuric hypercalcemia (FHH)→ difference: primary hyperparathyroidism: ↑ urinary calcium because of excessive calcium mobilization from bone and FHH:↓ urinary calcium
- Can occur due to humoral hypercalcemia of malignancy due to secretion of PTH related protein

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA

- Benign autosomal dominant mutation in calcium sensing receptor (CaSR)
- High levels of calcium needed to suppress PTH.
- Usually very low serum calcium (typically <100mg/24hr)
- Urine calcium can be more precisely calculated using calcium/creatinine clearance ratio (UCCR): UCCR= $(Ca_{urine}/Ca_{serum})/(Creatinine_{urine}/Creatinine_{serum})$
- UCCR is usually <0.01 in FHH compared to >0.02 in primary hyperparathyroidism
- Usually asymptomatic
- Potential complications: pancreatitis and chondrocalcinosis

Management of hypercalcemia	
Severe (calcium >14 mg/dL) or symptomatic malignancy	**Short-term (immediate) treatment** • Normal saline hydration plus calcitonin • Avoid loop diuretics unless volume overload (heart failure) exists **Long-term treatment** • Bisphosphonate (zoledronic acid)
Moderate (calcium 12–14 mg/dL) hyper PTH	• Usually no immediate treatment required unless symptomatic • Treatment is similar to that for severe hypercalcemia
Asymptomatic or mild (calcium <12 mg/dL) thiazides	• No immediate treatment required • Avoid thiazide diuretics, lithium, volume depletion & prolonged bed rest

Restore intravascular volume and promote urinary calcium excretion. Aggressive hydration is needed i.e. several liters of saline

- **Severe hypercalcemia Sx:** weakness, GI distress, and neuropsychiatrist sx (e.g. confusion, stupor, coma) esp. with rapid rise in serum calcium. Polyuria from hypercalcemia induced nephrogenic DI and ↓ oral intake→ volume depletion
- Hemodialysis is an effective treatment for hypercalcemia, but is typically reserved for patients with renal insufficiency or heart failure in whom aggressive hydration cannot be administered safely.

CAUSES OF PERIPHERAL EDEMA

Causes of peripheral edema	
Primary mechanism	**Clinical examples**
Increased capillary hydrostatic pressure	• Heart failure (left ventricular & cor pulmonale) • Primary renal sodium retention (renal disease & drugs) • Venous obstruction (eg, cirrhosis & venous insufficiency)
Decreased capillary oncotic pressure (hypoalbuminemia)	• Protein loss (eg, nephrotic syndrome & protein-losing enteropathy) • Decreased albumin synthesis (eg, cirrhosis & malnutrition)
Increased capillary permeability	• Burns, trauma & sepsis • Allergic reactions • Acute respiratory distress syndrome • Malignant ascites
Lymphatic obstruction/increased interstitial oncotic pressure	• Malignant ascites • Hypothyroidism • Lymph node dissection

↓GFR→ volume overload—occurs in nephritic syndrome & ESRD

CASTS IN URINE

*Extremely high yield question for the USMLE!!!

- Muddy brown granular cast—Acute tubular necrosis
- RBC casts— Glomerulonephritis and vasculitis
- WBC casts— Interstitial nephritis and pyelonephritis—indicate that WBC in urine arise from kidneys
- Fatty casts— Nephrotic syndrome
- Broad and waxy casts— Chronic renal failure→ broad casts arise in dilated tubules of enlarged nephrons that have undergone compensatory hypertrophy. Waxy casts are shiny and translucent
- Hyaline casts—Asymptomatic pts and pts with pre-renal azotemia→ almost entirely proteins and pass unchanged along urinary tract

  epithelial cell casts reflect damage to tubule (aminoglycosides)j

URINARY TRACT INFECTIONS

- Dipsticks: commercially available kits→ detect presence of leukocyte esterase and nitrites in urine in pts with suspected UTI
  - Leukocyte esterase indicate significant pyuria

- Nitrites signify presence of Enterobacteriaceae which convert urinary nitrates to nitrites (most common cause of UTI is E.coli)
- High false positive and false negatives→ -ve test in suspected UTI should be confirmed with culture

Treatment of acute cystitis & pyelonephritis in nonpregnant women	
Uncomplicated cystitis	• **Nitrofurantoin** for 5 days (avoid in suspected pyelonephritis or creatinine clearance <60 mL/min) • **Trimethoprim/sulfamethoxazole** for 3 days (avoid if local resistance rate >20%) • **Fosfomycin** single dose • Fluoroquinolones only if above options cannot be used • Urine culture needed only if initial treatment fails
Complicated cystitis*	• **Fluoroquinolones**** (5-14 days), extended-spectrum antibiotic (eg, ampicillin/gentamicin) for more severe cases • Obtain sample for urine culture prior to initiating therapy & adjust antibiotic as needed
Pyelonephritis	• **Outpatient:** Fluoroquinolones (eg, ciprofloxacin, levofloxacin) • **Inpatient:** Intravenous antibiotics (eg, fluoroquinolone, aminoglycoside +/- ampicillin) • Obtain sample for urine culture prior to initiating therapy & adjust antibiotic as needed

*Associated with diabetes, pregnancy, renal failure, urinary tract obstruction, indwelling catheter, urinary procedure (eg, cystoscopy), immunosuppression & hospital-acquired.

**Do not use fluoroquinolones in pregnancy. Consider cefpodoxime, cephalexin, amoxicillin-clavulanate & fosfomycin

The increased incidence of urinary tract infections in women is due to the shorter length of the female urethra compared to males. Other predisposing factors for UTis include sexual intercourse, recent antibiotic use, the use of spermicidal contraceptives, and a close proximity of the urethra to the anus.

GLOMERULAR AND NON-GLOMERULAR HEMATURIA

	Glomerular hematuria	Non-glomerular hematuria
Type of hematuria	Microscopic >gross hematuria	Gross >microscopic hematuria
Common etiologies	• Glomerulonephritis • Basement membrane disorders (eg, Alport syndrome)	• Nephrolithiasis • Cancer (eg, renal cell, prostate) • Polycystic kidney disease • Infections (eg, cystitis) • Papillary necrosis, renal infarction
Clinical presentation	• Nonspecific or no symptoms • Nephritic syndrome (hypertension, oliguria, elevated creatinine)	• Dysuria or symptoms of urinary obstruction (flank pain, renal or ureteral colic, anuria)
Urinalysis	• Blood **and** protein • RBC casts, dysmorphic RBCs	• Blood but **no** protein • Normal appearing RBCs

- Non-glomerular causes are more common

GLOMERULAR DISEASES

DIFFERENTIAL DIAGNOSIS OF GLOMERULAR DISEASES

Differential diagnosis of glomerular disease		
Classification	**Definition**	**Etiologies**
Mild GN	Nephritic urine sediment without renal insufficiency or nephrotic syndrome	• IgA nephropathy • Lupus nephritis • Thin basement membrane disease
Moderate to severe GN	Nephritic urine sediment, decreased GFR & variable proteinuria (can be nephrotic range)	• Postinfectious, lupus nephritis • MPGN, vasculitis (eg, cryoglobulinemia) • Rapidly progressive glomerulonephritis
Nephrotic syndrome	Bland urinary sediment, proteinuria >3.5 g/day, possible microscopic hematuria	• FSGS, minimal change disease • Diabetes, lupus nephritis • Membranous nephropathy • IgA nephropathy, primary amyloidosis

Bland sediment i.e. few cells or casts. Can present with significant edema and hyperlipidemia

GN = glomerulonephritis; **MPGN** = membranoproliferative GN; Low complement levels usually suggest postinfectious GN, lupus nephritis, MPGN, or mixed cryoglobulinemia associated with hepatitis C.

NEPHRITIC VS NEPHROTIC SYNDROME

Nephrotic versus nephritic syndrome		
	Nephrotic syndrome	**Nephritic syndrome**
Clinical features	• Edema • Fatigue • Proteinuria • Absence of hematuria • Hypoalbuminemia	• Hypertension • Oliguria • Hematuria • Proteinuria • Casts
Pediatric etiologies	• Minimal change disease	• Poststreptococcal glomerulonephritis • Hemolytic uremic syndrome
Adult etiologies	• FSGS • Membranous nephropathy • Membranoproliferative glomerulonephritis	• IgA nephropathy • Membranoproliferative glomerulonephritis • ~~Crescentic glomerulonephritis~~ Rapidly progressive glomerulonephritis (RPGN)

Adolescents &

NEPHRITIC SYNDROME

ALPORT SYNDROME

- Familial disorder
- Presents in childhood as recurrent gross hematuria and proteinuria
- Sensorineural deafness
- **EM:** alternating areas of thickened and thinned capillary loops with splitting of GBM

IgA NEPHROPATHY VS POSTINFECTIOUS GLOMERULONEPHRITIS

	IgA nephropathy	Postinfectious glomerulonephritis
Clinical presentation	• Usually within 5 days of upper respiratory tract infection (**synpharyngitic**) • More common in young adult men (age 20-30) • Recurrent gross hematuria	• Usually 10-21 days after upper respiratory tract infection (post-pharyngitic) • More common in children (age 6-10), but can occur in adults • Gross hematuria • Adults can be asymptomatic or develop acute nephritic syndrome
Diagnosis	• Normal serum complements • Mesangial IgA deposits seen in kidney biopsy	• Low C3 complement • Elevated anti-streptolysin O &/or anti-DNAse B • Kidney biopsy with subepithelial humps consisting of C3 complement
Prognosis	• Usually benign • Possible rapidly progressive glomerulonephritis or nephrotic syndrome with worse prognosis	• Children have good prognosis • Possible chronic kidney disease in adults

- IgA nephropathy may also follow GI infection
- Post-streptococcal glomerulonephritis can also occur after streptococcal skin infection

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

- Nephrotic range proteinuria and hematuria
- **Type 2 (dense deposit disease):** Dense intramembranous deposits that stain for C3 is characteristic. Unique among glomerulopathies, because it is caused by IgG antibodies (termed C3 nephritic factor) directed against C3 convertase of the alternative complement pathway→ persistent complement activation and kidney damage

MIXED ESSENTIAL CRYOGLOBULINEMIA

- Presents with immune complex deposition in small blood vessels→ endothelial injury, inflammation, and end-organ damage.
- Immune complexes are IgM antibodies (similar to rheumatoid factor) that form complexes with IgG anti-hepatitis C virus antibodies, HCV RNA and complement
- Can be asymptomatic or develop signs in skin (e.g. **palpable purpura**, Raynaud's phenomenon), kidney (e.g. MPGN), nervous system (e.g. motor sensory axonopathy, **peripheral neuropathy**) and musculoskeletal system (e.g. **arthralgias**), **hepatosplenomegaly**
- Suspect if: palpable purpura, hematuria, proteinuria are present—majority have underlying HCV infection
- Dx: serologically (**serum cryoglobulins, low complement**), ↑ RF and liver transaminases or with kidney or skin biopsy. Demonstration of circulating cryoglobulins is confirmatory

- Rx: treat underlying hep C and plasmapheresis to remove cryoglobulins and immunosuppressants (e.g. glucocorticoids, cyclophosphamide)

THIN BASEMENT MEMBRANE SYNDROME

- Presents in adulthood—hematuria without proteinuria
- Biopsy reveals markedly thin basement membrane

NEPHROTIC SYNDROME

PRIMARY CAUSES OF NEPHROTIC SYNDROME

Primary renal causes of nephrotic syndrome	
Etiology	**Clinical associations**
Focal segmental glomerulosclerosis	African American & Hispanic ethnicity; obesity; HIV & heroin use
Membranous nephropathy	Adenocarcinoma (eg, breast, lung); nonsteroidal antiinflammatory drugs (NSAIDs); hepatitis B; systemic lupus erythematosus
Membranoproliferative glomerulonephritis	Hepatitis B & C; lipodystrophy
Minimal change disease	NSAIDs; lymphoma
IgA nephropathy	Upper respiratory tract infection

Also known as HIV-related nephropathy—can be manifested even if HIV markers are -ve

Most common form of nephrotic syndrome in solid tumors—knowledge helps screening for tumors

Nephrotic syndrome usually resolves with successful rx of lymphoma

- HIV related glomerulopathies with nephrotic range proteinuria: FSGR (most common), membranous esp. if concomitant hep. B, mesangioproliferative and diffuse proliferative glomerulonephritis

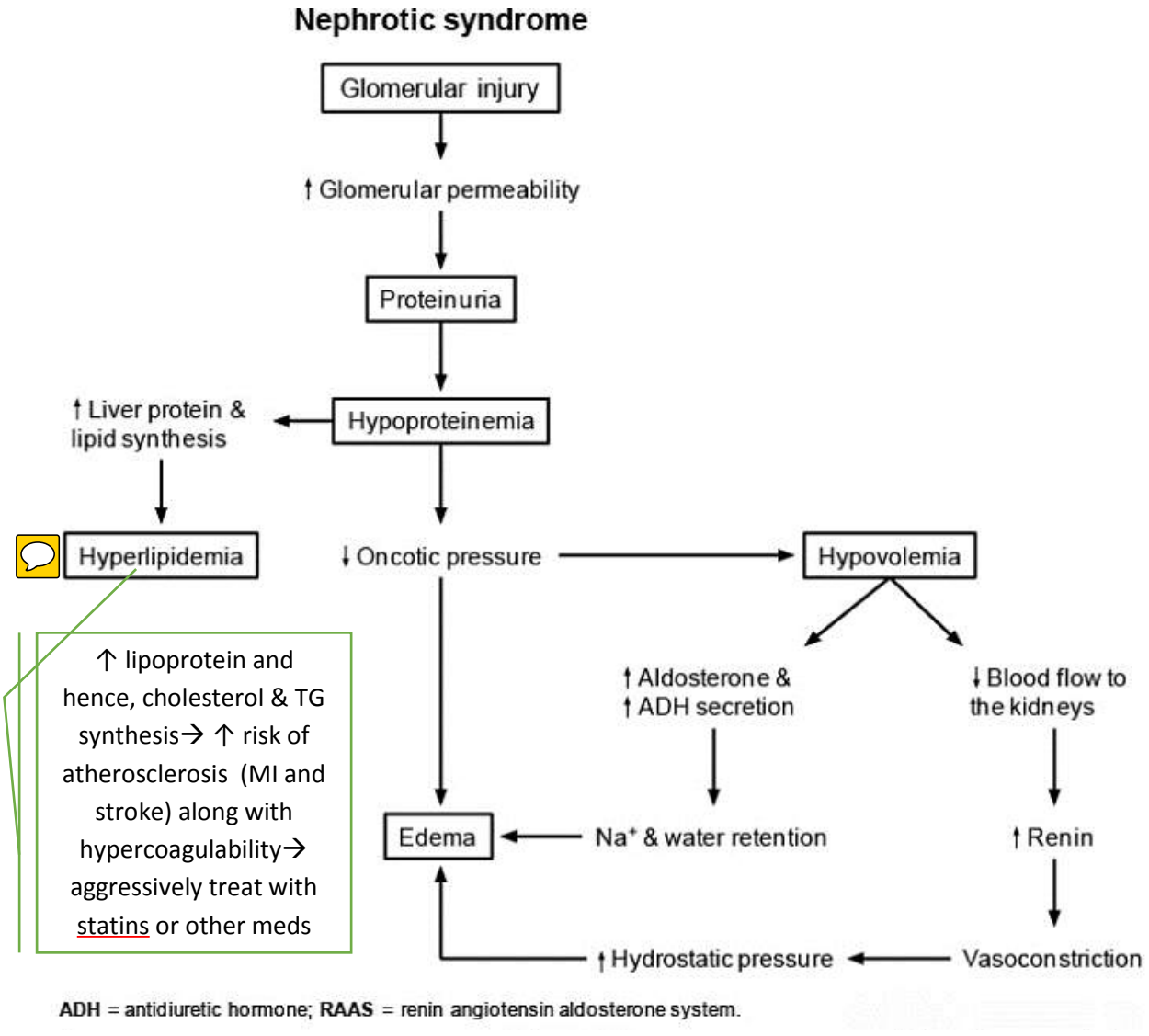
Nephrotic syndrome		
Disease	**Histopathology**	**Epidemiology**
Minimal change disease	Normal	Most common cause in pre-adolescent children
Focal glomerulosclerosis	Crescent formation	Most common cause in adults
Membranous glomerulonephritis	Thickened basement membrane, subepithelial spikes	Second most common cause in adults

COMPLICATIONS

1. **Hypercoagulation**→ risk of thromboembolic complications**. Multifactorial**: increased urinary loss of antithrombin 3, ~~altered levels of protein C and S, increased platelet aggregation, hyperfibrinogenemia due to increased hepatic synthesis, and impaired fibrinolysis~~. Veins more affected than arteries. **Renal vein thrombosis is the most common manifestation of coagulopathy** (especially with membranous glomerulopathy), but arterial thrombosis and pulmonary embolism may also occur. Coagulopathy is less common but more severe in children as compared to adults with nephrotic syndrome.
   - **Renal vein thrombosis:** can present acutely with abdominal pain, fever, and hematuria. More commonly progressive, causing gradual worsening of renal function, proteinuria in an asymptomatic pt.—most common with **membranous nephropathy** than any other cause of nephrotic syndrome

Qid: 2243

2. Protein malnutrition,
3. Iron-resistant microcytic hypochromic anemia due to transferrin loss
4. Vitamin D deficiency due to increased urinary excretion of cholecalciferol-binding protein,
5. Decreased thyroxin levels due to loss of thyroxine-binding globulin, and
6. Increased susceptibility to infection



MEMBRANOUS NEPHROPATHY

- Strong association with hep B and vaccination ↓es the risk
- The pathogenesis of HBVMN: deposition of HBeAg or its corresponding antibody in the glomeruli.
- **Workup:** nephrotic syndrome in pts from Hep. B endemic areas→ screen for hep. B→ a 24-hour urine sample (protein excretion >3 g/day is consistent with NS), serum C3 (typically low with HBVMN), antinuclear antibody (elevated in lupus), and renal biopsy.

MINIMAL CHANGE DISEASE

Minimal change disease	
Epidemiology	• Most common cause of nephrotic syndrome in children • Median age 2–3; 85% of cases occur before 10 years of age
Pathogenesis	• T-cell mediated injury to podocytes causes increased molecular permeability to albumin • Majority of cases are idiopathic
Clinical features	• Edema • Fatigue • No hematuria
Diagnosis	• Proteinuria • Hypoalbuminemia • Renal biopsy without microscopic changes
Treatment	Corticosteroids

- Confirmation of nephrotic range proteinuria: 24 hour urine collection although random level can be used in appropriate clinical situation
- **Dx of MCD**: based on age, clinical presentation and response to steroids
- Empiric steroid therapy should be initiated upon suspicion of the diagnosis. Approximately 85% of children will respond to their first steroid course.
- Renal biopsy is indicated in children age > 10 with nephrotic syndrome, or in any child with nephritic syndrome or minimal change disease that is unresponsive to steroids

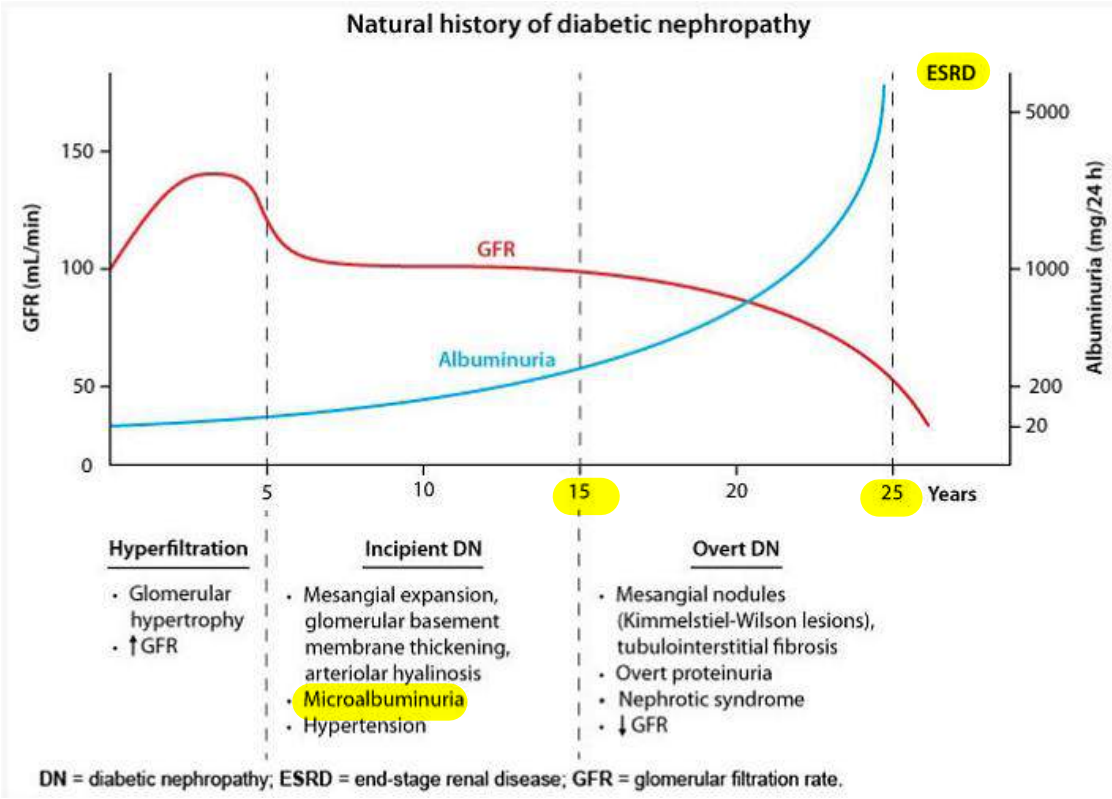
AMYLOIDOSIS

	AL amyloidosis	AA amyloidosis
Associated conditions	• Multiple myeloma • Waldenström macroglobulinemia	• Chronic inflammatory conditions: **rheumatoid arthritis**, inflammatory bowel disease • Chronic infections: osteomyelitis, tuberculosis
Composition of amyloid	• Light chains (usually lambda)	• Abnormally folded proteins: beta-2 microglobulin, apolipoprotein or transthyretin

AA amyloidosis = inflammatory amyloidosis; **AL amyloidosis** = amyloid light-chain amyloidosis.

- Amyloidosis can lead to enlargement of kidneys and liver
- **Renal biopsy**: amyloid deposits that stain with Congo red and demonstrate a characteristic apple-green birefringence under polarized light—deposits are seen in glomerular basement membrane, blood vessels and interstitium of kidney—appear as randomly arranged thin fibrils on electron microscopy
- **Rheumatoid arthritis—** most common cause of AA amyloidosis in US
- **Multiple myeloma—**most common cause of AL amyloidosis

DIABETIC NEPHROPATHY



DN = diabetic nephropathy; ESRD = end-stage renal disease; GFR = glomerular filtration rate.

The sequence of pathological changes in the kidneys of a patient with diabetes mellitus is as follows:

1. Within the first year of diabetes mellitus - **Glomerular hyperperfusion** and renal **hypertrophy** with increase in glomerular filtration rate.

2. First five years of diabetes mellitus - **Glomerular basement membrane thickening**, glomerular hypertrophy, and mesangial volume expansion with glomerular filtration
rate returning to normal.

3. Within 5-10 years of diabetes mellitus- **Microalbuminuria,** which later progresses to overt nephropathy.

- DM is most common cause of ESRD in US, occurring in 30-40% pts and 20% with type I and type II DM after 20 years, respectively

- **Risk factors for DN:** poor glycemic control, ↑ BP, cigarette smoking, increasing age, and ethnicity (eg African American and Mexican American)
- **Earliest renal abnormality:** glomerular hyperfiltration. **First change that can be quantified:** thickening of GBM
- **Most common histologic finding:** diffuse glomerulosclerosis but **pathognomonic finding:** nodular glomerulosclerosis (with Kimmelstiel Wilson nodules)
- **Pathophysiology:** hyperglycemia causes microvascular damage (microangiopathy)
- Development of nephropathy is preceded by excessive protein excretion—initial stages are termed as microalbuminuria
- Microalbuminuria: urine albumin excretion value between 30-300mg/24 hr (normal albumin excretion <30mg/24 hr)
- **Screening:** spot urine collection and timed urine collection for measurement of urine microalbumin to creatinine ratio→ good screening method for microalbuminuria. 24 hour urine collection is slightly more accurate but not preferred because of inconvenience
- Dipstick can detect only macroalbuminuria i.e. >300mg/24 hr→ not recommended in initial stages
- Disease progression can be slowed by strict glycemic control, treatment of HTN and angiotensin axis blockade.
- Diabetic autonomic neuropathy is responsible for overflow incontinence but not diabetic nephropathy
- **Clinical clues suggesting albuminuria due to nondiabetic renal disease** include onset of proteinuria <5 years after disease onset, active urine sediment (eg, red cells, cellular casts), and >30% reduction of GFR within 2-3 months of starting ACEi or ARB

The urine dipstick for proteinuria (albumin)	
Trace	Between 15 and 30 mg/dL
1+	Between 30 and 100 mg/dL
2+	Between 100 and 300 mg/dL
3+	Between 300 and 1000 mg/dL
4+	>1000 mg/dL

HYPERTENSIVE NEPHROPATHY

- HTN—2nd leading cause of end stage renal dis.
- HTN mainly affects renal vasculature
- Arteriosclerotic lesions of afferent and efferent arterioles and glomerular capillary tufts—most common renal vascular lesions seen
- As HTN progresses→ renal blood flow and GFR ↓
- Sequence of kidney damage evolves from nephrosclerosis to glomerulosclerosis
- Nephrosclerosis: hypertrophy and intimal medial fibrosis of renal arterioles

- Glomerulosclerosis: progressive loss of glomerular capillary surface area with glomerular and peritubular fibrosis
- Microscopic hematuria and proteinuria occur due to these glomerular lesions
- Kidneys generally ↓ in size

RENAL ARTERY STENOSIS

- Common finding in older pts
- High prevalence in those with severe HTN or peripheral arterial disease
- Most HTN pts have essential HTN but renovascular HTN (as RAS activates renin-angiotensin system) is the most common treatable cause of 2* HTN and should be suspected in pts with resistant HTN and diffuse atherosclerosis
- **Management:** pts with RAS and renovascular HTN→ manage with aggressive risk factor reduction (aspirin, optimal diabetes and hyperlipidemia control, smoking cessation) to prevent cardiovascular dis.
- **Pts with HTN** should be initially managed with ACEi or ARBs→ dilates glomerular efferent arteriole. Additional antihypertensives may be used for optimal BP control. In **U/L RAS,** stenotic kidney experiences ↓ RBF and ↓ GFR→ unaffected kidney compensates GFR as it is no longer under the effect of angiotensin II mediated renal vasoconstriction. In **B/L RAS,** fall in GFR can lead to ↑ creatinine (acceptable if ↑ is <30%); sometimes CI in such setting but still can be used with close renal function monitoring due to long-term nephroprotective effects
- Renal artery stenting or surgical revascularization is reserved for patients with resistant hypertension or recurrent flash pulmonary edema and/or refractory heart failure due to severe hypertension

Clinical clues to renovascular disease	
HTN-related symptoms	• Resistant HTN (uncontrolled despite 3-drug regimen) • Malignant HTN (with end-organ damage) • Onset of severe HTN (>180/120 mm Hg) after age 55 • Severe HTN with diffuse atherosclerosis • Recurrent flash pulmonary edema with severe HTN
Supportive evidence	**Physical examination** • Asymmetric renal size (>1.5 cm) • Abdominal bruit **Laboratory results** • Unexplained rise in serum creatinine (>30%) after starting ACE inhibitors or ARBs **Imaging results** • Unexplained atrophic kidney

ARBs = angiotensin receptor blockers; HTN = hypertension.

KIDNEY STONES

CAUSES OF STONE INVISIBILITY ON CONVENTIONAL RADIOGRAPHS

1. Radiolucent stones (uric acid stones, xanthine stones)

2. Calcium stones <1-3 mm in diameter
3. Non-stone ureteral obstruction (eg, blood clot, tumor)

CALCIUM STONES

- Most pts with calcium stones have hypercalciuria (24 hour urinary calcium excretion >4mg/kg)

CALCIUM OXALATE STONES

- 75-90% kidney stones are calcium oxalate
- Envelope shaped and seen on microscopic examination
- Radiopaque

CALCIUM OXALATE STONES IN CROHN DISEASE

- Crohn disease, small bowel disease, surgical resection, chronic diarrhea or other small intestinal disorder→ fat malabsorption→ calcium in gut binds fat (normally calcium binds oxalate and causes its excretion)→ oxalate unbound and free to be absorbed into bloodstream→ ↑ excretion of oxalate by kidneys and nephrolithiasis
- Impaired fat absorption also impairs bile salt absorption→ damages colonic mucosa→ ↑ oxalate absorption

CALCIUM PHOSPHATE STONES

- Common in primary hyperparathyroidism and RTA (renal tubular acidosis)

URIC ACID STONES

- **Risk factors**: acidic urine (may be due to defect in renal ammonia excretion), ↑ cell turnover leading to hyperuricemia and hyperuricosuria, dehydration
- **Radiolucent** but often can be seen on USG or CT
- **Rx:**
  - Hydration,
  - Alkalinization of urine—Alkalinization of urine to 6.0 to 6.5 with **oral potassium citrate**—uric acid stones highly soluble in alkaline urine. Citrate is also a stone inhibitor and reduces crystallization.
  - Low purine diet.
  - Allopurinol is added if recurrent despite above measures and esp. if hyperuricosuria and hyperuricemia develop

CYSTINE STONES

*Extremely high yield question for USMLE!!! Qid:3949

- Group of disorders characterized by impaired amino acid transport—several modes of inheritance—family history may be positive
- Defective transport of dibasic amino acids (cysteine, lysine, arginine, and ornithine) by brush border of renal tubular and intestinal epithelial cells→ ↑ urinary excretion
- Cysteine is poorly soluble in water→ hard, radiopaque, hexagonal renal stones
- Positive urine nitroprusside test: detect high level of urinary cysteine, used as qualitative screening procedure and help confirm diagnosis esp. in homozygotes

STRUVITE STONES

- Occur when urine is alkaline because of infection with urease producing bacteria eg Proteus. h/o recurrent UTI's +ve

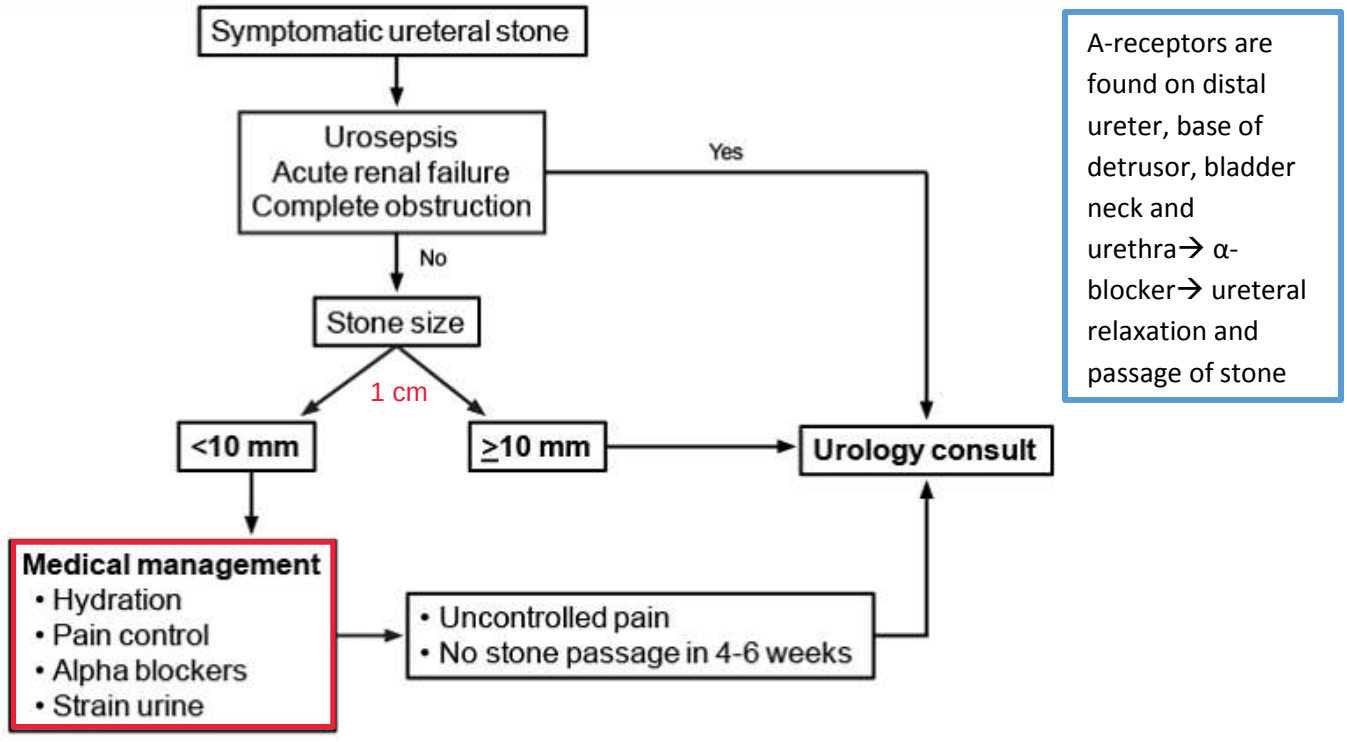
OBSTRUCTIVE UROPATHY Qid: 4749

- Can cause flank pain (renal capsule distention) and poor urine output (mechanical obstruction to urine outflow)
- **Intermittent** episodes of high volume urination can occur when obstruction is **overcome** by large volume of retained urine **(post-obstructive diuresis)**→excessive diuresis→ potassium wasting and dehydration→ weakness leads to
- **Post-obstructive diuresis:** can occur in pts with b/l or u/l functional kidney as affected kidney will produce large amount of urine. However, chances of acute kidney failure are more in pts with u/l functional kidney

MANAGEMENT OF NEPHROLITHIASIS

- Important concepts in management include:

1. **USG or CT without contrast** is better than plain abdominal x-ray (KUB) in detecting radiolucent stones. USG is preferred in pts with low likelihood of other diagnosis and in pregnant pts
2. Narcotics vs NSAIDS—if normal kidney function, then NSAIDS are preferred as narcotics can exacerbate nausea and vomiting
3. Stones <5mm in size usually pass spontaneously with conservative management—adequate hydration i.e. 2L/day→ ↑ urine flow and lowers solute concentration
4. Detailed metabolic evaluation is not needed when pt presents with first time stone. Recurrent stones require evaluation with 24hr urine collection and measurement of calcium, citrate, creatinine, uric acid, oxalate, pH and sodium levels.



A-receptors are found on distal ureter, base of detrusor, bladder neck and urethra→ α-blocker→ ureteral relaxation and passage of stone

Prevention of recurrent nephrolithiasis	
Dietary measures	• Increase fluids (produce >2L urine/day) • Reduce sodium (<100 mEq/dL) • Reduce protein • Normal calcium intake (1200 mg/day) • Increase citrate (fruits & vegetables) • Reduced-oxalate diet for oxalate stones (dark roughage, vitamin C)
Drug therapy	• Thiazide diuretic /amiloride • Urine alkalinization (potassium citrate/bicarbonate salt) • Allopurinol (for hyperuricosuria-related stones)

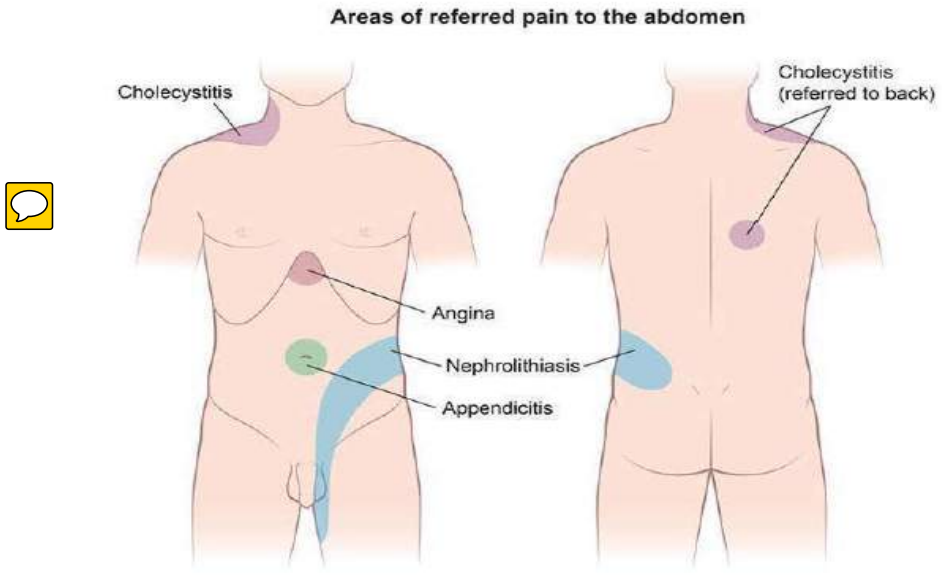
Low sodium intake→ ↑ Na+ and Ca++ reabsorption via medullary conc. Gradient, involving calcium sensing receptor in thick ascending limb of loop of Henle. If pt. continues to develop recurrent stones, urine sodium conc. Can be tested to check adherence to sodium restricted diet

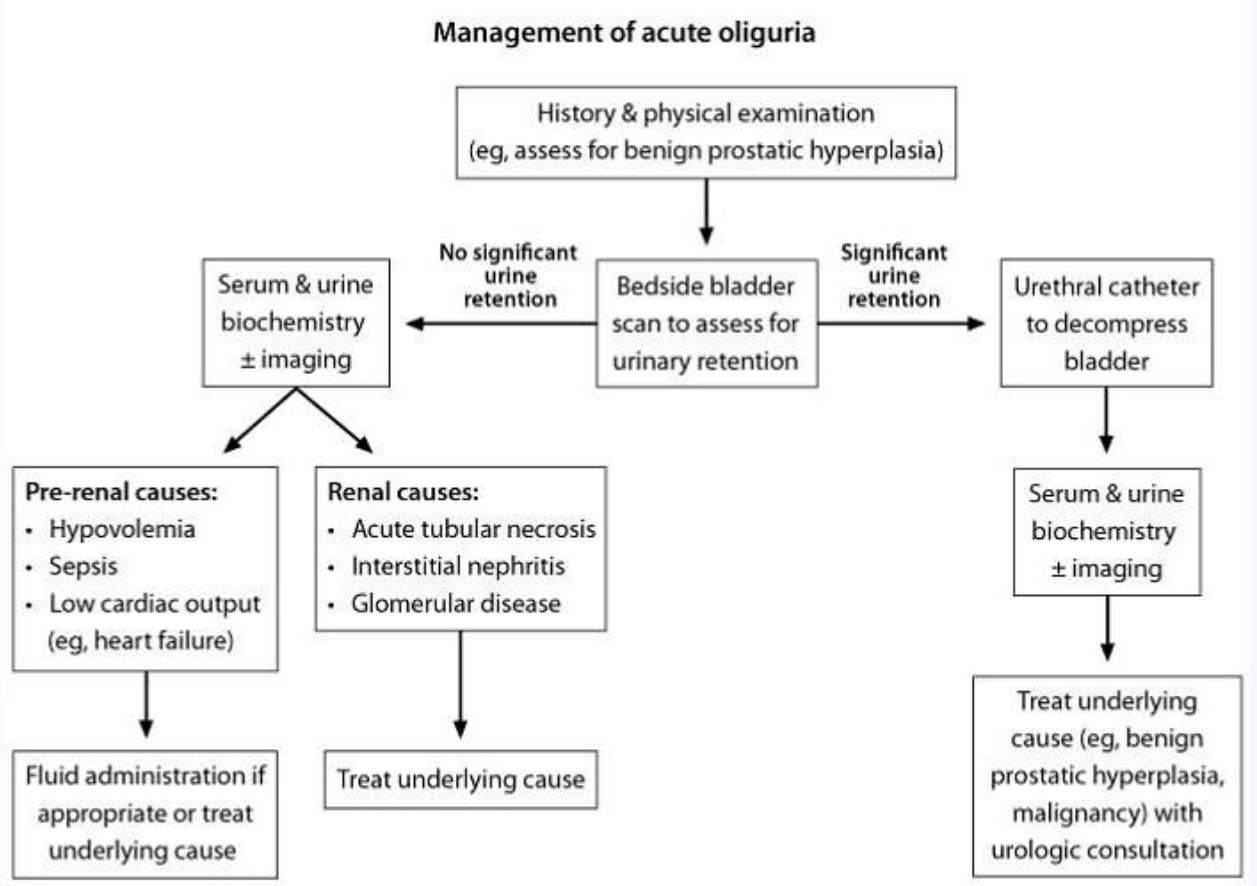
↓ intake of oxalate rich food like chocolate, tea, peanuts

- ➔ Kidney stones can cause ileus which resolves with treatment of ureterolithiasis
- ➔ Ileus occurs in such a case due to vagal reaction
- ➔ But perform CT abdomen if ileus occurs to rule out other causes

URINARY RETENTION

- Certain drugs like anticholinergics, antipsychotics, tricyclic antidepressants (have anti-cholinergic properties), sedative-hypnotics, post-op urinary retention (PUR e.g. bladder distention during general anesthesia, epidural anesthesia—risk of PUR ↑es with advancing age, high fluid intake during surgery and concomitant use of other meds) can cause urinary retention by blocking parasympathetic pathway→↓ detrusor contraction and ↓ internal sphincter relaxation→ oliguria (<250mL urine in 12 hours or </= 0.5mL/kg/hr or < 400 cc/day or <6cc/kg/day) and can lead to acute kidney injury
- Midline suprapubic fullness and tenderness. Bladder distention can cause constipation too
- Urgent urinary catheterization should be performed—bedside USG or bladder scan (if available) can confirm diagnosis but do not delay catheterization—1st step in any pt with recent oliguria is to change urinary catheter to ensure that it is not clogged
- Document post residual volume >50mL and provide symptomatic relief
- Discontinue causative med.
- Severe pain in a patient with a mild urinary obstruction, such as BPH, may cause urinary retention due to inability to Valsalva





- If urinary catheterization does not relieve oliguria or there is no significant urinary retention→ then AKI may be due to other reasons i.e. intrinsic, pre-renal

- oliguria (<250 ml urine in 12 hrs / 500 ml in 24 hrs).
- Postoperative oliguria (s 0.5 mUkg/hr) requires immediate assessment with initial portable bladder scan (if available) to assess bladder volume.
- Next step is foley's cath.
- Most of the Qs of urinary retention were in post op abdominal pain settings.

Qid: 4701

URINARY INCONTINENCE

CAUSES OF URINARY INCONTINENCE IN ELDERLY

Causes of urinary incontinence in the elderly	
Genitourinary	• ↓ detrusor contractility, detrusor overactivity • Bladder or urethral obstruction (eg, tumor, BPH) • Urethral sphincter or pelvic floor weakness • Urogenital fistula
Neurologic	• Multiple sclerosis • Dementia (eg, Parkinson, Alzheimer, normal pressure hydrocephalus) • Spinal cord injury, disc herniation
Potentially reversible	• **D**elirium • **I**nfection (eg, UTI) • **A**trophic urethritis/vaginitis • **P**harmaceuticals (eg, alpha blockers, diuretics) • **P**sychological (eg, depression) • **E**xcessive urine output (eg, diabetes mellitus, CHF) • **R**estricted mobility (eg, postsurgery) • **S**tool impaction • Alcohol

BPH = benign prostatic hyperplasia; CHF = congestive heart failure; UTI = urinary tract infection.

Reversible causes should be excluded 1st esp. UTI as it is the leading cause and then chronic causes should be evaluated

- Alpha-adrenergic antagonists (urethral relaxation)
- Anticholinergics, opiates, calcium channel blockers (urinary retention/overflow)
- Diuretics (excess urine production)

Urinary incontinence		
Type	**Symptoms**	**Treatment**
Stress	Leaking with coughing, sneezing, laughing, lifting	• Lifestyle modification • Pelvic floor exercises • Pessary • Pelvic floor surgery
Urge	Sudden, overwhelming, or frequent need to empty the bladder	• Lifestyle modification • Bladder training • Antimuscarinic drugs
Overflow	Constant involuntary dribbling of urine & incomplete emptying	• Cholinergic agonists • Intermittent catheterization for chronic retention

Kegel exercises—1st line. Urethral sling surgery—if above don't work. Pessary reserved for poor surgical candidates

E.g. oxybutynin→ ↑ bladder capacity and ↓ detrusor contraction→ monitor for urinary retention

E.g. bethanechol

Differential diagnosis of urinary incontinence		
Type	**Etiology**	**Symptoms**
Stress	Loss of urethral support & intraabdominal pressure exceeds urethral sphincter pressure	Leaking with coughing, sneezing, laughing, lifting
Urge	Detrusor overactivity	Sudden, overwhelming, or frequent need to empty bladder
Overflow	Impaired detrusor contractility, bladder outlet obstruction	Constant involuntary dribbling of urine & incomplete emptying

EVALUATION OF INCONTINENCE

- Should include urinalysis and urine culture to exclude UTI first and other reversible causes esp. if onset is acute and in elderly—elders usually do not present with typical signs and Sx of UTI
- Measurement of post void residual (PVR) may be considered to rule out overflow incontinence (</= 150 mL in women and </= 50 mL in men. In men >65 yrs, can be </=100 mL due to slowing of normal voiding mechanisms)

STRESS INCONTINENCE

- Occur in association with obesity, pregnancy, multiparity, pelvic surgery and menopause
- Pelvic floor (levator ani) muscles form a U-shaped sling around the pelvic viscera and hold the bladder and urethra in the appropriate anatomic position.
- Injury to pelvic floor muscles→ urethral hypermobility and urethral prolapse out of pelvis. Bladder may also prolapse (e.g. cystocele) causing vaginal bulge
- **Dx:**
  - **Q-tip test**: place pt in dorsal lithotomy position→ insert cotton swab into urethral orifice→ angle >/=30* from horizontal on ↑ in intra-abdominal pressure signify urethral hypermobility
  - Urinalysis and post void residual volume should be normal (<150ml in women and <50ml in men)
- **Another type of SUI:** result from **internal urethral sphincter deficiency (ISD)**
  - **Rx:** injectable bulking agents→ ↑ pressure at bladder neck and ↓ urine loss in pts with ISD (this Rx is not for urethral hypermobility)

URGE INCONTINENCE

- It is the result of **detrusor inactivity**
- **Risk factors:** age >40 years, female gender and pelvic surgery
- **Sx** occur throughout the day and not related to events that ↑ intra-abdominal pressure
- **Rx:** pelvic floor exercises and bladder training→ initial management. Bladder training involves resisting the urge to void for progressively longer periods to increase bladder capacity. Reducing consumption of alcoholic, caffeinated, and carbonated beverages is also recommended → no response→ pharmacologic therapy
- Sx of urge incontinence are exacerbated by pessary

INTERSTITIAL CYSTITIS

Interstitial cystitis (painful bladder syndrome)	
Epidemiology	• More common in women • Associated with psychiatric disorders (anxiety) & pain syndromes (fibromyalgia)
Clinical presentation	• Bladder pain with filling, relief with voiding • ↑ frequency, urgency • Dyspareunia
Diagnosis	• Bladder pain with no other attributable cause for ≥6 weeks duration • Normal urinalysis
Treatment	• Not curative; focus is on quality of life • Behavioral modification & trigger avoidance • Amitriptyline • Analgesics for exacerbations

Also worsened by exercise and alcohol consumption

- Symptom onset is gradual and worsen over a period of months
- Dx mainly clinical

CRYSTAL INDUCED NEPHROPATHY

Clinical features of crystal-induced acute kidney injury	
Common etiologies	• Acyclovir • Sulfonamides • Methotrexate • Ethylene glycol • Protease inhibitors
Clinical presentation	• Usually asymptomatic • Elevated creatinine within 1-7 days of starting drug • Urinalysis can show hematuria, pyuria & crystals • ↑ Risk with underlying volume depletion, chronic kidney disease
Treatment	• Discontinue drug, volume repletion • Concurrent volume repletion while giving drug can prevent kidney injury

Visualized with polarizing light

- Acyclovir is rapidly excreted by kidneys in urine but it has less solubility in urine→ precipitates in renal tubules→ intratubular obstruction and direct renal tubular toxicity. Less commonly causes AKI through acute tubular necrosis or acute interstitial nephritis. More common with large IV doses than with oral

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis	
Causes	• **Drugs (penicillins, TMP-SMX, cephalosporins,** NSAIDS)
Clinical features	• Maculopapular rash • Fever • New drug exposure • +/- Arthralgias
Laboratory findings	• Acute kidney injury • Pyuria, hematuria, WBC casts • Eosinophilia, **urinary eosinophils** • Renal biopsy: Inflammatory infiltrate, edema
Management	• Discontinue offending drug • +/- Systemic glucocorticoids

NSAIDS = nonsteroidal anti-inflammatory drugs;
TMP-SMX = trimethoprim-sulfamethoxazole; **WBC** = white blood cell.

Rifampin, diuretics. Less commonly may also be caused by infectious agents (e.g. Legionella, Mycobacterium tuberculosis, Streptococcus)

Eosinophils are less frequent and absent in NSAID induced AIN

- Sx appear 5 days to several wks after use of offending agent

ANALGESIC NEPHROPATHY

Clinical features of analgesic nephropathy	
Clinical presentation	• Associated with long-term use of 1 or multiple analgesics (eg, aspirin, ibuprofen) for chronic headaches or other somatic complaints • Usually asymptomatic but can have chronic tubulointerstitial nephritis or hematuria due to papillary necrosis
Diagnosis	• Elevated creatinine with urinalysis showing hematuria or sterile pyuria • Can have mild proteinuria (<1.5 g/day) • CT can show small kidneys with bilateral renal papillary calcifications

Polyuria & sterile pyuria are early findings. Chronic kidney disease occurs

WBC casts

- Most common form of drug-induced chronic renal failure
- Pts typically asymptomatic, found incidentally with ↑ creatinine
- Analgesics→ vasoconstriction of medullary blood vessels (vasa recta)→ papillary ischemia→ prominent and painless hematuria. Significant papillary necrosis and sloughing → renal colic
- HTN, mild proteinuria and impaired urinary concentration develop as disease progresses
- Advanced dis. may present with nephrotic range proteinuria
- Common in females average age 50-55 yrs
- Generally seen after cumulative ingestion of 2-3 kg (4.4-6.6 lbs) of index drug
- Patients with chronic analgesic abuse are also more likely to develop premature aging, atherosclerotic vascular disease, and urinary tract cancer

ACUTE TUBULAR NECROSIS

- Suggestive findings:
  - BUN:Cr→ <20:1
  - Urine osmolality of 300-350 mOsm/L (but never <300)
  - Urine sodium >20 mEq/L
  - FE—Na→ >2%
  - Muddy brown granular casts—consists of renal tubular epithelial cells—non-specific but very sensitive

RHABDOMYOLYSIS INDUCED ACUTE RENAL FAILURE

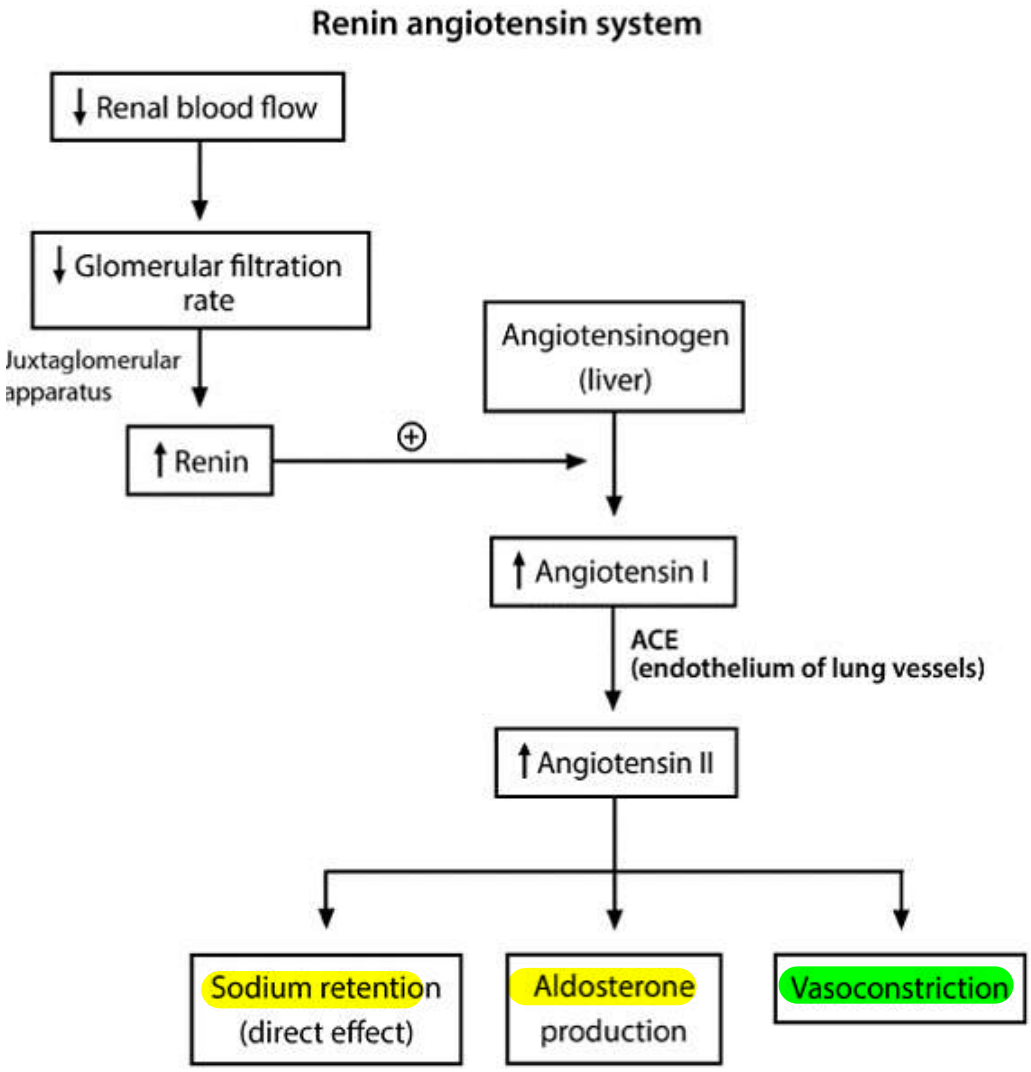
- Risk factors of rhabdomyolysis: immobilization, cocaine abuse.
  - Immobilization: cause direct muscle damage→ ↑ CPK, K+ and myoglobin
  - Cocaine: cause systemic vasoconstriction→ diffuse ischemia, seizures, agitation, incidental trauma, hyperpyrexia, and a direct toxic effect on myocytes→ all ↑ muscle breakdown→ ↑ CPK, K+ and myoglobin—occur in 20% cases of cocaine overdose
- Renal failure in rhabdomyolysis is caused by ATN
- Risk of myoglobin induced ARF ↑ if CPK is >20,000 units/L
- Dipstick: +ve for blood but not for RBCs

- Risk ↓ed with aggressive hydration. Mannitol and urine alkalinization may be beneficial

PRERENAL AZOTEMIA

- Hypotension and volume depletion e.g. due to sepsis→ pre-renal azotemia→give IV isotonic saline → improvement. Condition can temporarily worsen to cause ATN or septic shock.
- Hypotension→ ↓ effective renal blood flow (RBF)→ **activation of renin-angiotensin-aldosterone system**→ angiotensin constricts glomerular arteriole (efferent > afferent)→ maintains intraglomerular pressure and GFR despite ↓ RBF. ↓RBF→ release prostaglandins→ dilate afferent arteriole → maintain GFR. Continued volume depletion→overwhelms this response and intraglomerular pressure falls→ GFR falls despite maximal efferent arteriolar constriction Qid: 4567 see it
- In prerenal azotemia→ ↑ADH→ renal tubules avidly reabsorb sodium and water. Urea absorption also ↑es→ ↑ BUN:Cr → **>20**
- Persistent untreated renal hypoperfusion→ intrinsic renal failure due to ischemia→ ATN→ BUN:Cr becomes <20 due to impaired absorption
- **Aggravating factors:** nephrotoxic drug like NSAIDS (like aspirin by inhibiting prostaglandin effect), metformin, ACE and ARB (prevent the action of angiotensin on arterioles) and ↓ fluid intake commonly in elderly pts (leads to ↓ intravascular volume) and diuretics further worsen volume depletion
- Metformin can cause lactic acidosis in acute kidney injury, liver failure and sepsis and should be held until renal function improves.

Factors that may aggravate prerenal azotemia:
1. Decreased oral intake
2. Diuretics (woresen volume depletion)
3. ACEi (block RAAS response)
4. NSAIDs (block prostaglandin dilatation effect)



CT-CONTRAST INDUCED NEPHROPATHY

- **Pathogenesis:** renal vasoconstriction and tubular injury
- **Risk factors:** h/o diabetes and chronic renal insufficiency (elevated baseline creatinine) esp. at risk
- **Presentation:** spike in creatinine within 24 hours of contrast administration, followed by return to normal renal function within 5-7 days
- **Prevention:** adequate pre-CT IV hydration with isotonic bicarb or normal saline is single most imp intervention for prevention—start prior to procedure and should continue several hours after procedure. Acetylcysteine has also been shown to prevent nephropathy, likely due to vasodilatory and antioxidant properties. Also advise to discontinue NSAIDs cox of vasoconstriction effect
  - ➔ **Prednisone** prevents contrast induced hypersensitivity in pt with known allergy—Sx include flushing, angioedema, urticarial, bronchospasm etc. Does not prevent nephropathy. But can cause fluid retention in pts with renal insufficiency, leading to HTN

CHRONIC RENAL FAILURE

- Chronic renal failure→ gradual loss of nephrons→ remaining nephrons maintain kidney's ability to excrete daily acid load by producing more NH3 buffer that removes H+ as NH4+ in urine
- Metabolic acidosis rarely seen until advance renal dysfunction (GFR <20 mL/min)

- Non-anion gap metabolic acidosis and hyperkalemia that occur out of proportion to the renal dysfunction indicate a renal tubular disorder.

UREMIC COAGULOPATHY

*Extremely high yield question for USMLE!!!

Qid: 3951

- Commonly seen in CRF
- Abnormal bleeding and bruising—characteristic
- Nowadays, ecchymosis and epistaxis—major bleeding manifestations seen due to advent of dialysis; however, GI bleeding, hemopericardium, subdural hematoma, and bleeding from surgical or invasive sites can still occur due to uremic coagulopathy
- **Pathophysiology:** multifactorial—major defect involves platelet-vessel wall and platelet-platelet interaction. Several uremic toxins have been implicated in the pathogenesis of **platelet dysfunction** seen in chronic renal failure (CRF), the chief among which is guanidinosuccinic acid

.**Labs:** PT, aPTT, TT normal -
.Bleeding time (BT)—reflect platelet function→ abnormal
Platelet count is normal

- **Rx:** no. of agents like desmopressin (DDAVP), cryoprecipitate, and conjugated estrogen have been used to correct coagulopathy in uremic pts. DDAVP increases the release of factor VIII: von Willebrand factor multimers from endothelial storage sites. Platelet transfusion—not indicated as transfused platelets quickly become inactive

END STAGE RENAL DISEASE

- Only two treatment options: transplant or dialysis. Transplant from living relative donor preferred over everything
- Advantages of transplant:
  - Better survival and quality of life
  - Better control on anemia, bone disease and HTN (persist with dialysis)
  - Normal return of endocrine, reproductive and sexual functions and enhanced energy; thus, fulltime employment and more strenuous activity possible
  - Improvement or stabilization of autonomic neuropathy in diabetics (persists or become worse in dialysis pt)
  - 1 year survival 95% and 5 year survival 88% —dialysis: 5 year survival in non-diabetics 30-40% and in diabetics 20%

DIALYSIS

Indications for urgent dialysis (AEIOU)	
Acidosis	• Metabolic acidosis ◦ pH <7.1 refractory to medical therapy

Electrolyte abnormalities	• Symptomatic hyperkalemia
	  ◦ ECG changes or ventricular arrhythmias
	• Severe hyperkalemia
	  ◦ K >6.5 mEq/L refractory to medical therapy

Ingestion	• Toxic alcohols (methanol, ethylene glycol) • Salicylate • Lithium • Sodium valproate, carbamazepine
Overload	Volume overload refractory to diuretics

Uremia	• Symptomatic:
	  ◦ Encephalopathy
	  ◦ Pericarditis
	  ◦ Bleeding

Asterixis: due to interruption of neural pathway that sustain muscle contraction. Can occur in uremic enceph., hepatic enceph., and CO2 retention. Rx: Dialysis in uremic enceph. and lactulose in hepatic enceph. (↓ albumin and ↑ bilirubin will be present)

- Most common cause of death in dialysis and renal transplant pt: cardiovascular disease. Accounts for 50% deaths in dialysis pts: 20% due to acute MI and 60% due to sudden cardiac death
- **Risk factors for cardiovascular disease not related to dialysis:** pts on dialysis have already multiple risk factors for cardiovascular dis. These are:
  - HTN (96%)
  - DM (54%)
  - Low serum HDL cholesterol (33%)
  - Left ventricular hypertrophy by ECG criteria (22%)
  - Coronary artery disease: approx. 75% pt with total ESRD have atleast 50% narrowing of atleast one coronary artery
  - ↑ age: average age at start of dialysis is 60 yrs
- **Risk factors for cardiovascular disease due to ESRD and dialysis:**
  - ESRD: by itself is independent risk factor for cardiovascular dis.
  - Anemia
  - Metabolic abnormality, esp. hyperphosphatemia and ↑ PTH
  - ↑ homocysteine level due to impaired metabolism and ↓ excretion
  - ↑ atherogenesis due to oxidant stress due to uremia and bio-incompatible renal replacement therapies
  - Increased calcium intake (calcium is given to correct hyperphosphatemia in dialysis patients): This enhances coronary artery calcification

- Inhibition of NO: This is a common finding in dialysis patients, and can cause vasoconstriction and hypertension
- Infection in 15-20% dialysis pts
- Withdrawal of dialysis in 20% pts cause death

*Extremely high yield question for the USMLE!!!

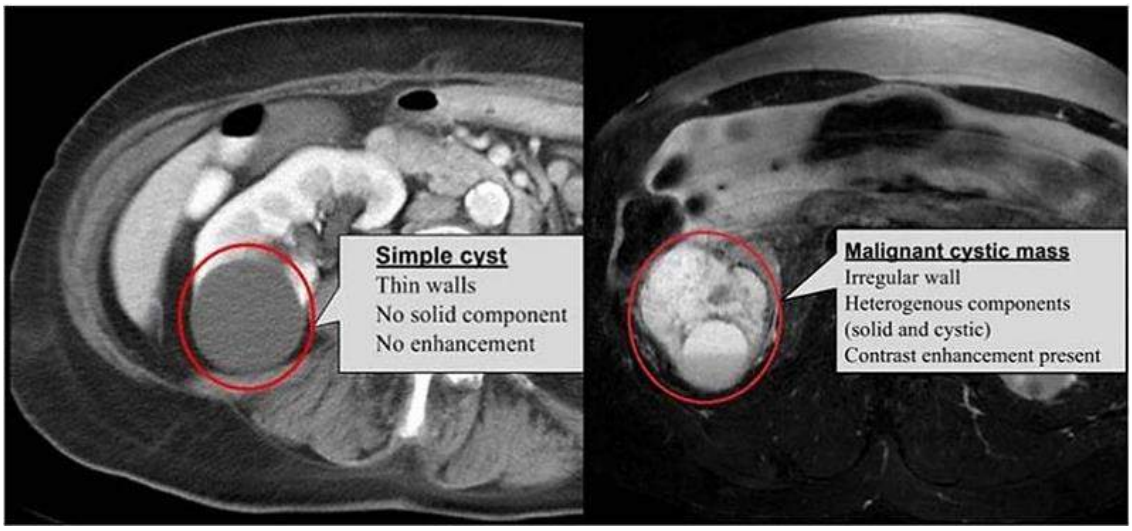
Qid: 4152

RENAL TRANSPLANT DYSFUNCTION

- In early post-op period, manifests as: oliguria, HTN, and ↑ creatinine/BUN ratio
- Can be explained by no. of causes: ureteral obstruction, acute rejection, cyclosporine toxicity, vascular obstruction, ATN etc
- **Dx:** Radioisotope scanning, renal ultrasound, MRI, and renal biopsy can be employed in conducting a differential diagnosis. Serum cyclosporine levels for cyclosporine toxicity
- **Rx:** If acute rejection is suspected→ rapid institution of anti-rejection therapy, including high dose IV steroids, is important

RENAL CYSTS

Characteristics of renal cysts	
Simple renal cyst	**Malignant cystic mass**
• Thin, smooth, regular wall	• **Thick, irregular wall**
• Unilocular	• Multilocular
• No septae	• Multiple **septae**, occasionally thick & calcified
• Homogenous content	• Heterogenous content (solid & cystic)
• Absence of contrast enhancement on CT/MRI	• Presence of **contrast enhancement** on CT/MRI
• Usually asymptomatic	• May cause pain, hematuria, or hypertension
• No follow-up needed	• Requires follow-up imaging & urological evaluation for malignancy



AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

- HTN, palpable b/l flank masses and microhematuria
- Extra-renal complications:
  - Intracranial berry aneurysms (common and dangerous when coupled with HTN but routine screening not needed)—seen in 5-10% cases
  - Hepatic cysts—most common extra renal manifestation
  - Valvular heart disease (MVP and aortic regurgitation)
  - Colonic diverticula
  - Abdominal wall and inguinal hernia

PROSTATE

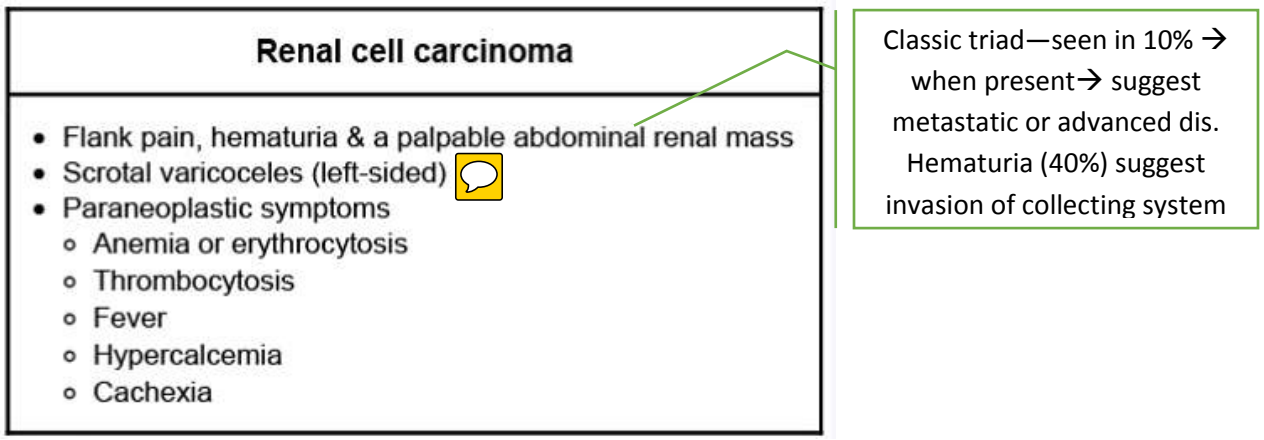
COMPARISON OF BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER

Comparison of benign prostatic hyperplasia & prostate cancer		
	BPH	**Prostate cancer**
Risk factors	Age >50	Age >40, **African American** & family history
Affected part	**Central** portion (transitional zone)	Usually **lateral** lobes of prostate, but can be anywhere
Examination	• Symmetrically enlarged & smooth • Can have elevated PSA	• Asymmetrically enlarged, **nodules** & firm prostate • Markedly elevated PSA

BENIGN PROSTATIC HYPERPLASIA

- **Evaluation**:
  - Current recommendations suggest **urinalysis** in pts with BPH, based on history and rectal examination, to evaluate hematuria (for bladder and kidney stones) and infection
  - PSA is recommended for prostate cancer in men with life expectancy of >10years
  - Serum creatinine test—bladder outlet obstruction should be considered in any pt with BPH and acute kidney injury→ ↑ creatinine→ kidney imaging preferably with renal USG to exclude other causes of obstruction and assess for hydronephrosis. (creatinine usually not ↑ed in u/l obstruction)
- **Rx:**
  - **Urinary catheterization** for quick relief of obstruction
  - **Medical treatment:** α-1 blocker (e.g. tamsulosin, doxazosin) alone or in combo with 5-α reductase inhibitor (e.g. finasteride) for symptomatic relief
  - **Surgery:** for severe symptoms (eg, bladder outlet obstruction, recurrent UTIs) or failing medical therapy

RENAL CELL CARCINOMA



- Most RCC pts are asymptomatic until disease is advanced
- 20% pts may have constitutional symptoms: fever, night sweats, weight loss, anorexia or easy fatigability
- CT scan of abdomen—most sensitive and specific—should be obtained when index of suspicion is high

BLADDER CANCER

WORK-UP

- Initial evaluation of gross hematuria: urinalysis to rule out infection and confirm microhematuria (>/=3 RBCs/hpf) as red urine can occur in other conditions like microglobinuria, beet ingestion, rifampin intake
- Cystoscopy is recommended for all patients with unexplained gross hematuria or with microscopic hematuria and other risk factors for bladder cancer

Indications for cystoscopy
• Gross hematuria with no evidence of glomerular disease or infection • Microscopic hematuria with no evidence of glomerular disease or infection but increased risk for malignancy • Recurrent urinary tract infections • Obstructive symptoms with suspicion for stricture, stone • Irritative symptoms without urinary infection • Abnormal bladder imaging or urine cytology

- CT scan with contrast should also be performed to evaluate bladder and urethra
- Average age of diagnosis is 65 years
- Screening is not recommended because of low incidence and poor predictive value of current screening tests

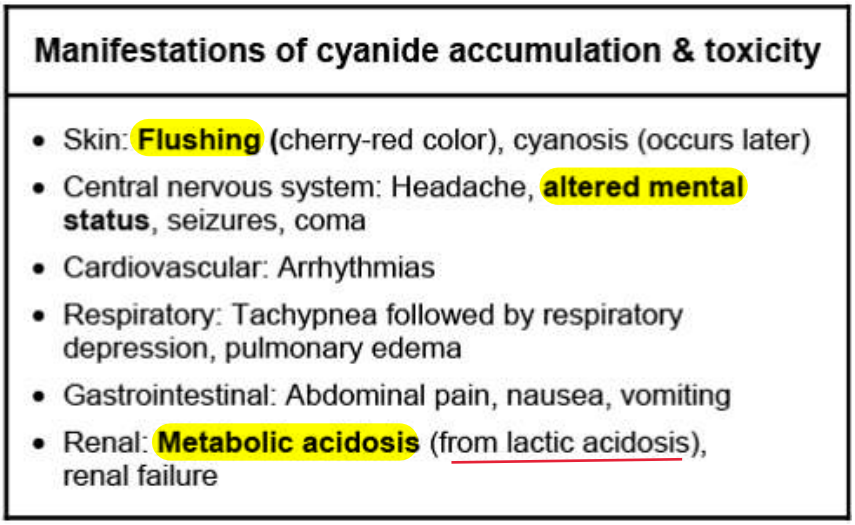
CAUSES OF GROSS OR MICROSCOPIC HEMATURIA

- Renal (eg, renal cell cancer, lgA nephropathy),
- Ureteral (eg, stricture, stone),
- Bladder (eg, cancer, cystitis), and
- Prostate/urethral (eg, BPH, prostate cancer, urethritis) abnormalities→ though BPH can cause hematuria, still rule out bladder cancer with cystoscopy→ if –ve→ start BPH meds

RISK FACTORS FOR BLADDER CANCER

1. Cigarette smoking—Cigarette smoking is the most important risk factor for bladder cancer. While smoking cessation decreases this risk, patients still have a higher risk than nonsmokers even up to 20 years after smoking cessation
2. Age >35
3. Certain occupational exposures (eg, painters, metal workers),
4. Chronic cystitis,
5. Iatrogenic causes (eg, cyclophosphamide), and
6. Pelvic radiation exposure. ~~Cigarette smoking is the most important risk factor for bladder cancer. While smoking cessation decreases this risk, patients still have a higher risk than nonsmokers even up to 20 years after smoking cessation~~

CYANIDE TOXICITY



- **Causes:**
  - Combustion of carbon and nitrogen containing compounds (e.g. wool and silk)
  - Industrial exposure (e.g. metal extraction in mining)
  - Medications (e.g. sodium nitroprusside)
- **Pathophysiology:** cyanide binds to cytochrome oxidase and inhibit mitochondrial oxidative phosphorylation→ anaerobic metabolism starts→↓ ATPs→ lactic acidosis

SODIUM NITROPRUSSIDE

- Potent arterial and venous vasodilator→ often used for HTN emergencies
- Contains 5 cyanide groups→ rapid conversion to cyanide and eventually thiocyanate→ eliminated by kidneys eventually
- Prolonged infusion (>24hours) at high rate (>5-10 µg/kg/min) can lead to cyanide toxicity, esp. in pts with CKD
- **Prevention:** low infusion rates (<2 µg/kg/min), short-term use and close monitoring
- **Rx:** sodium thiosulfate

PHARMACOLOGY

THIAZIDE DIURETICS think glucose / lipids / uric acid (all increase) anything else decrease

- E.g. chlorthalidone, hydrochlorothiazide
- **S/E:** impair insulin release from pancreas and glucose utilization in peripheral tissue→ **glucose intolerance**—seen more commonly in diabetes mellitus and metabolic syndrome (HTN, dyslipidemia, abdominal obesity)
- ~~**Metabolic adverse effects**— dose-dependent—more commonly occur with chlorthalidone than other thiazides. However, chlorthalidone is preferred in this class as compared to other thiazides based on ALLHAT trial. In this trial, chlorthalidone was associated with an overall ↓ in cardiovascular mortality comparable to that with other novel anti-HTN meds (e.g. ACEi, dihydropyridine CCB)~~
  - ~~Diuretics- often used in cor pulmonale but should be used cautiously—can cause acute kidney failure by lowering volume→ ↓ cardiac output→↓ renal perfusion→ prerenal azotemia/acute kidney injury~~

SUCCINYLCHOLINE UW 4428

- Depolarizing neuromuscular blocker
- **Use:** rapid-sequence intubation as it has rapid onset (45-60 sec) and offset (6-10 min) of action
- **S/E:** can cause significant potassium release and life-threatening arrhythmia
- **Contraindications:** pts with or at risk of hyperkalemia. Includes pts with: crush or burn injuries >8hours old (high risk of rhabdomyolysis), pts with demyelinating syndromes like Guillain-Barre and pts with tumor lysis syndrome. Non-depolarizing agents such as vecuronium or rocuronium are better in such pts.
- Hepatic dysfunction is not a CI for succinylcholine but lower doses should be used.
- No effect of and on calcium conc.

DIURETIC ABUSE

- Some people abuse is for weight loss→ hypovolemia with hyponatremia, hypokalemia and hypochloremia and elevated urinary Na+ and K+. (cerebral salt wasting also leads to hypovolemia with hyponatremia and ↑ urinary Na+ (>20mEq/L)—but is always 2* to brain surgery or injury)

Diagnosis of orthostatic (postural) hypotension
Within 2-5 minutes of standing from supine position: • Drop in systolic blood pressure ≥20 mm Hg OR • Drop in diastolic blood pressure ≥10 mm Hg

➔ Target blood glucose in acutely ill pt: 140-180 mg/dl→ short acting insulin typically recommended

POINTERS

- Aminoglycosides can be used in pts with renal dysfunction but their serum levels and the pt's renal function must be monitored closely—cox' of their S/E, they are being used with ↓ing frequency in older pts
- Phenazopyridine is an analgesic for urinary tract mucosa frequently used to treat the dysuria of cystitis (eg, after infection or instrumentation). It may worsen stone formation (mechanism unknown).

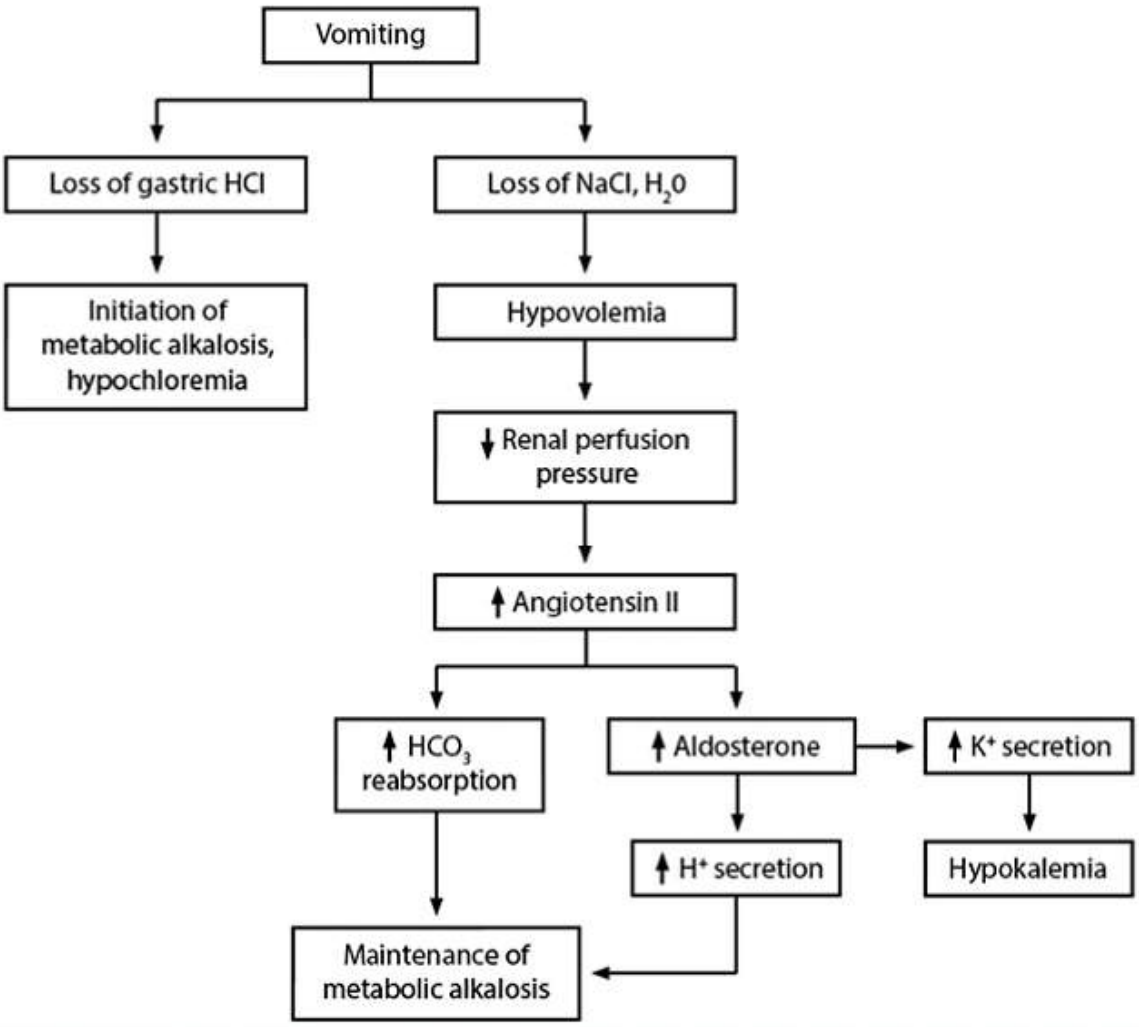
Contents

HYPOVOLEMIC HYPERNATREMIA

- When giving IV food boluses, only isotonic fluids like normal saline or Ringer's lactate should be used

ELECTROLYTE DERANGEMENT IN PYLORIC STENOSIS

Laboratory derangements in pyloric stenosis



URINARY TRACT INFECTIONS

Urinary tract infection		
Microbiology	*E coli* most common cause	
Clinical features	**Cystitis**	Dysuria, frequency, urgency, hematuria, suprapubic pain
	Pyelonephritis	Fever >38 C (100.4 F), chills, flank pain, costovertebral angle tenderness & nausea/vomiting, +/– cystitis symptoms
Diagnosis	Urinalysis & urine culture	
Treatment	Antibiotics	

Children < 2years are at ↑ risk of complications and should be treated for 1-2wks with antibiotics

- Must be diagnosed and treated promptly as involves kidneys
- **Risk factors:** girls of all ages (short urethra), sexual intercourse (introduces bacteria in to introitus→ bacteria ascends up the urethra to bladder), uncircumscribed boys (age </=1 year) and underlying renal anomalies (e.g. VUR, posterior urethral valve)
- **Sx during infancy:** non-specific and vague (e.g. fever, fussiness, ↓ urine output), abdomen/flank pain and dysuria are difficult to determine as infants are non-verbal
- The presence of fever **>39 C (102.2 F)** in any child age <3 should prompt evaluation for occult UTI.
- **Dx:**

Diagnostic tests in urinary tract infections	
Serum BUN & creatinine	Estimate renal function
Urine dipstick	Qualitative measurement of urine properties
Urinalysis	Quantitative measurement of urine properties
Urine culture	Identification, quantification & susceptibility testing of bacterial colonies

- Mid-stream clean-catch urine specimen for **children who do not wear diapers**—external genitalia thoroughly cleaned to prevent contamination wit skin flora
- **Infants and toddlers in diapers** should **undergo straight catheterization** of the urethra to obtain a sterile urine specimen. Clean-catch specimens are unreliable in diapered patients due to a high likelihood of stool or skin flora confounding the result.

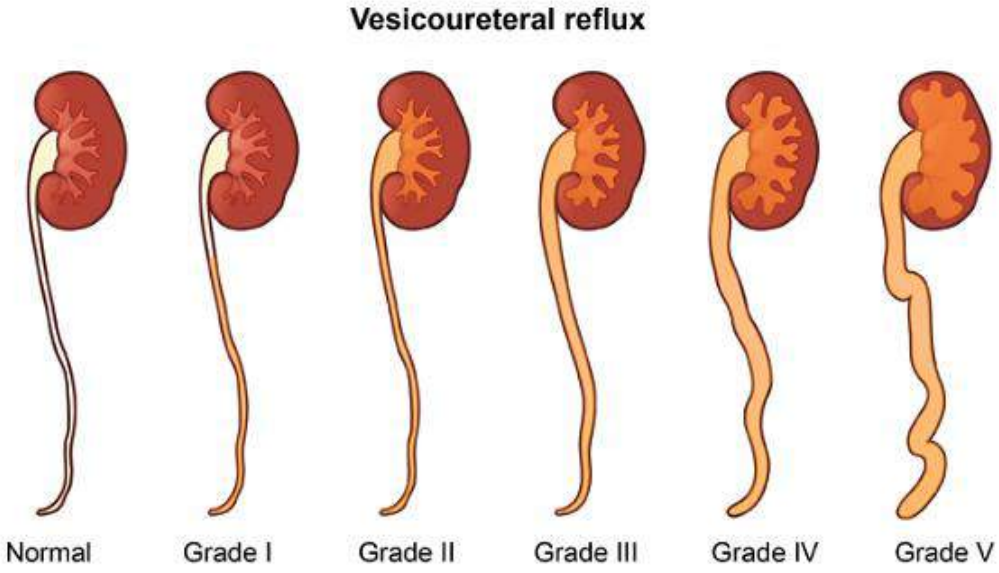
Indications for renal & bladder ultrasound
• Infants and children age < 24 months with a first febrile UTI • Recurrent febrile UTIs in children of any age • UTI in a child of any age with a family history of renal or urologic disease, hypertension, or poor growth • Children who do not respond to appropriate antibiotic treatment

- Ideally USG should be performed after improvement of fever and Sx to avoid false positive result from acute inflammation
- If persistent of worsening Sx→ perform USG immediately to assess for renal abscess
- Repeat blood work and urine culture only in those who fail to improve after 2-3 days of antibiotics—no need to prove a cure if clinical improvement seen

RECURRENT UTI'S IN INFANTS AND CHILDREN

- Serious problem as often involve kidney and indicate congenital urinary tract abnormality
- Most common abnormality is **vesicoureteral reflux (VUR)**

VESICOURETERAL REFLUX

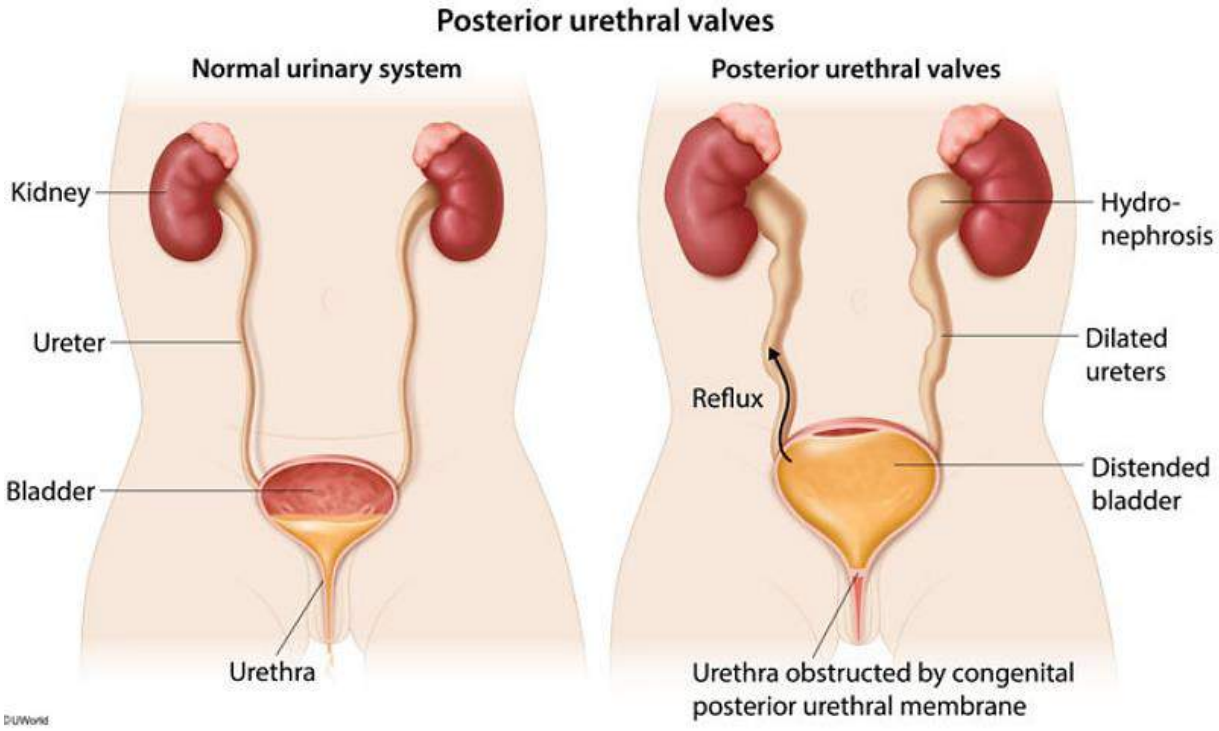


Grade	Description
I	Into a nondilated ureter
II	Into the pelvis & calyces without dilation
III	Mild to moderate dilation of the ureter, renal pelvis & calyces, with minimal blunting of the fornices
IV	Moderate ureteral tortuosity & dilation of the pelvis & calyces
V	Gross dilation of the ureter, pelvis & calyces; loss of papillary impressions; ureteral tortuosity

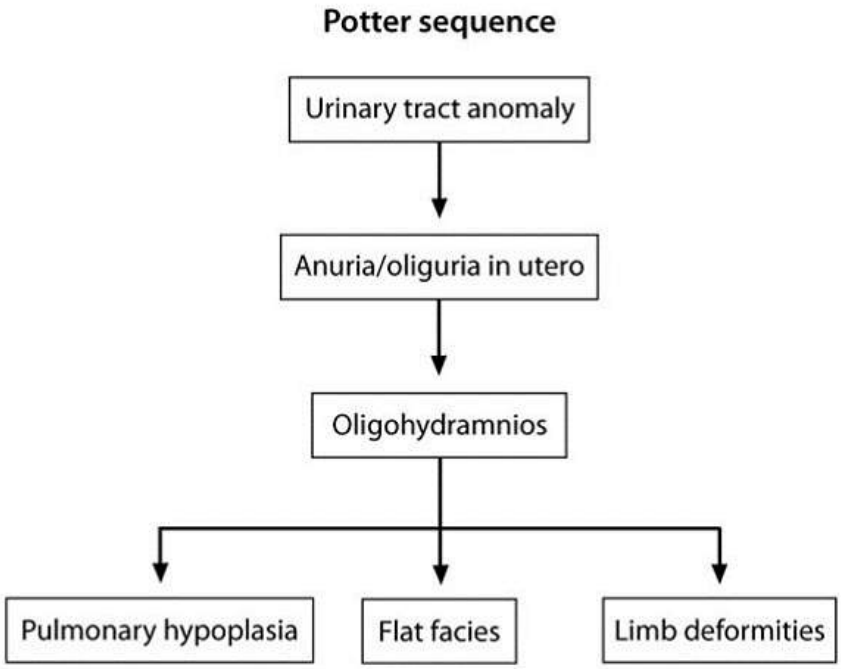
- Can cause hydroureter and hydronephrosis
- **Dx:**
  - **1st UTI** at 2-24 mo→ **renal and pelvic USG** to look for any anatomic abnormality that predispose to VUR→ normal→ reassuring and no need to perform VCUG after 1st one
  - Children <2 year with recurrent UTI's, or newborns <1 mo, or 1st UTI from organism other than E.coli, or renal USG showing renal scarring or hydronephrosis→definitive dx made by **voiding cystourethrogram**
  - **Renal USG** to screen for hydronephrosis
  - Recurrent and/or chronic pyelonephritis can lead to blunting of calices (calyceal clubbing) and focal parenchymal scarring. **Renal scintigraphy with dimercaptosuccinic acid** is the preferred modality for long-term evaluation for renal scarring
  - Renal function followed by **serial creatinine**
  - Monitor closely for complications of **chronic renal insufficiency** like HTN and anemia

POSTERIOR URETHRAL VALVES

- Most common cause of urinary tract obstruction in newborn boys



- Abnormal folds in the distal prostatic urethra obstruct urinary flow→ progressive dilation of bladder, ureter and kidneys
- Oligohydramnios in 2nd trimester is ominous→ ↑ perinatal mortality



- Other affected infants can present with poor urinary stream, straining with voiding, urosepsis, failure to thrive, and renal failure.
- **Diagnosis** is confirmed by voiding cystourethrogram and cystoscopy.
- **Treatment** options include PUV ablation and urinary diversion.
- **Prognosis:** Despite prenatal diagnosis and early surgical intervention, patients are at high risk for permanent kidney damage.

ENURESIS

- Urinary incontinence in children >/5 years
- **Primary:** child who never achieved dryness
- **Secondary:** return of incontinence after >/= 6mo of dryness

PRIMARY ENURESIS

Monosymptomatic (isolated) enuresis	
Definition	Urinary incontinence in children age ≥5
Workup	• Urinalysis • Urologic imaging for children with significant daytime symptoms & history of recurrent UTI

Management	• Behavior modifications
	  ◦ Avoid sugary/caffeinated beverages
	  ◦ Void regularly during the day & immediately before bedtime
	  ◦ Drink ample fluids in the morning & early afternoon; minimize fluid intake before bedtime
	  ◦ Reward system (eg, "gold star" chart)
	• **Enuresis alarm**: 1st-line intervention when behavior modifications fail; best long-term outcome
	• Pharmacotherapy: Best for short-term improvement; high risk of relapse
	  ◦ 1st-line: **Desmopressin**
	  ◦ 2nd-line: Tricyclic antidepressants

UTI = urinary tract infection.

Can take 3-4 mo to be effective

Oral desmopressin is used: S/E: risk of relapse 70% and hyponatremia if too much fluid consumed in evening. Intranasal desmopressin not used cox of ↑ risk of hyponatremic seizure

- **Monosymptomatic enuresis:** that is not explained by any other medical condition and that occurs atleast twice a week after 5 years
- **Oxybutynin→** anticholinergic medication→ causes urinary retention. Reserved for use in combination with desmopressin to increase bladder capacity in children with daytime incontinence.

SECONDARY ENURESIS

Causes of secondary enuresis	
Etiology	**Associated symptoms**
Psychological stress	• Behavior regression, mood lability
Urinary tract infection	• Dysuria, hesitancy, urgency, abdominal pain
Diabetes mellitus	• Polyuria, polydipsia, polyphagia, weight loss, lethargy, candidiasis
Diabetes insipidus	• Polyuria, polydipsia
Obstructive sleep apnea	• Snoring, dry mouth, fatigue, hyperactivity, irritability

Due to impaired sleep arousal

- **DM type 1:** bimodal distribution:**4-6 years** and **early puberty**
  - **Next step in evaluation of DM:** include urinalysis, serum chemistry, hemoglobin A1c, and blood gas analysis. When euglycemia is achieved with insulin therapy, glucosuria and polyuria should resolve, curing the enuresis.

PROTEINURIA IN CHILDREN

- Urine dipstick can be positive in 10% school-aged children
- Proteinuria in children can be of three types:
  - Transient (intermittent)
  - Orthostatic
  - Persistent

TRANSIENT PROTEINURIA

- Most common
- Causes: fever, stress, exercise, seizures, volume depletion

ORTHOSTATIC PROTEINURIA

- Very common in adolescent boys
- ↑ Protein when pt is upright and returns to normal when pt is recumbent

  - ➔ If the urinalysis shows no hematuria and is otherwise normal**, the urine dipstick should be repeated on at least two additional specimens**. If these **subsequent tests are negative for protein**, the diagnosis is transient proteinuria. Transient and orthostatic proteinurias are usually benign conditions that require no further evaluation
  - ➔ Proteinuria persistent on repeat sample or if any additional studies abnormal→ refer to pediatric nephrologist and evaluate for underlying renal disease
  - ➔ Further investigations may include: 24 hour urine collection, renal USG and renal biopsy

HENOCH-SCHONLEIN PURPURA

Henoch-Schönlein purpura	
Pathogenesis	• IgA-mediated leukocytoclastic vasculitis
Clinical manifestations	• Palpable purpura • Arthritis/arthralgia • Abdominal pain, intussusceptions • Renal disease similar to IgA nephropathy
Laboratory findings	• Normal platelet count & coagulation studies • Normal to ↑ creatinine • Hematuria +/- RBC casts +/- proteinuria
Treatment	• Supportive (hydration & NSAIDs) for most patients • Hospitalization & systemic glucocorticoids in patients with severe symptoms

RBC = red blood cell; **NSAIDs** = nonsteroidal antiinflammatory drugs.

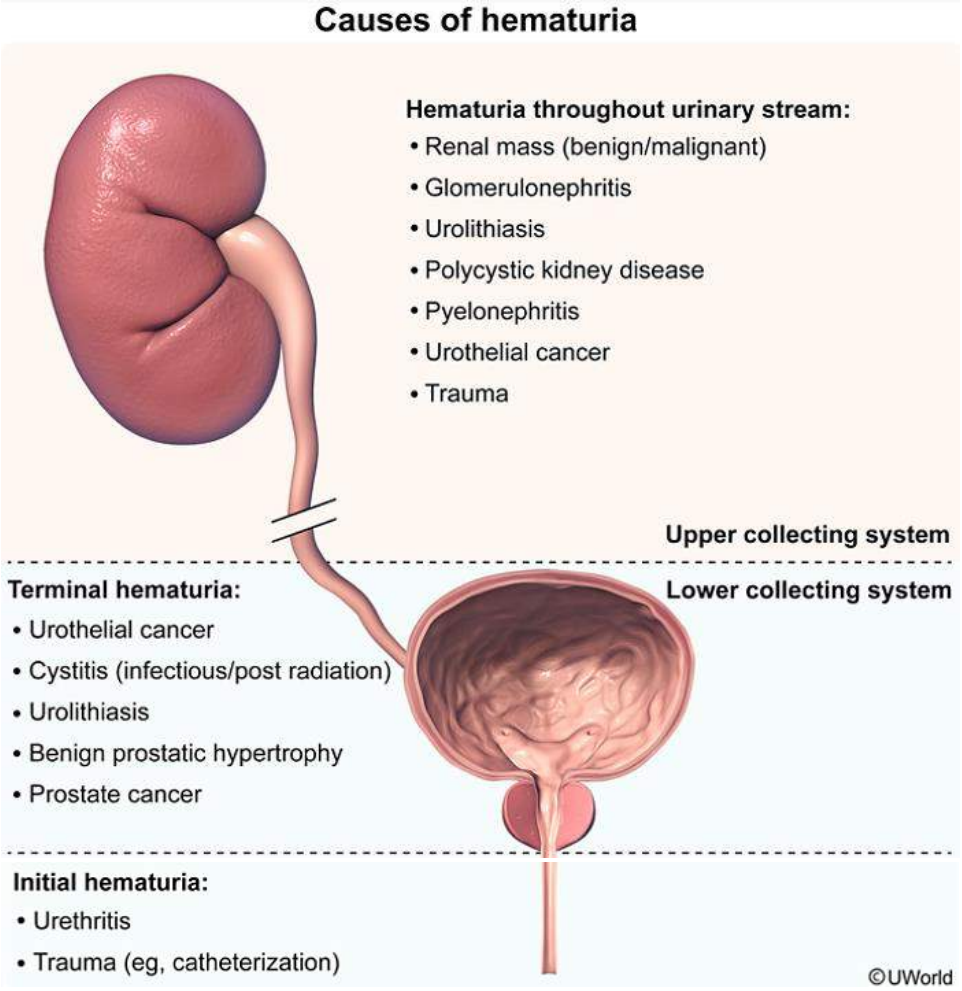
Symmetrically involve lower legs, buttocks and arms

Most commonly affects knees and ankles— transient and no permanent damage to joint

- Renal involvement in 20-50% cases:
  - May occur 4-6wks after onset of illness
  - Mild disease: more common—microscopic or macroscopic hematuria, RBC casts, proteinuria (usually non-nephrotic range), normal or slightly ↑ creatinine
  - Severe disease: nephrotic syndrome, HTN and ARF
- **Dx:** clinical in pts with typical presentation.
  - Dx requires lower extremity purpura or petechiae with at least one of the following: arthritis/arthralgia, renal involvement, abdominal pain (colicky and is thought to be due to bowel wall vasculitis) or positive serology
  - Atypical symptoms→ renal biopsy to help confirm diagnosis: deposition of IgA in mesangium

Contents

HEMATURIA



TRAUMA

- All trauma pts→ evaluate for cardiorespiratory stability→ spine immobilized until spinal injury has been ruled out→ perform neurological examination as part of primary survey→ if weakness and ↓ pain sensation suggesting spinal cord injury and absence of obvious pelvic injury and blood at urethral meatus→ place urinary catheter to assess for urinary retention and prevent possible bladder injury from acute distension→ imaging to diagnose and evaluate spinal cord damage→ surgical intervention for acute cord compression with neurologic defects or unstable vertebral fracture/dislocation
- Airway protection and mechanical ventilation→ not needed if pt is awake and has a normal respiratory examination
- Peripheral IV access→ additional IV access, e.g. femoral line, not needed in hemodynamically stable pts if adequate peripheral IV access is established

URETHRAL INJURY

- Classified based on anatomical location

ANTERIOR URETHRAL INJURY

- Anterior urethra: portion distal to urogenital diaphragm
- **Causes**: blunt trauma to perineum (straddle injuries) or instrumentation of urethra
- **C/F**:
  - Perineal tenderness or hematoma,
  - Normal prostate
  - Bleeding from urethra
  - May not complain of inability to urinate
  - Delayed presentation may be complicated by sepsis 2* to extravasation of urine into scrotum, perineum and/or abdominal wall

POSTERIOR URETHRAL INJURY

- Consists of prostatic and membranous urethra
- **Causes:** commonly associated with fractures of pelvis
- **C/F:** suprapubic pain and inability to void following major trauma despite urge to void
- **Examination:**
  - Blood at urethral meatus
  - High riding prostate due to displacement of prostate by a pelvic hematoma, and
  - Scrotal hematoma
  - Distended bladder
  - Signs and symptoms of pelvic fracture
- Urethral injury suspected clinically→ **retrograde urethrogram** prior to Foley's catheter placement → determines whether damage has occurred to urethra and where occurred
- Blind insertion of Foley's is CI in suspected cases as it can cause infection of periurethral hematoma and can ↑ severity of urethral tear
- An immediate surgical repair is occasionally done in cases of anterior urethral injury. Most cases of urethral injury are treated with urinary diversion via a suprapubic catheter while the primary injury and associated hematomas are allowed to heal. After healing is complete, residual damage, such as urethral stricture, is assessed and repaired.

BLADDER INJURY

- A retrograde cystogram with post void films is used for diagnosis of bladder injury. Bladder injury may occur following major trauma, especially pelvic fracture. Patients typically complain of gross hematuria.

POINTERS

- **IV cefazolin—**antimicrobial prophylaxis before surgery to prevent wound infections—usually given within 60 minutes of procedure

Contents

RENAL STONES

- Need special consideration—usual diagnostic studies can expose fetus to radiation
- Renal and pelvic USG is the diagnostic study of choice—also detects signs of obstruction e.g. hydroureter, hydronephrosis
- Physiologic hydronephrosis in pregnancy should be distinguished from pathological hydronephrosis due to obstruction
- CT and IV pyelogram→ CI in pregnancy→ limited CT/low dose CT urography can be considered in 2nd and 3rd trimester only if safer procedures not helpful
- Shockwave lithotripsy—CI in pregnancy. If a pregnant patient fails to improve with conservative measures, ureteroscopy or nephrostomy may be considered.

URINARY TRACT INFECTION (UTI) IN PREGNANCY

Urinary tract infection & asymptomatic bacteriuria during pregnancy

Condition	Clinical features	Management
Asymptomatic bacteriuria	• Positive urine culture (>100,000 colonies/mL) in asymptomatic patient • Screening usually done at 12-16 weeks gestation • Treatment reduces progression to UTI & complications (eg, preterm birth, low birth weight)	• Nitrofurantoin for 5-7 days • Amoxicillin or amoxicillin-clavulanate for 3-7 days • Fosfomycin as single dose • Avoid fluoroquinolones in all trimesters • Avoid trimethoprim/sulfamethoxazole in 1st & 3rd trimesters
Acute cystitis	• Symptomatic patient (eg, dysuria, urgency) with positive urine culture • Considered a complicated UTI	
Acute pyelonephritis	• Flank pain, nausea/vomiting, fever (>38 C [100.4 F]) &/or costovertebral angle tenderness • May or may not have cystitis symptoms	• Hospitalization & intravenous antibiotics (eg, β-lactams, meropenem) • Avoid aminoglycosides unless other agents cannot be used • Change to 10- to 14-day course of oral antibiotics after afebrile for 24 hours

Congenital malformations in 1st trimester and ↑ risk of kernicterus in 3rd

- 40% ↑ risk of bacteriuria-- ↑ risk of upper UTI due to progesterone induced smooth muscle relaxation and dilation of ureter
- E.coli accounts for >70% cases.
- A follow-up urine culture should be done after a week to document resolution of bacteriuria.
- Monthly urine cultures are recommended for the duration of the pregnancy to monitor for recurrent infection.
- Patients with persistent bacteriuria after >/=2 courses of therapy require daily suppressive therapy (eg, nitrofurantoin) for the duration of the pregnancy.

UTI antibiotics in pregnancy	
Recommended	**Contraindicated**
• Nitrofurantoin • Amoxicillin • Amoxicillin-clavulanate • Cephalexin	• Tetracyclines • Fluoroquinolones • Trimethoprim-sulfamethoxazole

- Amoxicillin—is appropriate first choice but as some E. coli strains have developed resistance, antibiotic may need to be changed on the basis of culture and sensitivity result

POSTPARTUM URINARY RETENTION

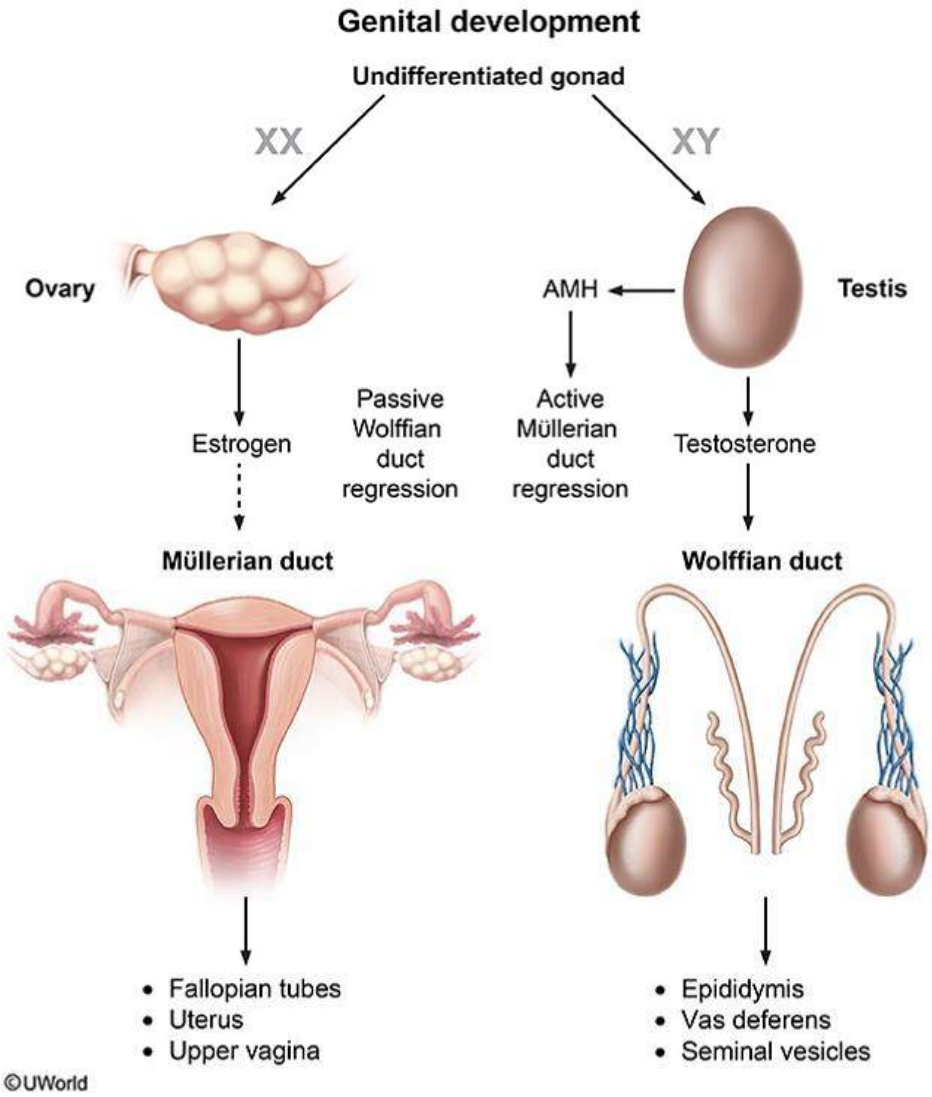
Postpartum urinary retention	
Risk factors	• Nulliparity • Prolonged labor • Perineal injury • Regional analgesia • Cesarean delivery • Instrumental vaginal delivery
Clinical features	• Inability to void • Sensation of bladder fullness • Dribbling of urine or small-volume voids
Management	• Analgesics • Encourage ambulation • Urinary catheterization

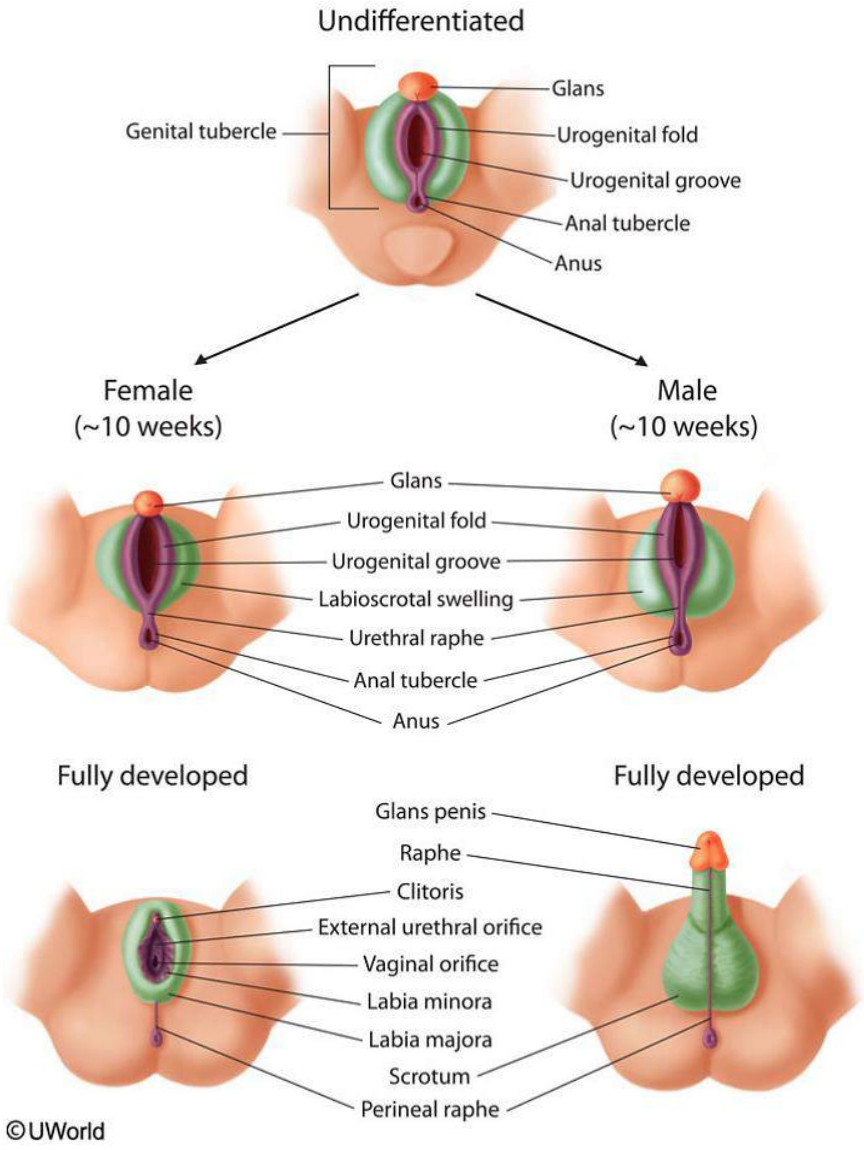
- Normal bladder capacity: 350-400 ml and normal post-void residual volume : <150 ml in women
- Epidural anesthesia→ require urethral catheterization during labor due to temporary loss of voluntary bladder function
- Voiding resumes after few hours of anesthesia but may be delayed in some due to bladder overdistention and perineal swelling around urethra

- Urethral catheterization better than USG for diagnosis (post void residual volume >150 ml diagnostic) and for relieving bladder distension. Can remain in place until urination is possible as perineal edema lessens. Most regain bladder function after this intervention

Contents

GENITAL DEVELOPMENT



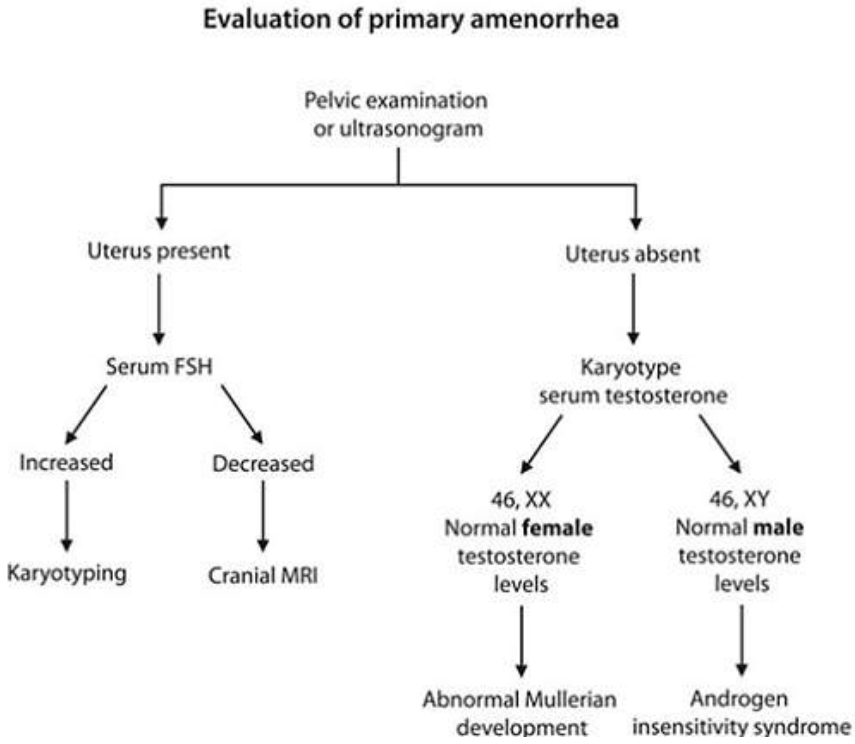

Undifferentiated
Genital tubercle
Glans
Urogenital fold
Urogenital groove
Anal tubercle
Anus
Female
(~10 weeks)
Male
(~10 weeks)
Glans
Urogenital fold
Urogenital groove
Labioscrotal swelling
Urethral raphe
Anal tubercle
Anus
Fully developed
Fully developed
Glans penis
Raphe
Clitoris
External urethral orifice
Vaginal orifice
Labia minora
Labia majora
Scrotum
Perineal raphe
©UWorld

DISORDERS OF SEXUAL DEVELOPMENT

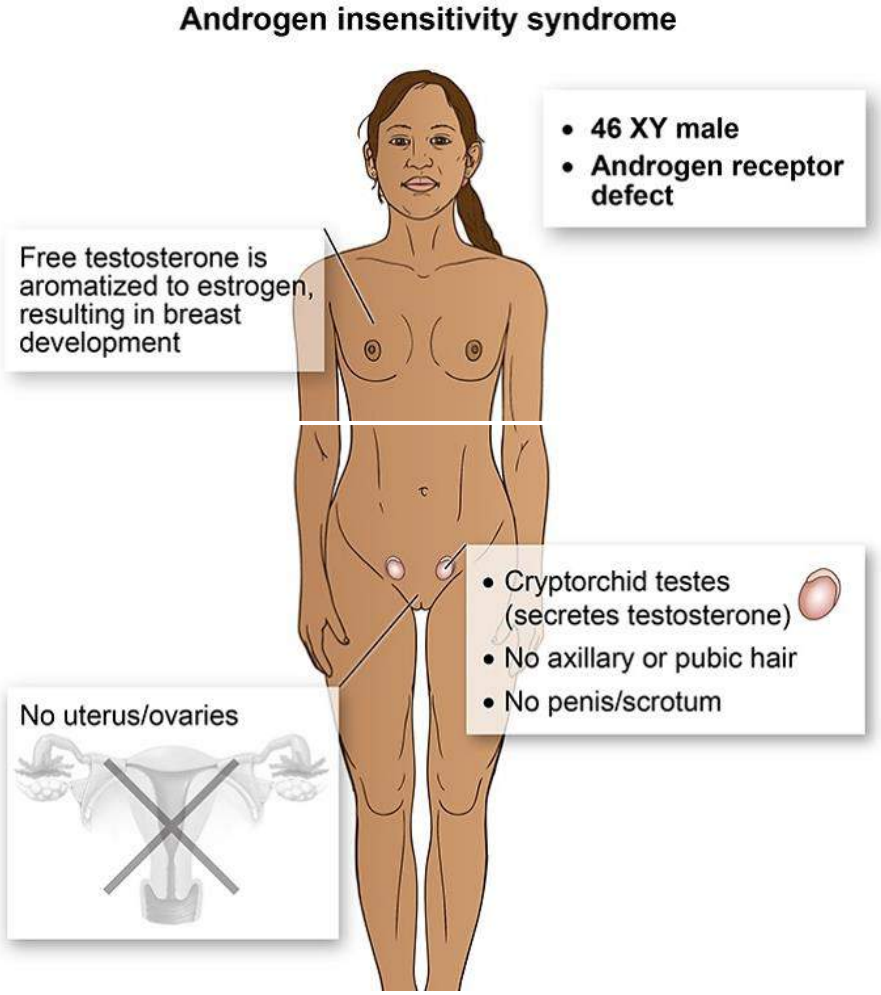
Disorders of sexual development					
Diagnosis	**Cause**	**Breast development**	**Reproductive organs**	**Axillary & pubic hair**	**Karyotype**
Complete androgen insensitivity syndrome	X-linked mutation of androgen receptor	Yes	Absent uterus & upper vagina; cryptorchid testes	Minimal to absent	46,XY
Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)	Hypoplastic or absent müllerian ductal system	Yes	Absent or rudimentary uterus & upper vagina; normal ovaries	Normal	46,XX
Transverse vaginal septum	Malformation of urogenital sinus & Müllerian ducts	Yes	Normal uterus, abnormal vagina; normal ovaries	Normal	46,XX
Turner syndrome	Complete/partial absence of 1 X chromosome	Variable (depending on ovarian function)	Normal uterus & vagina; streak ovaries	Normal	45,X

PRIMARY AMENORRHEA

- Isolated amenorrhea **with** well-developed 2* sexual characters may be considered **normal up to age 16**
- Amenorrhea **without** proper development of 2* sexual characters—work-up should not be delayed **beyond age 14**—absence of breast development indicate ↓ estrogen and so need not be measured
- Most commonly due to anatomical and genetic abnormality that affect structures needed for menses (uterus, vagina and ovaries)



ANDROGEN INSENSITIVITY SYNDROME/ TESTICULAR FEMINIZATION SYNDROME



- Testes also secrete **anti-Mullerian hormone (AMH**)→ regression of Mullerian ducts
- **Wollfian ducts degenerate**, **fetal urogenital sinus** cannot differentiate in to penis and scrotum (default development in to female external genitalia), **male secondary sexual characters minimal or absent**
- Functionally normal gonads are cryptorchid as testicular descent is an androgen dependent process
- Cryptorchid gonads have 1-5% risk of developing a dysgerminoma or gonadoblastoma after puberty
- In general, benefits from undergoing gonad stimulated puberty (e.g. **attainment of adult height**) outweigh the low risk of malignancy—therefore, **gonadectomy should be deferred until completion of puberty—**estrogen supplementation is given after b/l gonadectomy as source of sex hormones has been removed
- Most pts have female gender identity—pt should receive age appropriate disclosure and families should be ordered psychosocial support

5-α REDUCTASE DEFICIENCY

- Testosterone cannot be converted to dihydrotestosterone
- Ambiguous genitalia (female or undermasculinized external genitalia) at birth (undervirilization)
- Male internal urogenital tract (due to AMH)
- At puberty, they experience masculinization due to testosterone (e.g. ↑ in phallus size, muscle growth, voice deepening) but lack breast development

TURNER SYNDROME

- One of the most common causes of primary amenorrhea
- **Gold standard of diagnosis**: karyotype analysis of 30 blood lymphocytes showing 45, XO—shows complete or partial deletion of X chromosome→ if normal karyotype but clinical suspicion is high→ perform **FISH** to look for mosaicism (e.g. 45XO/46XX), that is beyond resolution of normal karyotype
- **Supportive investigations for comorbidities** after Dx confirmed: **Bone age** is usually delayed in TS and testing (skeletal xray) is performed to evaluate growth potential. **Thoracic magnetic resonance imaging** should be performed in all children with TS, especially if there are echocardiography abnormalities, to look for other areas of aortic narrowing.
- Gonadal dysgenesis in Turner syndrome is associated with a higher risk of malignancy (15%-30%), requiring closer surveillance and earlier gonadectomy

AROMATASE DEFICIENCY

- Rare genetic disorder
- Total absence or poor functioning of enzyme aromatase that converts androgens to estrogen
- **In utero:** placenta will not be able to make estrogens → masculinization of mother that resolves after delivery, virilization of XX child with normal internal genitalia but ambiguous external genitalia, clitoromegaly when ↑ androgens in utero
- **Later in life:** osteoporosis, delayed puberty, undetectable circulating estrogen, ↑ gonadotropins and polycystic ovaries

VULVAR LESIONS

LICHEN PLANUS

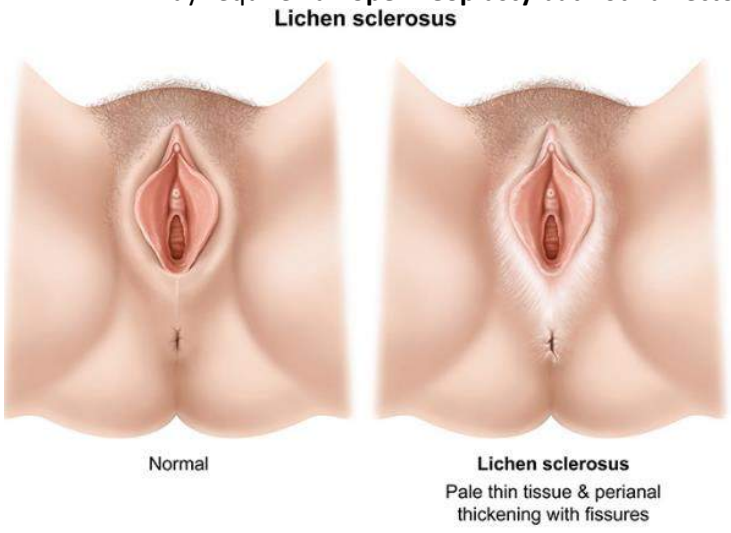
- Chronic, inflammatory, skin dystrophy resulting in glazed, brightly erythematous lesions on the vulva with erosive (eg, ulcerated) areas. The vagina as well as extragenital sites may be involved.

LICHEN SCLEROSIS

DIFFERENCE BETWEEN LICHEN SCLEROSIS AND ATROPHIC VAGINITIS

Atrophic vaginitis vs. lichen sclerosus		
Condition	**Clinical features**	**Treatment**
Atrophic vaginitis	• Vulvovaginal dryness • Loss of vaginal elasticity/rugae • Thinning vulvar skin/loss of minora • Decreased vaginal diameter	Low-dose vaginal estrogen
Lichen sclerosus	• While vulvar plaques/loss of minora • Vulvar dryness, intense pruritus • Perianal "figure of 8" involvement • Spares vagina	High-potency vaginal steroids

- **Chronic inflammatory condition** of anogenital region. Can affect extragenital regions like buttocks, lower back, under breast, armpits, shoulders and abdomen.
- Can affect women at any age
- **Pathogenesis: autoimmune** and can coexist with other autoimmune disorders like DM-type 1, thyroid disorders
- **Anogenital Sx:** intense pruritis, dyspareunia, dysuria and painful defecation
- **PE:** porcelain white polygonal patches with atrophy (e.g. regression, obliteration) of clitoris, labia majora and minora and ↓ in diameter of introitus, as well as scarring (e.g. sclerosis) of normal genital structures. Vulvar skin appears thin, white and wrinkled like "**cigarette paper**".
- **Dx:** Clinical but "punch biopsy" of lesion for definitive diagnosis and to rule out malignancy. It is premalignant for vulvar squamous cell CA
- **Rx:** one of the few conditions for which **high potency topical steroids** e.g. **clobetasol** are used—counsel pt that it is not known whether it can prevent scarring and SCC or not. > once daily use→↑ risk of skin atopy, discoloration and striae. Cryotherapy is not 1st line for this (1st line for genital warts)
  - Patients who develop severe adhesions/scarring due to vulvar LS despite control with medication may require **vulvoperineoplasty** but not vulvectomy



CONDYLOMATA LATA

- Caused by 2* syphilis
- Broader base, flatter surface and are lobulated or plaque like

CONDYLOMATA ACUMINATA

Genital warts (condylomata acuminata)	
Etiology	• HPV 6 & 11
Clinical features	• Multiple pink or skin-colored lesions • Lesions ranging from smooth, flattened papules to exophytic/cauliflower-like growths
Treatment	• Chemical: Podophyllin resin, trichloroacetic acid • Immunologic: Imiquimod • Surgical: Cryotherapy, laser therapy, excision
Prevention	• Vaccination • Barrier contraception

HPV = human papillomavirus.

Most are exophytic and cauliflower-like, some are sessile and flat

For small lesions

For larger lesions

- Most common STD in US.
- 6 and 11 cause warts and 16 and 18 associated with high grade cervical intraepithelial neoplasia and cervical cancer
- External and/or internal vaginal lesions as well as anogenital lesions occur in women
- Most often asymptomatic, pruritus and bleeding from lesion are possible
- **DX:** based solely on characteristic appearance of lesion
- Recurrence rates are high, regardless of treatment modality

VULVAR INTRAEPITHELIAL NEOPLASIA

- Caused by HPV
- White or erythematous plaques, hyperpigmented lesions or multifocal verruciform lesions, not atrophic changes.

VULVAR CANCER

- Follows HPV infection (e.g. VIN) or vulvar dystrophies (e.g. lichen sclerosis)
- Typically singular, fleshy lesion on labia majora that may bleed
- More common in postmenopausal women

VAGINAL LESIONS

ATROPHIC VAGINITIS/ GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary syndrome of menopause (atrophic vaginitis)	
Clinical features	• Vulvar &/or vaginal dryness, itching, dyspareunia • Narrow introitus, pallor, ↓elasticity, ↓rugae • Urinary frequency, urgency, incontinence, infection
Treatment	1st-line: Vaginal moisturizer & lubricant 2nd-line: Topical vaginal estrogen Low dose

For mild atrophic vaginitis without urinary sx

Used for moderate to severe and with urinary sx, even if oral estrogen replacement is in use

- **Estrogen receptors location**: bladder trigone, urethra, pelvic floor muscles, and endopelvic fascia
- Natural, medical (pelvic radiation or chemo), or surgical (e.g. b/l oophorectomy) menopause→ ↓ estradiol level
- In premenopausal women, smoking also ↓ estrogen levels
- Ulceration due to atrophy is unlikely, and visible lesion almost never occurs in isolated atrophy
- **Urinary symptoms:** ↓ estrogen→ atrophy of intermediate and superficial layers of vagina and urethral mucosal epithelium→ ↓ urethral closure pressure and loss of urethral compliance→ urinary symptoms (as in table). Can be stress or urge incontinence.
  - Urinary sx of incontinence and recurrent UTI can mimic→ perform urinalysis and culture to differentiate the two

VESICOVAGINAL FISTULA

Vesicovaginal fistula	
Risk factors	• Pelvic surgery • Pelvic irradiation • Prolonged labor/childbirth trauma • Genitourinary malignancy
Clinical feature	• Painless, continuous urine leakage from the vagina
Diagnostic studies	• Physical examination • Cystourethroscopy

Most common cause in industrialized countries

- **Pathophysiology:** may result from **occult bladder injury during surgery** or from **tissue ischemia due to excessive surgical dissection**.
- May present **within a month of surgery**
- **Dx:**
  - Clinically by visualization of urine leaking into vagina.
  - Sometimes small area of granulation tissue or a hole may be seen

- **Dye tests and/or cystourethroscopy**—performed to detect small fistula which may be difficult to detect on visual inspection
- **Complication:** cystitis—urinalysis may detect infection
- **Bladder catheterization** in immediate post-op period allows a small fistula to heal. Otherwise, surgical correction is indicated

VAGINAL CUFF DEHISCENCE

- Vaginal cuff dehiscence (eg, vaginal wound separation) is a rare but serious postoperative complication after hysterectomy.
- Although peritoneal leakage through the vagina may be seen, the apex would appear inflamed or indurated.

VAGINISMUS/GENITO-PELVIC PAIN/PENETRATION DISORDER

DSM-5 diagnostic criteria: Genito-pelvic pain/penetration disorder

- Ongoing difficulties with at least 1 of the following:
  - Vaginal penetration during intercourse
  - Vaginal or pelvic pain during intercourse or attempted penetration (or fear or anxiety about pain in anticipation of, during, or after)
  - Tenseness of pelvic floor muscles during attempted vaginal penetration
- At least 6 months in duration
- Significant distress
- Not accounted for by other medical, mental, substance use, or relationship issues

- Treatment includes relaxation, Kegel exercises (to relax the vaginal muscles), and insertion of dilators with a gradual ↑ in size, fingers, etc. to bring about desensitization

FEMALE ORGASMIC DISORDER

- Persistent delay in or absence of orgasm on all or nearly all occasions of sexual activity

FEMALE SEXUAL INTEREST/AROUSAL DISORDER

- Pt lacking or having significantly less interest in sexual activity

VAGINAL CANCER

Vaginal cancer		
Type	**Squamous cell**	**Clear cell adenocarcinoma**
Epidemiology	Age > 60	Age <20
Risk factors	• HPV 16 or 18 • History of cervical dysplasia or cancer • Cigarette use	In utero exposure to diethylstilbestrol
Location of cancer	Upper 1/3 of the posterior vaginal wall	Upper 1/3 of anterior vaginal wall
Clinical features	• Malodorous vaginal discharge • Postmenopausal or postcoital vaginal bleeding • Irregular mass, plaque, or ulcer on vagina	
Diagnosis	Biopsy	

- SCC more common than adenocarcinoma
- Treatment is based on staging. Surgical excision may be appropriate for stage 1 or 2.
- Vaginal cancer is usually a result of metastatic CA, with direct extension from cervix, vulva or endometrium being more common than primary vaginal CA

EFFECTS OF VARIOUS HORMONES IN PREGNANCY AND LACTATION

AMENORRHEA IN LACTATING MOTHER

- Lactating mother→ ↑ level of circulating prolactin→ inhibit hypothalamic GnRH production→↓LH and FSH→ suppress ovulation→ suppress menses
- Used as a contraceptive method but is not reliable as 50% nursing mothers start ovulating by 6-12 months

PLACENTAL ESTROGEN

- Inhibit gonadotropin secretion during pregnancy
- Level suddenly drop after delivery

OXYTOCIN

- Important in uterine involution post-partum
- Levels ↑ in lactation as it helps in expulsion of milk from lactiferous ducts

HUMAN PLACENTAL LACTOGEN

- Produced by the placenta

- Serum levels quickly decrease after delivery of the placenta.
- hPL has an insulin antagonist effect and plays an important role in nutrition of the fetus by causing maternal lipolysis and insulin resistance thus increasing delivery of fatty acids and glucose to the fetus.

INFERTILITY WORKUP

- **Primary infertility**: failure to conceive after a year of unprotected, timed sexual intercourse in nulliparous woman <35 years. In >35 years, infertility investigation can begin after 6 mo.
- **Male factor**: account for 20-30% infertility cases
- **Semen analysis** should be performed early in evaluation of infertile couple as initial screening test→ evaluates sperm concentration, motility, and morphology and allows identifying azoospermia and severe oligospermia as obvious causes—cutoff values exist but broad overlap exists—borderline values should be evaluated with caution
- **Anovulaton:** can be evaluated using basal body temperature (BBT), serum progesterone measurement and endometrial sampling. Serum progesterone measurement to detect ovulation should be measured in mid-luteal phase
- **History of PID**: imp risk factor of infertility→ perform hysterosalpingogram to assess fallopian tube patency—laparoscopy with chromotubation can be done during laparoscopy to assess patency of fallopian tubes but it is invasive and expensive and not 1st line

PRE-MENSTRUAL SYNDROME OR PRE-MENSTRUAL DYSPHORIC DISORDER

- **Physical manifestations:** bloating, fatigue, headache, and breast tenderness
- **Psychological symptoms:** anxiety, mood swings, difficulty concentrating, ↓ libido and irritability
- **Sx begin 1-2wks prior to menses and regress around the time of menstrual flow.** Sx are then absent until after next ovulation
- **PMDD** is severe variant with prominent irritability and anger
- Many pts recognize relation of sx to menstrual cycle.
- If symptoms are irregular or vary in severity→ maintain **menstrual diary for 2-3mo** and note associated sx
- PMS is confirmed when Sx occur **repeatedly and predictably in days prior to menses and resolve with onset of menses**
- If Sx occur irregularly and throughout menstrual cycle→ primary mood disorder is more likely
- **Rx: SSRI** such as fluoxetine is the first line treatment after confirmation of Dx. Can be given intermittently during luteal phase or throughout the cycle. They are generally safe with a favorable side effect profile. **Caffeine reduction** is also advised

INFERTILITY DUE TO AGING

- Significant drop in oocyte number (ovulatory reserve) occurs in fourth decade of life→ 1 in 5 women age 35-39 is no longer fertile
- Evaluation: early follicular phase FSH, clomiphene challenge test or inhibin B levels

CERVICAL MUCUS CHARACTERISTICS IN VARIOUS STAGES

- Evaluation of cervical mucus is important part of infertility workup

EARLY FOLLICULAR PHASE

- Immediately follows menstruation
- Cervical mucus: thick, scant and acidic
- Does not allow penetration by spermatozoa

OVULATORY PHASE

- Profuse, clear and thin in contrast to mucus in pre- and post- ovulatory phase which is scant, opaque and thick
- Stretches to 6 cm when lifted vertically (spinnbarkeit)
- pH 6.5 or greater (more basic than other phases)
- demonstrate “ferning” when smeared on a microscope slide

MID AND LATE LUTEAL PHASE

- Ovulation has already occurred
- Mucus becomes increasingly thicker and exhibits less stretching ability
- Inhospitable to sperm

DIFFERENTIAL DIAGNOSIS OF DYSMENNORHEA

Differential diagnosis of dysmenorrhea	
Diagnosis	**Clinical features**
Primary dysmenorrhea	• Crampy lower abdomen &/ back pain during menses • Normal examination
Endometriosis	• Pain peaks before menses • Dyspareunia • Infertility
Fibroids	• Heavy menses with clots • Constipation, urinary frequency, pelvic pain/heaviness • Enlarged uterus on examination
Adenomyosis	• Dysmenorrhea, pelvic pain • Menorrhagia • Bulky, globular & tender uterus
Pelvic congestion	• Dull & ill-defined pelvic ache that worsens with standing • Dyspareunia

Dysmenorrhea			
Type	**Examples**	**Examination**	**Pain pathophysiology**
Primary	N/A	Normal	Release of prostaglandins from endometrium causes uterine contractions
Secondary	Endometriosis	Uterosacral nodularity, adnexal tenderness	Bleeding from ectopic endometrium
	Adenomyosis	Uterine tenderness & enlargement	
	Pelvic infection	Cervical motion tenderness, purulent cervical discharge	Bacterial infection & inflammatory response
	Uterine leiomyomata	Uterine contour irregularity	May be associated with heavy bleeding

PRIMARY DYSMENORRHEA

- Dysmenorrhea is absence of any other pathology (e.g. dyspareunia and GI symptoms). **Pain during first few days of menses** and improves as the endometrium lining becomes thin
- Onset generally occurs in adolescents and improve with age
- **Treatment objective**: pain relief to minimize disruption in pt's life
- **Rx:**
  - NSAIDs and/or hormonal contraception—1st line. NSAIDS—inhibit prostaglandin synthetase→↓ prostaglandin
  - Most women respond to oral meds within 3 mo

PELVIC CONGESTION

- Pain worsens prior to menstruation or with long periods of standing and is relieved by menses
- Also associated with history of sexual problems

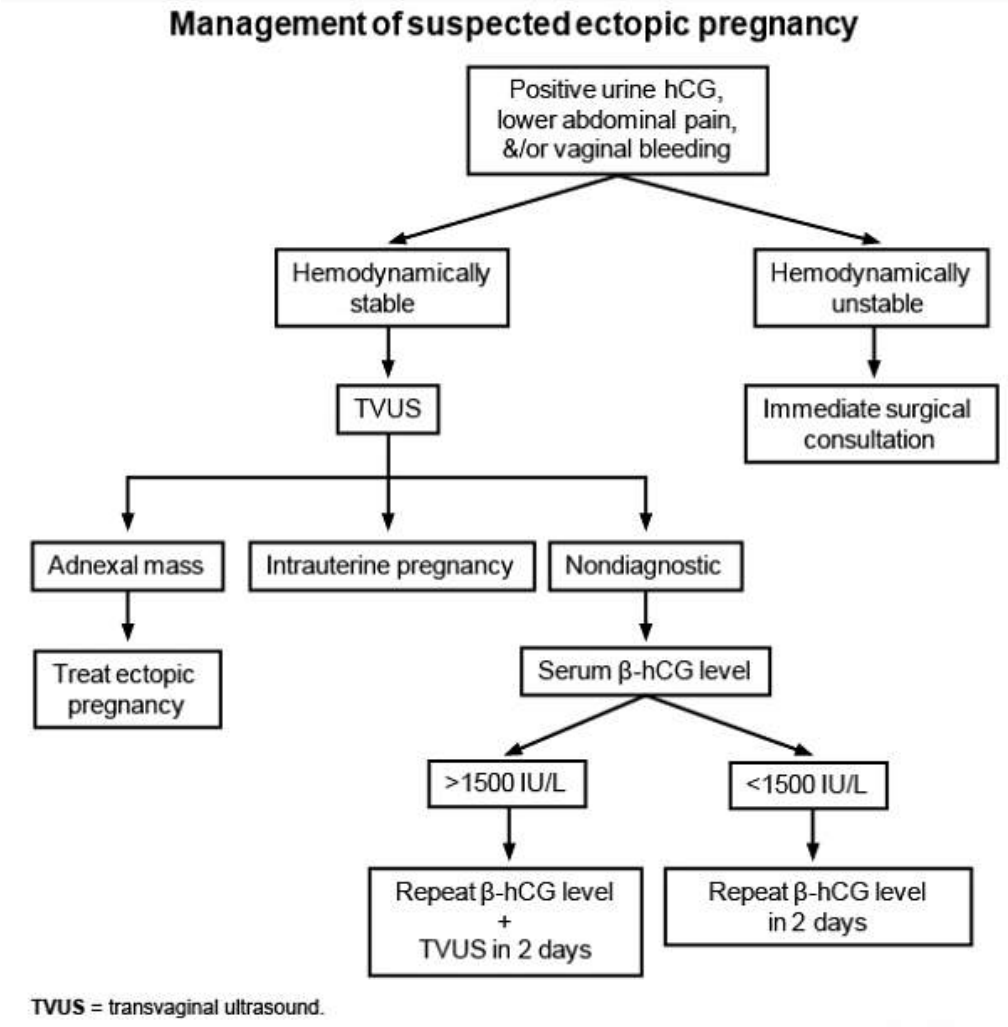
ACUTE ABDOMINAL/PELVIC PAIN IN WOMEN

Acute abdominal/pelvic pain in women		
Diagnosis	**Clinical presentation**	**Ultrasound findings**
Mittelschmerz	• Recurrent mild & unilateral midcycle pain prior to ovulation • Pain lasts a few hours to couple of days	Not indicated
Ectopic pregnancy	• Amenorrhea, abdominal/pelvic pain & vaginal bleeding • Positive hCG	No intrauterine pregnancy
Ovarian torsion	• Sudden onset severe unilateral lower abdominal pain, nausea & vomiting • Unilateral, tender adnexal mass on examination	Enlarged ovary with decreased blood flow
Ruptured ovarian cyst	• Sudden-onset severe unilateral lower abdominal pain immediately following strenuous or sexual activity	Free fluid near ovarian cyst
Pelvic inflammatory disease	• Fever/chills, vaginal discharge, lower abdominal pain, & cervical motion tenderness	+/- Tuboovarian abscess

MITTELSCHMERZ

- Common in women who are not taking OCPS i.e. who are ovulating
- Due to enlargement of developing follicle which irritates peritoneum

ECTOPIC PREGNANCY



- Serial β-hCG is **not needed** if TVUS shows intrauterine pregnancy or ectopic pregnancy
- At β-hCG level 1500-2000 IU/L, intrauterine pregnancy should be visible on TVUS
- Intrauterine pregnancy is not visible at β-hCG of 1000 IU/L. no need to repeat TVUS until the level rise to 1500

β-hCG

- Hormone normally secreted by syncytiotrophoblast
- Responsible for **maintaining corpus luteum** during early pregnancy→ maintain progesterone levels until placenta is able to produce progesterone on its own. Other biological functions of hCG: promotion of male sexual differentiation and stimulation of maternal thyroid gland
- Production begins about 8 days after fertilization
- Levels normally double every 2 days/48 hours in viable pregnancy until they peak at 6-8 wks gestation and much slower rate in ectopic and non-viable pregnancy
- Two subunits: α-subunit common among LH, FSH, hCG and TSH. β-subunit is unique

OVARIAN TORSION

Ovarian torsion	
Risk factors	• Ovarian mass • Women of reproductive age • Infertility treatment with ovulation induction
Clinical presentation	• Sudden-onset unilateral pelvic pain • Nausea & vomiting • +/- Palpable adnexal mass
Ultrasound	• Adnexal mass with absent Doppler flow to ovary
Treatment	• Laparoscopy with detorsion • Ovarian cystectomy • Oophorectomy if necrosis or malignancy

With voluntary guarding. Peritoneal signs (rebound or involuntary guarding if ovary becomes necrotic

Low-grade fever

Directed at excluding other causes of pain like ectopic pregnancy and appendicitis. Also perform urine pregnancy test

- Ovarian torsion: Partial or complete rotation of ovary around infundibulopelvic (suspensory ligament of ovary) and/or utero-ovarian ligament→ occlusion of blood supply
- Gynecological emergency

OVARIAN CYST RUPTURE

- Most commonly in women of reproductive age
- May be asymptomatic. N/V –ve (as opposed to torsion)
- May be light vaginal bleeding from endometrial sloughing due to drop in ovarian hormones
- **PE:**
  - Lower abdomen tender to palpation
  - Possible adnexal mass on bimanual exam
  - Periumbilical ecchymoses (Cullen's sign) in significant intraperitoneal bleeding
- **Labs:** CBC and pregnancy test to rule out ectopic pregnancy
- **Management:**
  - **Uncomplicated cyst rupture:** i.e. no fever, hypotension, tachycardia, or signs of hemoperitoneum/infection—can be conservatively managed with analgesics on outpatient basis
  - **Complicated cyst rupture: Unstable pt or significant hemoperitoneum—** surgical intervention

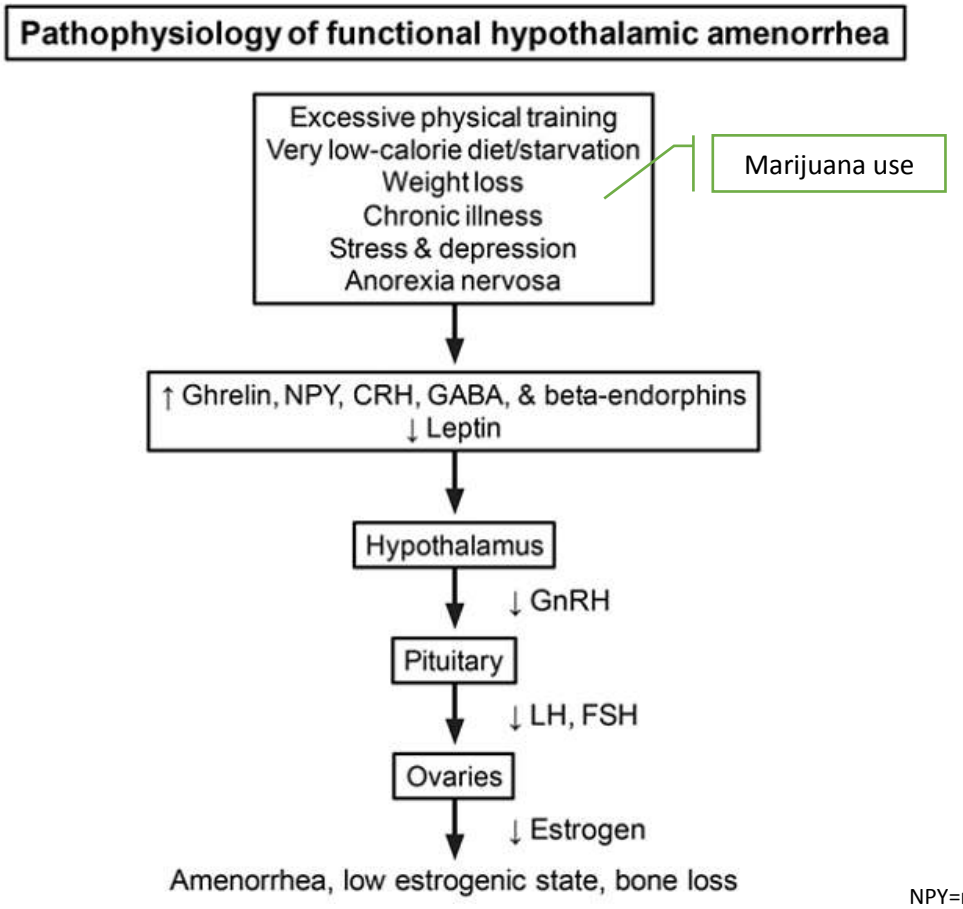
ANOVULATION

POLYCYSTIC OVARIAN SYNDROME/ STEIN-LEVENTHAL SYNDROME

- Anovulation, androgen excess and ovarian cysts
- **Pathophysiology:** abnormal GnRH secretion→ secrete ↑ LH and ↓ FSH→ LH stimulates androgen production by ovarian theca cells→ hirsutism, male escutcheon, acne and androgenic alopecia

- Infertile or subfertile as menstrual cycles are frequently anovulatory—exact reason unknown—possibly due to imbalance in LH and FSH production and insulin resistance→ can cause amenorrhea, irregular menses occasionally accompanied by menometrorrhagia
- **Rx:** ovaries are functional → ovulation can be induced by **clomiphene citrate (CC). CC** is estrogen analog→improve GnRH release→ ↑FSH→ improves chances of ovulation. PCOS also treated with metformin→ also improve ovulation independently

ACQUIRED HYPOGONADOTROPIC HYPOGONADISM



NPY=neuropeptide Y

- Excessive exercise (with or without weight loss or caloric restriction)—more in long distance runners—infertility is less likely with daily 30-60min of aerobic exercise
- Studies have shown that fat restriction may play a role
- **Can lead to all complications associated with ↓ estrogen** i.e. infertility, vaginal atrophy, breast atrophy and osteopenia
- May have **TFTs resembling euthyroid sick syndrome**: low T3, low/low-normal T4, low/low-normal TSH and ↑ reverse T3
- **1st line treatment**: cut down stressor and exercise intensity→ if fails→ **pulsatile GnRH** considered

ANOVULATION IN 1ST YEAR OF MENARCHE

- Approx. 90% cycles are anovulatory during 1st year
- **Immature hypothalamic-pituitary-ovarian axis**→may fail to produce LH and FSH in proper amount and ratio to induce ovulation→ some anovulatory cycles → endometrium is responsive to baseline estrogen

levels→ endometrium develops→ eventually slough due to breakthrough phenomenon or heavy bleeding when ovulation does occur
- Can cause menorrhagia (>7days or >80ml)

ANOVULATION SECONDARY TO MORBID OBESITY

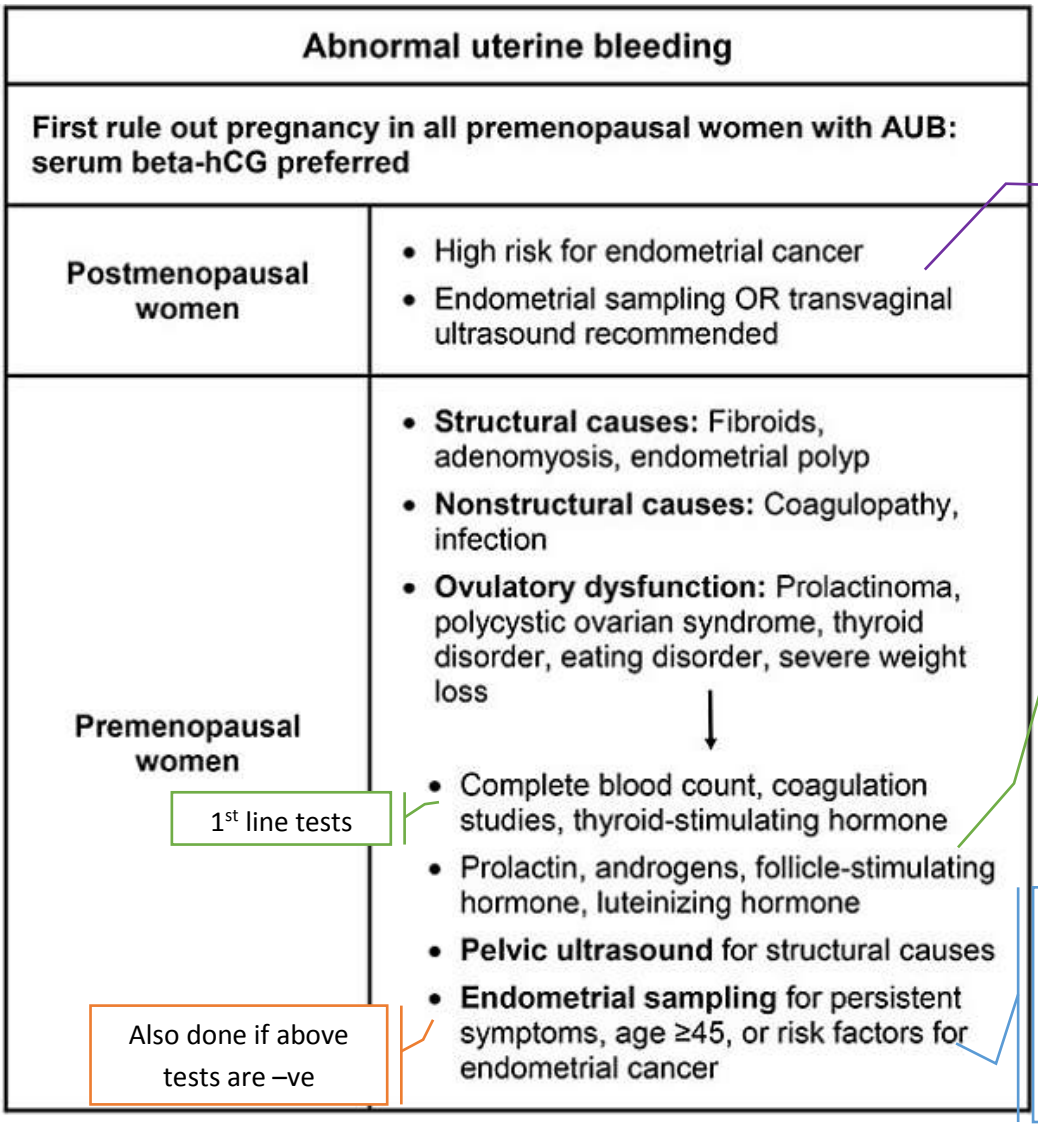
- In anovulation 2* to morbid obesity, FSH and LH levels are normal
- Ovaries still produce estrogen but progesterone is not being produced at normal post-ovulation levels→progesterone withdrawal menses at the end of cycle does not occur.

PREMATURE OVARIAN FAILURE

- **Definition**: primary hypogonadism in a woman under 40
- May be 2* to accelerated follicular atresia or low initial no. of primordial follicles
- **Causes:** chemotherapy, radiation, mumps, oophoritis, autoimmune ovarian failure (associated with autoimmune conditions like DM 1, Hashimoto's thyroiditis, Addison's disease and pernicious anemia), Turner's syndrome, fragile X syndrome
- Developing follicles are the main source of estrogen→ impaired follicular development (primary hypogonadism)→ ↓ estrogen→ loss of feedback inhibition on FSH and LH →↑ FSH and LH→ FSH more ↑ than LH due to slower clearance of FSH from circulation
- All pts with 2* amenorrhea should receive **pregnancy test, prolactin level and FSH levels**
- Markedly ↑ed FSH in menopausal range (defined by lab assay) in a woman under 40 with >/=3 mo of amenorrhea confirm diagnosis of premature ovarian failure—no need to wait for 1 year to make dx to prevent osteoporosis at young age
- Patients lack viable oocytes, so the only option available to allow pregnancy is in vitro fertilization using donor oocytes.

CAUSES OF ABNORMAL UTERINE BLEEDING

- **Abnormal uterine bleeding** (AUB): abnormal duration, quantity or schedule. Menstrual bleeding that is prolonged (>5 days) and heavy (>1 pad every 2 hours) with an irregular frequency


Abnormal uterine bleeding
First rule out pregnancy in all premenopausal women with AUB: serum beta-hCG preferred
Postmenopausal women
High risk for endometrial cancer
Endometrial sampling OR transvaginal ultrasound recommended
Premenopausal women
Structural causes: Fibroids, adenomyosis, endometrial polyp
Nonstructural causes: Coagulopathy, infection
Ovulatory dysfunction: Prolactinoma, polycystic ovarian syndrome, thyroid disorder, eating disorder, severe weight loss
1st line tests
Complete blood count, coagulation studies, thyroid-stimulating hormone
Prolactin, androgens, follicle-stimulating hormone, luteinizing hormone
Pelvic ultrasound for structural causes
Also done if above tests are –ve
Endometrial sampling for persistent symptoms, age ≥45, or risk factors for endometrial cancer
Post-MP women may start with TVUS and proceed to EMB if endometrial thickening is found. TVUS not sensitive in pre-MP due to variation in thickness during cycle but can diagnose fibroids etc
If ovulatory dysfunction is suspected (e.g. anovulation, perimenopause, intermittent cycles)
Risk factors for endometrial cancer: age >/=45, obesity, diabetes, unopposed estrogen exposure, PCOS, early menarche/late menopause)

Abnormal uterine bleeding	
Diagnosis	**Clinical features**
Endometriosis	• Dysmenorrhea, pelvic pain, dyspareunia • Infertility
Fibroids	• Heavy menses +/- clots • Constipation, urinary frequency, pelvic pain/heaviness • Irregularly enlarged uterus
Adenomyosis	• Dysmenorrhea, pelvic pain • Heavy menses • Bulky, globular & tender uterus
Endometrial cancer/hyperplasia	• History of obesity, nulliparity, or chronic anovulation • Irregular, intermenstrual, or postmenopausal bleeding • Small, nontender uterus

Normal sized, non-tender and immobile (e.g. fixed) uterus. Does not cause heavy menstrual bleeding

Firm uterus

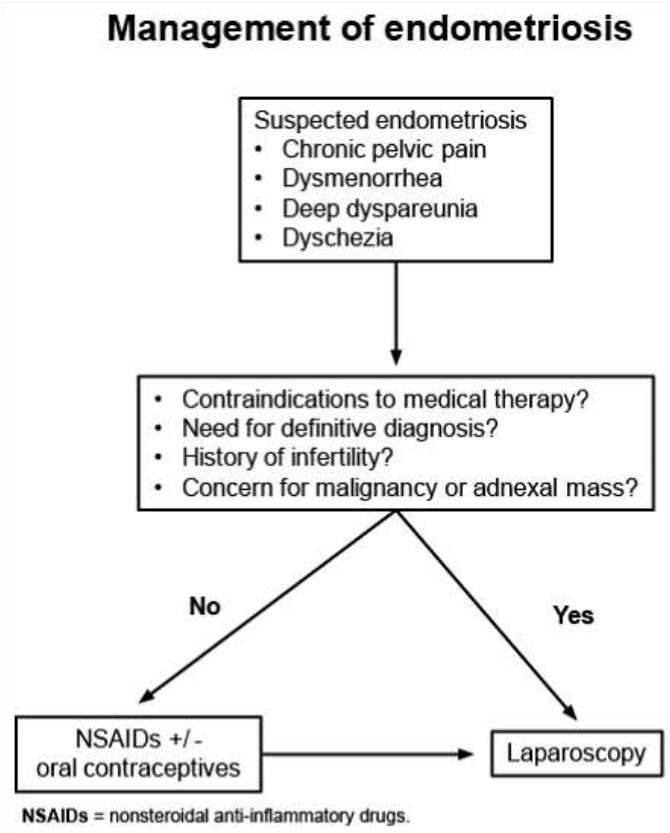
Enlarged, soft and mobile uterus

ENDOMETRIOSIS

Endometriosis	
Clinical features	• Dyspareunia • Dysmenorrhea • Chronic pelvic pain • Infertility • Dyschezia
Physical examination	• Immobile uterus • Cervical motion tenderness • Adnexal mass • Recto-vaginal septum, posterior cul-de-sac, uterosacral ligament nodules
Diagnosis	• Direct visualization & surgical biopsy
Treatment	• Medical (oral contraceptives, NSAIDs) • Surgical resection

>6mo. Can be exacerbated by exercise

NSAIDs = nonsteroidal anti-inflammatory drugs.



Combined estrogen and progesterone OCPs ↓ pain by ovulation suppression, which may result in atrophy of endometrial tissue. Progesterone IUD can also be used. No treatment needed in asymptomatic pt

Laparoscopy: direct visualization, biopsy and removal of endometrial tissue. Reappear without estrogenic suppression. Definitive Rx in women who have completed child-bearing→ hysterectomy and oophorectomy

- Location, quality and timings of pain are unique to each pt and depends on exact location of implant. Mostly start 1-2 wks prior to menses and peak just before menstruation
- Not associated with heavy bleeding
- Homogenous, cystic ovarian mass is highly suggestive of endometrioma→ can be the only manifestation and can cause infertility
- Surgical resection of endometrioma usually improves fertility

FIBROIDS

Uterine leiomyoma (fibroids)	
Clinical features	• Urinary frequency, constipation, pelvic pressure/pain (secondary to compression) • Heavy, prolonged menses with clots • Pregnancy difficulties associated with submucosal or intramural tumors (eg, impaired fertility, pregnancy loss, preterm labor) • Enlarged, irregular uterus
Workup	• Ultrasound
Treatment	• Observation if no significant symptoms • Hormonal contraception, embolization, or surgery if symptomatic

- Proliferation of smooth muscles within myometrium

- Submucosal and intramural esp. can cause heavy menstrual bleeding. Intramural, submucosal and intracavitary—all can cause recurrent pregnancy loss. Subserosal and pedunculated are more likely to cause compression of adjacent organs→ can cause stress incontinence. Rarely, extremely large fibroids can cause ureteral impingement→ hydronephrosis and urinary retention
- **Rx:** OCPs→ ↓ bleeding duration and volume but may not completely resolve sx. Anemia may still persist and require transfusion and more invasive therapy e.g. myomectomy, uterine artery embolization, hysterectomy

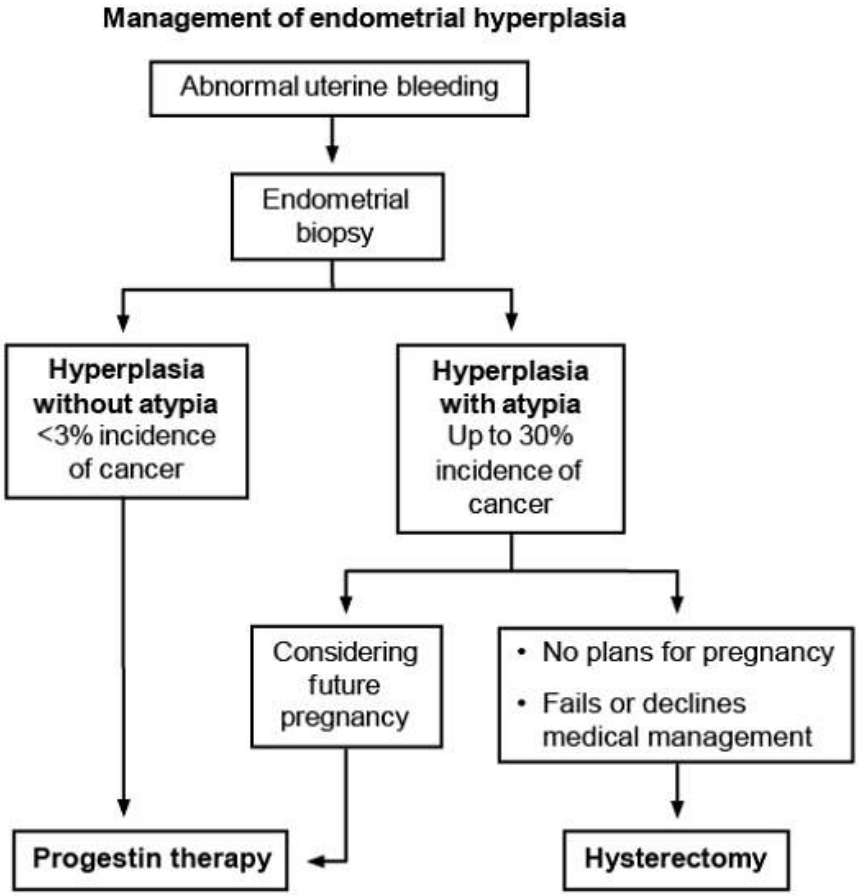
ABORTING SUBMUCOUS MYOMA

- Firm, smooth, round mass at cervical os—diagnosis clinical—USG can be performed to assess additional fibroids
- Sx: heavy and prolonged menstrual bleeding, labor like pain due to cervical dilatation by solid mass
- Rx: surgical removal of aborting myoma and can be accomplished vaginally

ADENOMYOSIS

- Endometrial glands in uterine musculature→ cause blood deposits in myometrium with each cycle→ disrupt arrangement of myometrium smooth muscle fibers→ interferes with normal uterine contraction→ **dysmenorrhea (new-onset) and heavy menstrual bleeding** (soaking pad or tampon more often than every 2hours)→ can progress **to chronic pelvic pain.** Uterus gradually enlarges but remains smaller than 12 wks (below pubic symphysis)
- Typically **in multiparous women > 40 years**
- **DX:** Initial diagnostic workup→ pelvic USG and/or MRI. Definitive dx made by surgical pathology after hysterectomy. This is also the definitive treatment if hormonal methods (e.g. OCPs, levonorgestrel intrauterine device) are unsuccessful

ENDOMETRIAL HYPERPLASIA



- **Endometrial hyperplasia**= proliferation of endometrial glands→ can progress to endometrial adenocarcinoma
- **Pathophysiology:** chronic stimulation by estrogen (e.g. obesity, anovulation) without balancing effect of progesterone
- **S/S:** abnormal uterine bleeding in peri and post-menopausal women
- **Work-up:** biopsy to rule out cancer and identify severity of hyperplasia
- **Classification:** based on histologic findings:
  - **Simple:** mildly crowded and cystically dilated glands
  - **Complex:** more crowded and disorganized glands
  - **With atypia:** dangerous and imp. Prognostic factor for progression to CA
  - **Without atypia**
- **Rx: Progestin**→ stimulate progesterone receptors in endometrium→ decidualization of stroma and thinning of endometrium
- Repeat endometrial biopsy after 3 mo to assess response to rx

TREATMENT OF ACUTE ABNORMAL UTERINE BLEEDING

- Evaluate for coagulation disorder if clinically appropriate.
- Test sexually active pts for pregnancy
- Acute AUB in hemodynamically stable pts may be managed medically:

Medical treatment options for acute abnormal uterine bleeding
• High-dose intravenous or oral estrogen • High-dose combined oral contraceptive pills • High-dose progestin pills • Tranexamic acid

Conjugated equine estrogen

- **Estrogen:** promotes rapid regrowth of endometrium over denuded epithelial surface that results from prolonged heavy bleeding
- **Progesterone:** given to those with CI to estrogen or acute AUB due to anovulation—stabilizes disorganized endometrial lining and prevents further growth—less effective once epithelial surface has been denuded
- **Tranexamic acid:** antifibrinolytic—used in pt with CI to both estrogen and progesterone
- **Emergency dilation and curettage** may be needed if medical treatment fail after 24-36 hours

CERVICAL CANCER

CERVICAL CANCER SCREENING

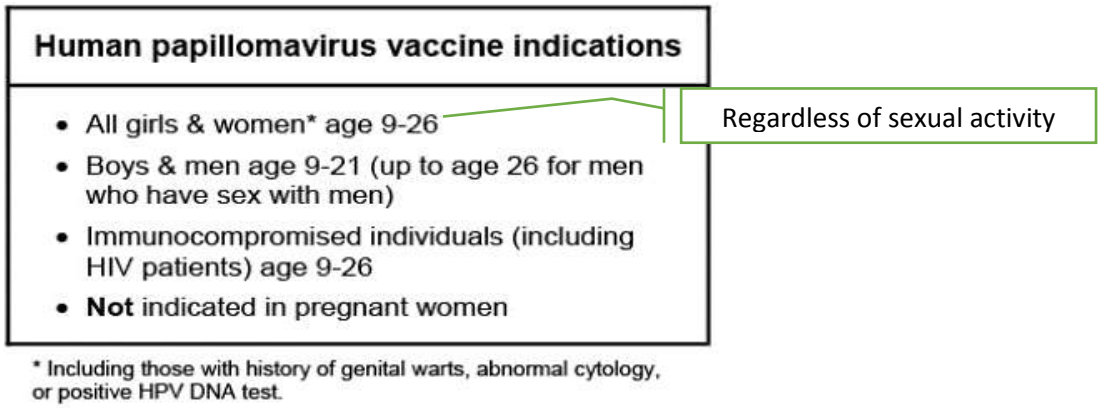
Cervical cancer screening	
Demographics	**Screening guidelines**
Immunocompromised (HIV, SLE/organ transplant patients on immunosuppressants)	• Onset of sexual intercourse • Every 6 months x 2 then annually
Age <21	• No screening
Age 21-29	• Cytology every 3 years
Age 30-65	• Cytology every 3 years OR • Cytology PLUS HPV testing every 5 years
Age ≥65	• No screening if negative prior screens and not high risk for cervical cancer
Hysterectomy (with cervix removed)	• No screening if no history of high-grade precancerous lesion, cervical cancer, or exposure to diethylstilbestrol

Regardless of onset of sexual activity

HPV = human papillomavirus; **SLE** = systemic lupus erythematosus.

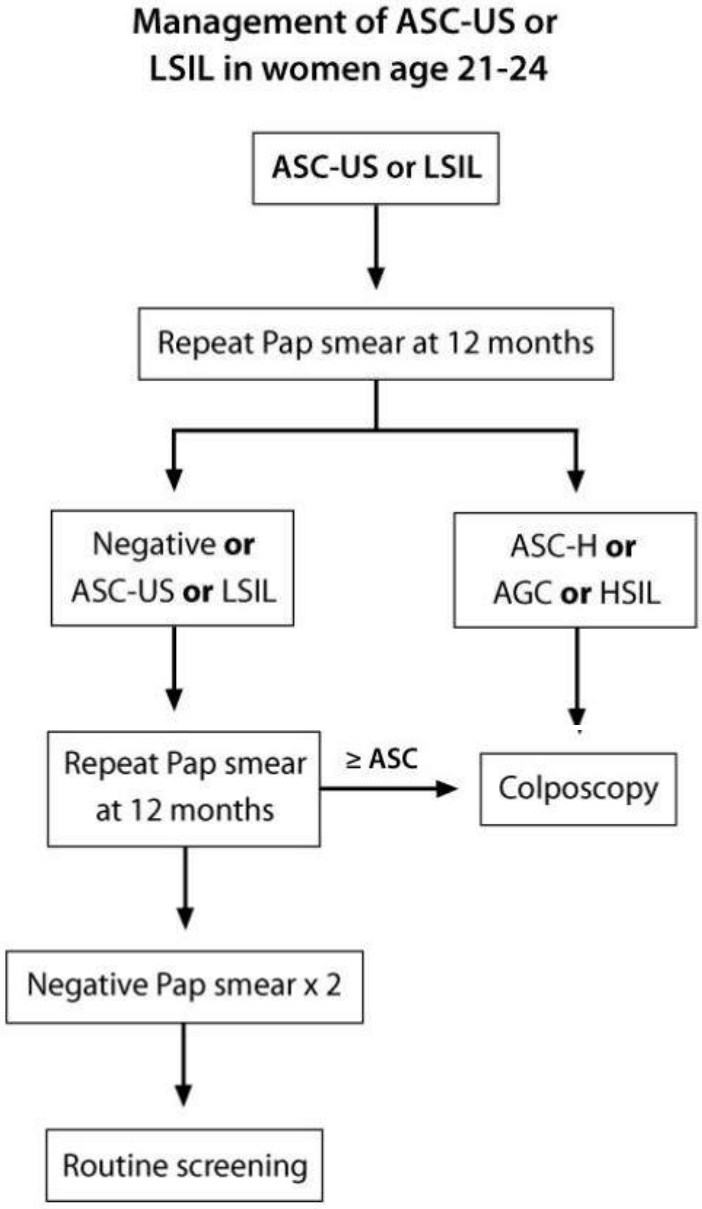
- Nearly 50% pts (including adolescents) in US will be infected with HPV within 3 years of onset of sexual activity
- HPV infection is transient in most young women and usually clear within 2 year—hence primary HPV testing has lower sensitivity and specificity in women <30 years—not recommended

HPV VACCINATION CRITERIA



- **Cytology= PAP smear**→ shows abnormalities with ↑ing risk from "atypical squamous cells" to low grade squamous intraepithelial lesion LGSIL) to high grade squamous intraepithelial lesion (HGSIL) to overtly malignant cells (squamous cell CA)

MANAGEMENT OF ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE OR LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION IN WOMEN 21-24 YEARS



ATYPICAL SQUAMOUS CELLS (ASC)
Atypical squamous cells represent cellular abnormalities more marked than simple reactive changes, but which do not meet the criteria for squamous intraepithelial neoplasia (SIL). These cells are not of typical appearance and are, therefore, atypical.

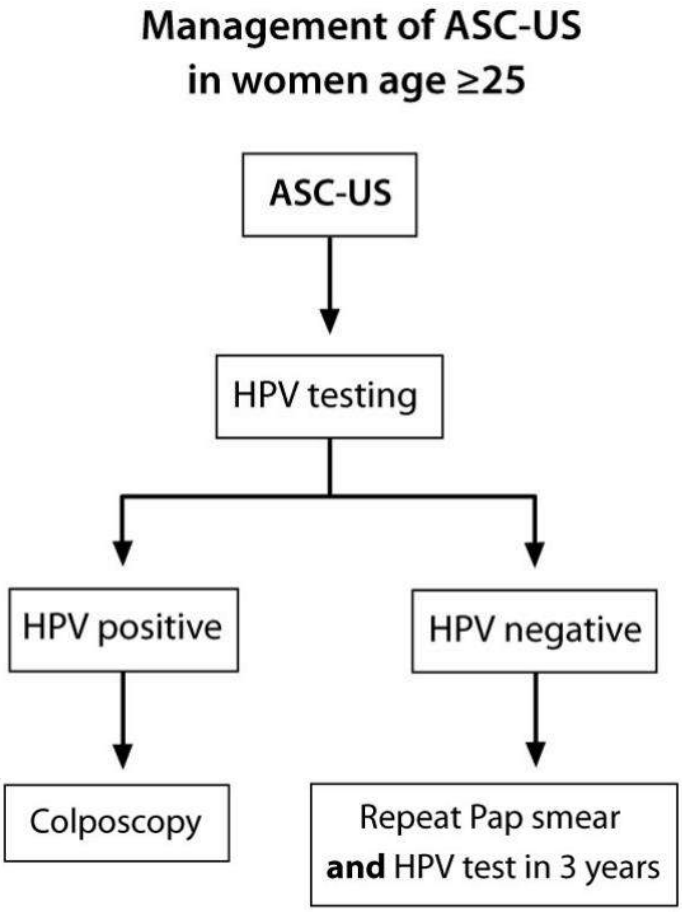
CATEGORIES OF ASC
The Pap diagnosis of Atypical Squamous Cells (ASC) is the most common abnormal finding during cervical cancer screening and is reported in about 5 percent of all cervical screening tests.
There are two subtypes of ASC:

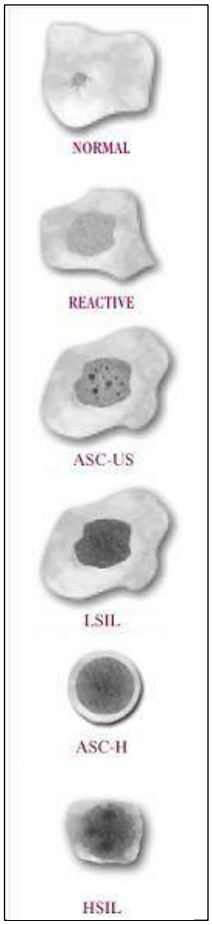
1. Atypical Squamous Cells of Undetermined Significance (ASC-US)
2. Atypical Squamous Cells, Cannot Rule Out High-Grade Squamous Intra-epithelial Lesion (ASC-H).

AGC: atypical glandular cells

- HPV infection is transient and malignant transformation is rare in this age group. Hence, HPV testing is not done. Colposcopy is done unless pt demonstrates ASC on 3 consecutive Pap smears

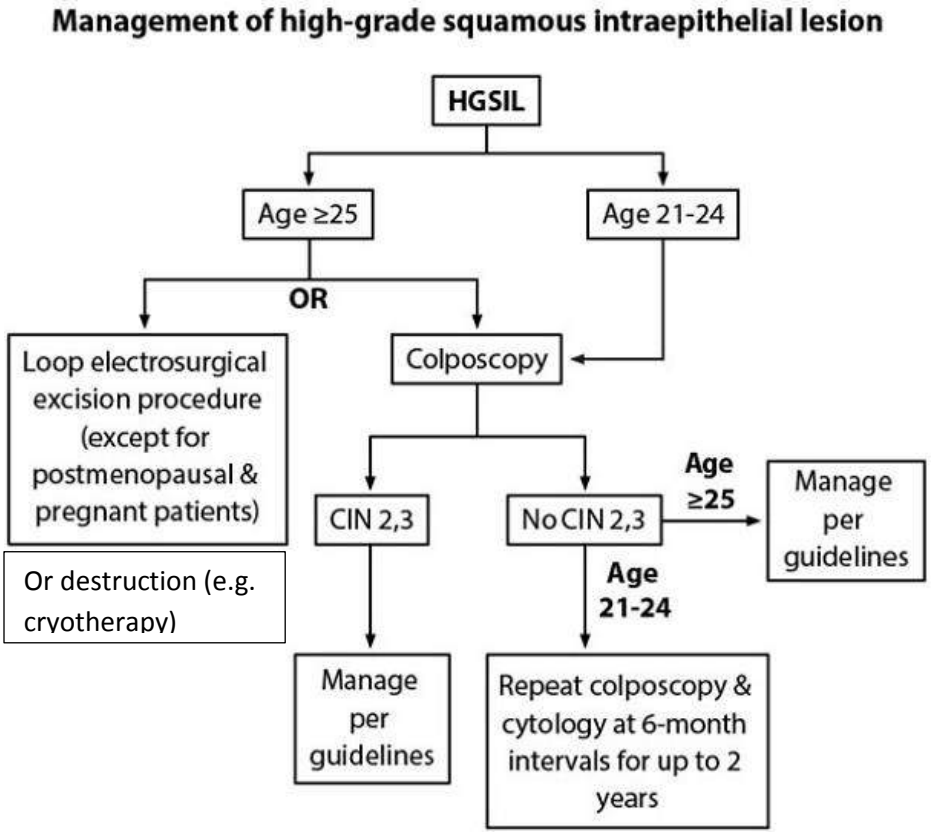
MANAGEMENT OF ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE OR LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION IN WOMEN >25 YEARS





- ASC-US—most common cervical cytologic abnormality—risk of invasive CA is low, as 40-60% cases are not associated with high risk HPV. This is in contrast to atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H), which is associated with premalignant lesions. However, a finding of ASC requires further investigation to rule out precancerous lesions.

MANAGEMENT OF HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HGSIL)



- **HGSIL**→ ↑ risk of cancerous and precancerous disease→ colposcopic examination must (shows magnified view of cervix and allows to take biopsy if needed). However pt >/=25 may skip colposcopy and directly proceed to excision or destruction. Pt <25—low-grade usually regress—excise only after colposcopy
  - If no suspicious area on colposcopy and adequate visualization → no need of biopsy
  - If suspicious area→ take biopsy→ biopsy graded as CIN 1, 2, 3 depending on depth of dysplastic cells
- Loop electrosurgical excision: excision of cone shaped portion of cervix, including transformation zone and portion of endocervix
- Endocervical curettage—indicated when physician cannot visualize squamocolumnar junction during colposcopy and there is suspicion of deeper lesion—CI in pregnancy
- **HGSIL in pregnant pt:**
  - Management of abnormal PAP smear during pregnancy is **mostly conservative**→ approx. 50% HGSIL and CIN 2 and 3 **will regress spontaneously** during pregnancy and <0.5% will progress to invasive CA
  - Rx may result in hemorrhage and pregnancy loss
  - **HGSIL**→ initial colposcopy must to exclude invasive disease
    - Negative colposcopy→ repeat Pap smear and colposcopy at least 6 wks after delivery
    - Abnormal colposcopy→ biopsy of suspicious area
      - **CIN 2 or 3**→ repeat cytology and biopsy not more frequently than every 12 wks

→ All sexually active women </=25 and pregnant women should be screened for chlamydia and gonorrhea

OVARIAN CANCER

BRCA CARRIERS

BRCA mutations & ovarian cancer	
Genetics	• *BRCA1* & *BRCA2* mutations • Autosomal dominant inheritance • Ashkenazi Jewish ancestry
Cancer risks	• Premenopausal epithelial ovarian cancer • Fallopian tube cancer • Primary peritoneal cancer • Breast cancer at age <50 • Breast cancer in male
Risk modification	• Bilateral salpingo-oophorectomy • Oral contraceptive use • Age <30 at first live birth • Breastfeeding • Tubal ligation

- Typically identified in individuals with breast cancer <50 or ovarian cancer at any age
- BRCA-1 and BRCA-2→ 60% and 20% lifetime risk of ovarian cancer, respectively
- **Pre-menopausal prophylactic b/l salpingo-oophorectomy (BSO)** → significantly ↓ incidence ovarian cancer as well as breast cancer and overall mortality in BRCA carriers—recommended as soon as childbearing is complete
  - Counsel regarding S/E of BSO from **surgical menopause:** ↓ libido, ↓BMD, ↑ risk of heart disease
  - Not offered in individuals without hereditary ↑ed risk
- OCPs not as effective as BSO but still have protective effect

SCREENING

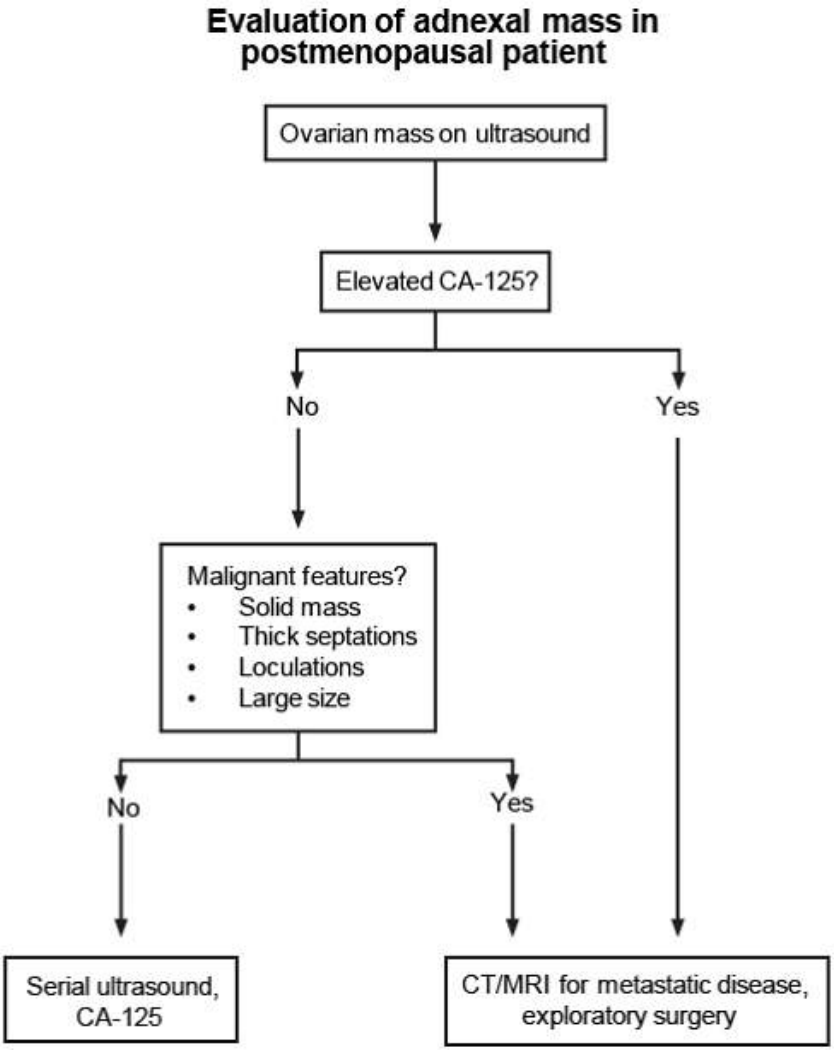
- For average risk pts (e.g. no hereditary cancer syndrome)→ **No screening tests exists**
- Very strong family history of ovarian cancer→ testing for BRCA 1 and BRCA 2 mutations, preferably starting from individual diagnosed with cancer

EPITHELIAL OVARIAN CANCER

Epithelial ovarian carcinoma	
Clinical presentation	• Acute: Shortness of breath, obstipation/constipation with vomiting, abdominal distension • Subacute: Pelvic/abdominal pain, bloating, early satiety • Asymptomatic adnexal mass
Laboratory findings	• ↑ CA-125
Ultrasound findings	• Solid mass • Thick septations • Ascites
Management	• Exploratory laparotomy

Drawn to correlate with clinical findings and to monitor treatment in future

Pelvic USG—1st line for palpable adnexal mass—combination of transabdominal and transvaginal USG used for full overview—fallopian tubes not visible unless pathology present



Even if no malignant features present on USG and CA-125 is ↑→ perform further imaging

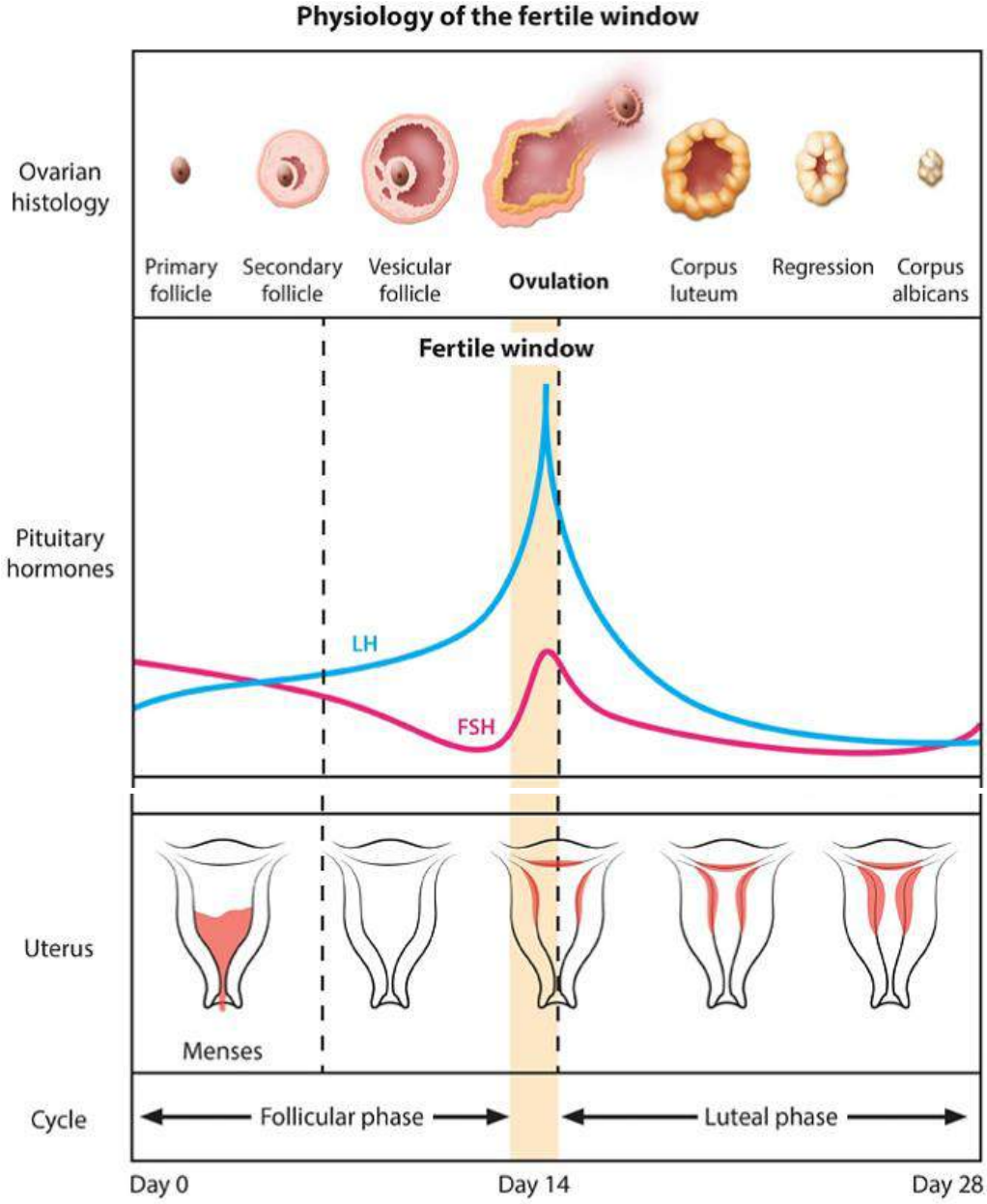
- **Epithelial ovarian cancer:** refers to malignancy involving **ovary, fallopian tube and peritoneum epithelium**. Abnormality can **begin at any of these sites**→ presents with hallmark large ovarian mass, and widespread pelvic and abdominal mets regardless of primary origin
- **Risk factors: P**ostmenopausal women, FH of ovarian and breast cancer (e.g. BRCA carriers), nulliparity, use of fertility drugs
- Usually presents with advanced dis. as early symptoms are non-specific
- **PE:** may present with firm, non-mobile **pelvic mass with nodularity—**concerning for EOC extension beyond adnexa. **Ascites –** due to peritoneal spread→ ↑ capillary permeability and ↓ intravascular oncotic pressure
- **CA-125**: little specificity in premenopausal women—can be ↑ from many benign conditions like endometriosis, leiomyomata and lupus. Mainly useful in post-menopausal women. Can also be used to monitor recurrence of proven malignancy after treatment
- **Exploratory laparotomy** with cancer resection, staging and inspection of entire abdominal cavity, esp. in acute presentation, is definitive rx. During surgery, ovaries, uterus, omentum and any visually apparent cancerous lesion will be removed and pelvic and paraaortic LN dissected
- **Chemotherapy with platinum based agents**—initiated after cancer is removed
- **Image guided biopsy is CONTRAINDICATED→** can cause spread of cancerous cells to entire abdominal cavity

GRANULOSA CELL TUMOR

Granulosa cell tumor of the ovary	
Clinical features	• Child: Precocious puberty • Postmenopausal woman: Bleeding/endometrial hyperplasia • Large adnexal mass
Diagnostic findings	• ↑ estrogen • Pelvic ultrasound: Ovarian mass, thickened endometrium

- Occurs in post-menopausal and rarely in prepubertal girls
- Tumor secretes **estrogen→** breast tenderness, endometrial CA (other feature in table)
- Thickened endometrium on USG requires immediate evaluation for concomitant endometrial malignancy with **endometrial biopsy**—gold standard to obtain endometrial sample
- **Rx:** surgical excision

CONTRACEPTION



- Fertilization is possible 24 hours after ovulation→ takes 6-12 days to implant

EMERGENCY CONTRACEPTION OPTIONS

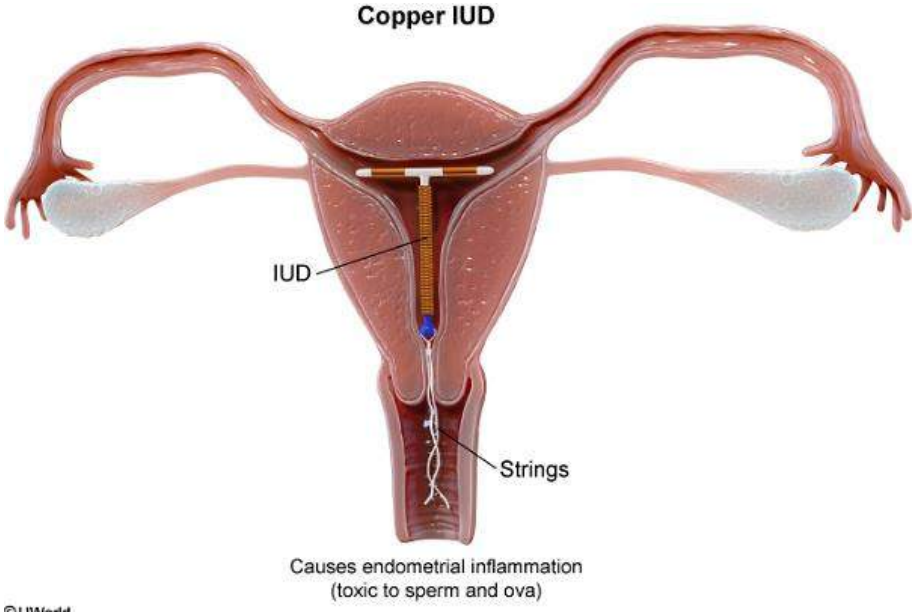
Emergency contraception options			
Method	**Mechanism**	**Time after intercourse (hours)**	**Efficacy**
Copper IUD	Copper causes inflammatory reaction that is toxic to sperm & ova & impairs implantation	0-120	99%
Ulipristal pill	Antiprogestin; delays ovulation	0-120	≥85%
Levonorgestrel pill	Progestin; delays ovulation	0-72	85%
OCPs	Progestin; delays ovulation	0-72	75%

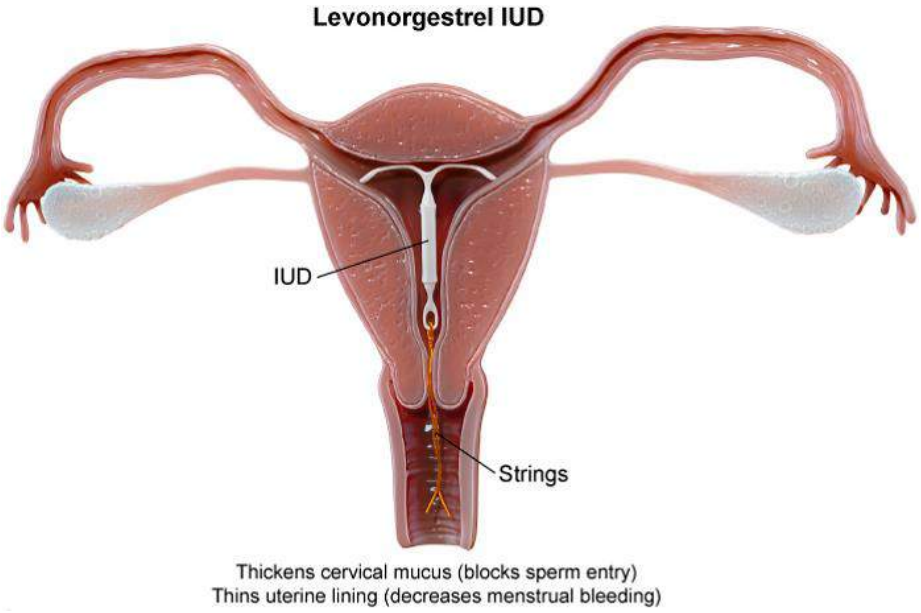
IUD = intrauterine device; OCP = combined oral contraceptive pill containing progestin levonorgestrel or norgestrel.

More effective than levonorgestrel but less readily available

COPPER IUD

- MOST EFFECTIVE emergency and long-term contraception
- Needs a professional to insert
- Hormone free method so can be used in breast cancer pts undergoing treatment for long term contraception and to avoid hormonal effects of OCPS
- Can be placed for a max. of 10 years
- Levonorgestrel IUD can be used too for long-term (can be placed for 5 years) but NOT emergency contraception
- Age and parity are not contraindications. Acute cervicitis and PID are contraindications.
- Use in conjunction with condoms to prevent STDs





ORAL LEVONORGESTREL

- Also known as plan B—most readily available emergency contraception
- Ulipristil and levonorgestrel are more are more effective before ovulation has occurred as they prevent oocyte release and delays ovulation
- Ineffective after fertilization
- Efficacy ↓ over course of 72 hours so give asap

OCPS

- For emergency contraception, multiple pills must be taken in 2 doses 12 hours apart to achieve an effective progestin level
- May be easy to obtain but less effective

ORAL CONTRACEPTIVE PILLS (OCPS)

BENEFITS OF COMBINATION OCPS

Benefits	of combined estrogen-progestin contraceptives
Benefits	• Pregnancy prevention • Endometrial & ovarian cancer risk reduction • Menstrual regulation with reduction in iron deficiency anemia • Reduction in risk of benign breast disease

ADVERSE EFFECTS

Side effects & risks of combination oral contraceptives

- Breakthrough bleeding
- Breast tenderness, nausea, bloating
- Amenorrhea
- Hypertension
- Venous thromboembolic disease
- Decreased risk of ovarian & endometrial cancer
- Increased risk of cervical cancer
- Liver disorders (eg, hepatic adenoma)
- Increased triglycerides (due to estrogen component)

Because of low estrogen dose in drugs (10-35µg estrogen)

Very rarely stroke and MI can occur

- H/o benign breast disease or FH of breast CA→ NOT a contraindication of OCP use
- Pts with uncontrolled HTN, who smoke and age >35 should consider some other method of contraception
- Controlled HTN→ can be given OCPs but with BP monitoring to ensure ongoing control
- Weight gain:
  - Though some clinicians believe that OCPs cause weight gain, but they do not.
  - Old high dose combined OCPs were associated with weight gain but new low dose formulation do not cause weight gain→ reassure pts
  - Medroxyprogesterone causes ↑ in body fat and ↓ in muscle mass

CONTRAINDICATIONS OF OCPS

Absolute contraindications to combined hormonal contraceptives

- Migraine with aura
- ≥15 cigarettes/day & age ≥35
- Stage 2 hypertension (≥160/100 mm Hg)
- History of venous thromboembolic disease
- History of stroke or ischemic heart disease
- Breast cancer
- Cirrhosis & liver cancer
- Major surgery with prolonged immobilization
- <3 weeks postpartum

Esp. in hormone receptor +ve breast cancer. BRCA-2 carriers tend to have estrogen receptor +ve breast cancer. All types of hormone containing contraception are CI— including progesterone IUD, patch and vaginal ring

PROGESTIN BASED PRE-COITAL CONTRACEPTIVES

- **Depot medroxyprogesterone acetate** and the **etonogestrel subdermal implant** are systemic progestin-based precoital contraceptives→inhibit the secretion of GnRH from the hypothalamus→↓ FSH and LH→ inhibit follicular development.

- They do not work as emergency contraception because they have no effect on an already maturing ovarian follicle
- **Depot medroxyprogesterone acetate (DMPA)—**given intramuscularly every 3 mo. S/E:
  - Menstrual irregularities such as prolonged bleeding and/or spotting—esp. during 1st 6 mo
  - About 50% have amenorrhea after 1 year of use
  - Fatigue, nausea, weight gain, breast tenderness—less common—but persist throughout use of DMPA—symptoms may mimic pregnancy

CONTRACEPTION IN LACTATING MOTHERS

- Acceptable contraceptive methods in post-partum period:
  - Sterilization
  - Barrier method
  - Intra-uterine devices
  - **Progestin only pills:** preferred hormonal contraceptives in lactating women→ do not affect volume or composition of milk produced by mother, no known effects on infant and no ↑ risk of venous thrombosis
- Combined OCPS: ↓ milk production and pass in milk—effect on infant unknown

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: Adjuvant treatment of breast cancer • Raloxifene: Postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only)

By causing protein C resistance

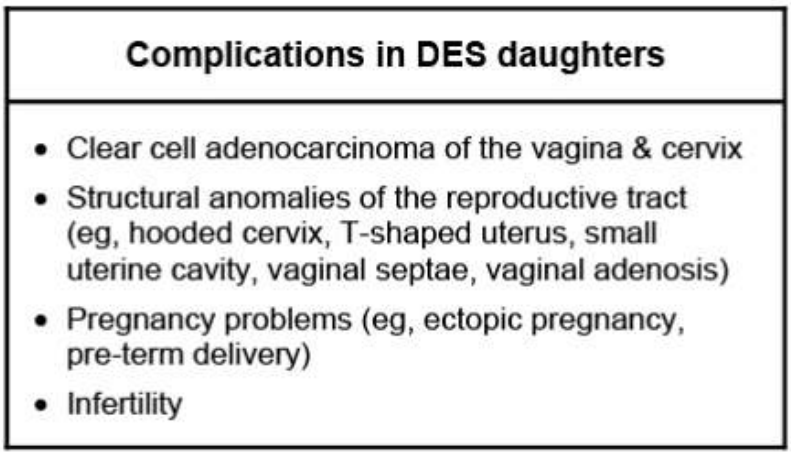
- Adjuvant endocrine therapy is commonly used for non-metastatic, hormone receptor positive breast cancer. **Most commonly used endocrine agents:** tamoxifen, aromatase inhibitors, and ovarian suppression via medicine or surgery.
- **Tamoxifen: Pre-menopausal at low risk of recurrence:** preferred endocrine drug for adjuvant treatment. Associated with endometrial polyps. **Post-menopausal:** 2nd line—prescribed to those who cannot use aromatase inhibitors. Associated with endometrial hyperplasia and cancer. Risk last for duration of therapy and resolve after discontinuation of treatment. Benefit outweighs risk. It also **↓es risk of cancer recurrence and development of new cancer in opposite breast.**
  - **Hot flashes** occur in 80% pts taking tamoxifen—it has antiestrogenic activity in CNS and cause thermoregulatory dysfunction in ant. hypothalamus (similar to menopausal hot flashes)

- **Raloxifene:** Although less effective than bisphosphonates for osteoporosis, still used in post-menopausal women who cannot tolerate bisphosphonates or have ↑ risk of breast cancer
- All meds with estrogen agonist activity like OCPS, HRT and SERMS→ CI in pts with current or past venous thromboembolism
- Raloxifene ↓ total and LDL, but does not ↑ or ↓ risk of coronary artery disease. But CAD and estrogen receptor positive breast cancer is CI for HRT

OVARIAN HYPERSTIMULATION SYNDROME

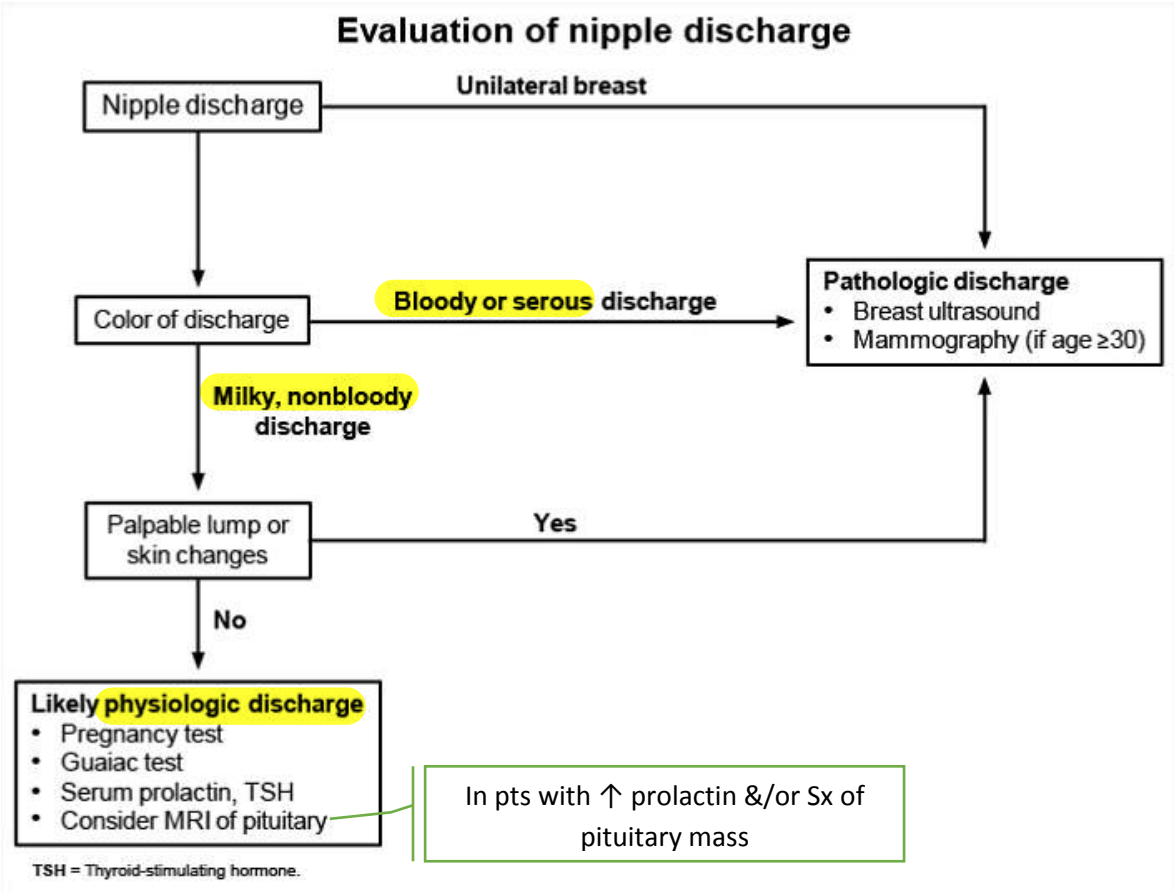
- Iatrogenic complication of ovulation inducing drugs
- Abdominal pain due to ovarian enlargement
- May be accompanied by ascites, respiratory difficulty, and other systemic findings

SIDE EFFECTS OF DIETHYLSTILLBESTROL USE IN PREGNANCY



- CCA can occur at any age but peak incidence is in teens and twenties
- **Complications in boys exposed to DES in utero:** cryptorchidism, microphallus, hypospadias, and testicular hypoplasia
- **Use of DES:** it was used to prevent spontaneous abortion, premature delivery and postpartum lactation suppression

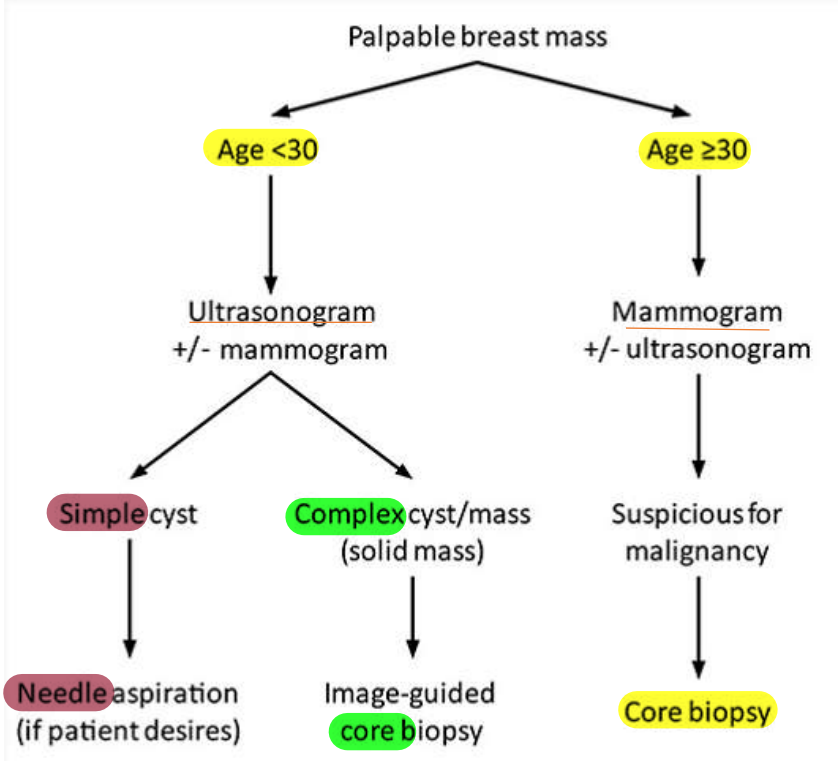
EVALUATION OF NIPPLE DISCHARGE



PHYSIOLOGIC GALACTORRHEA

- **Galactorrhea:** lactation in men and non-breastfeeding women
- Can be a sign of significant pathology
- Usually B/l and guaiac negative
- Typically milky or clear but can be yellow, brown, gray or green
- **Most common cause: hyperprolactinemia**—can be due to
  - Pituitary prolactinoma
  - Meds
  - **Hypothyroidism**
  - Pregnancy
  - Chest wall/nipple stimulation (e.g. surgery, trauma, shingles)

PALPABLE BREAST MASS



- **Tender, mobile mass** in young pt is most likely benign

SIMPLE BREAST CYST

- Presentation is variable: from no symptoms to severe, localized pain
- USG: shows acoustic enhancement (indicative of **fluid)** and no echogenic debris or solid components
- Symptomatic pt: may benefit from **aspiration (**should yield **clear fluid**)→ disappearance of mass and thereby confirm diagnosis
- As cystic fluid can reaccumulate, hence, **clinical breast examination follow-up 2-4 months later**→ no further signs and symptoms of recurrence→ **annual screening** can be resumed.
- If reappears or does not disappear after aspiration→ **core biopsy**

AGE >30 YEARS

- **Screening mammograms** are used for asymptomatic women without masses
- **Diagnostic (multiple view) mammograms** used to evaluate palpated mass or abnormal screening result
- **Targeted USG** to characterize the mass is often done along with mammography

➔ Solid, acellular masses (e.g. stromal)→ core biopsy
➔ Large or suspicious masses→ excisional biopsy
➔ Suspected cystic or small masses→ FNA

BENIGN BREAST DISEASES

Benign breast disease	
Diagnosis	**Clinical features**
Breast cyst	• Solitary, well-circumscribed, mobile mass • +/- Tenderness
Fibrocystic changes	• Multiple, diffuse nodulocystic masses • Cyclic premenstrual tenderness
Fibroadenoma	• Solitary, well-circumscribed, mobile mass • Cyclic premenstrual tenderness
Fat necrosis	• Post-trauma/surgery • Firm, irregular mass • +/- Ecchymosis, skin/nipple retraction

Fluid-filled. Rx: fine needle aspiration with drainage of cyst

Sx improve during or after menstruation. Pts can be offered NSAIDS and/or OCPS for symptomatic relief

FIBROADENOMA

Fibroadenoma	
Epidemiology	Age <30
Clinical features	• Single, unilateral, mobile, well-circumscribed mass • ↑ Pain &/or size prior to menses
Management	• Observation & reassurance (adolescent) • Ultrasound for a persistent mass or older patient

- Pathogenesis: fluctuating estrogen and progesterone levels
- Re-examine over at least one menstrual cycle right after menstruation→ if size and/or tenderness ↓es in adolescents→ no further workup is needed
- Excisional biopsy is indicated in adult pts or those with very large masses

FAT NECROSIS

- Clinical and radiographic findings may mimic breast cancer
- Usually presents as fixed mass
- Mammography usually shows calcifications
- USG: hyperechoic mass (often correlated with benign etiology)
- Biopsy: diagnostic. Shows fat globules and foamy histiocytes
- Despite benign biopsy results→ entire mass is often excised due to calcifications on mammography and fixed irregular mass on exam
- Once diagnosis confirmed with pathological analysis→ routine annual screening is sufficient as no ↑ risk of CA

INTRADUCTAL PAPILLOMA

Intraductal papilloma	
Clinical features	• Unilateral bloody nipple discharge • No associated mass or lymphadenopathy
Management	• Mammography & ultrasound • Biopsy, +/- excision

For confirmation of diagnosis. Subsequent pathologic evaluation is done

- Benign condition
- Discharge can be brown, pink or red confined to a single duct and can range from frank blood to serosanguinous
- Mammography and USG will reveal normal breast tissue or **single dilated breast duct**

MALIGNANT BREAST TUMORS

RISK FACTORS FOR BREAST CANCER

Breast cancer risk factors	
Modifiable	• Hormone replacement therapy • Nulliparity • Increased age at first live birth • Alcohol consumption
Non-modifiable	• Genetic mutation or breast cancer in first-degree relatives • White race • Increasing age • Early menarche or later menopause

Obesity.
Even low alcohol intake (<1 drink/day)→ ↑ risk of breast cancer in women. Moderate consumption is <2 drinks/day or <7 drinks/week→ although moderate ↓es overall mortality and possible cardiovascular benefits, it has **dose-dependent** causal effect on breast cancer. Also ↑ risk of head and neck cancer.

Breast cancer < 50 years and ovarian cancer at any age in 1st degree relative→ genetic mutation testing

- Exercise and breastfeeding is also protective
- Menarche at age >13 →↓ risk
- OCPs ↓ risk of ovarian CA and not breast CA

SCREENING FOR BREAST CANCER

- Clinical breast examination and mammography
- **Routine mammography at age >/=50** due to ↑ risk of cancer with ↑ing age
- **MRI** for BRCA carriers, first degree relative of BRCA carrier and pre and post-op management of breast cancer

IMPORTANT PROGNOSTIC AND TREATMENT FACTOR

- Prognostic factors in ↓ing order of significance:
  1. Tumor burden based on TNM staging
  2. ER and PR+ are good prognostic factors
  3. HER2/neu oncogene overexpression—worse prognosis
  4. Histological grade: poorly differentiated tumor has worse prognosis
- (size >2 cm is known as T2—breast conserving surgery is followed by chemo and radio)
- Presence of **overexpression of HER2 oncogene** is important prognostic and Rx factor—determined by **fluorescence in situ hybridization (FISH) or immunohistochemical staining (IHC)**
- HER2 overexpression +ve→ treat with **trastuzumab (Herceptin)**→ specifically targets cells that cause overexpression of oncogene
  - Trantuzumab—used as adjuvant therapy in early stage disease or in later stage metastatic disease
  - **SE:** cardiotoxicity
  - **Echocardiogram** recommended before therapy to determine baseline function for future reference and to consider other therapy if poor baseline heart function (borderline or low ejection fraction <55%)
- HER2 overexpression also effects chemotherapy regimen used→ **anthracyclines more effective**
- Initially HER2 overexpression was associated with poor prognosis before targeted therapy—now prognosis is less clear

NON-INVASIVE BREAST CANCER

PAGET DISEASE

- Persistent, eczematous, and/or ulcerating rash localized to nipple and spreads to areola. Vesicles, sales, bloody discharge and nipple retraction may be +ve
- 85% have underlying breast cancer
- Adenocarcinoma most common type of breast cancer and also in Paget disease
- Due to migration of neoplastic cells from through mammary duct to nipple surface
- Workup: mammography and biopsy

INVASIVE BREAST CANCER

INFLAMMATORY BREAST CANCER

- Rare but aggressive
- Rapid onset edematous cutaneous thickening with peau d'orange appearance
- Itching, palpable mass, nipple changed may be present. Can be confused with infection but fail to respond to antibiotics
- Axillary LAD—suggest metastatic dis. – common
- **Evaluation:** mammography and USG. Tissue biopsy to confirm dx

POINTERS

➔ Rule out pregnancy in a sexually active woman of child bearing age presenting with acute abdomen or N/V, abdominal bloating, constipation before performing USG and other imaging studies (e.g. x-ray, CT). serum pregnancy test more sensitive and can be positive within 4 days of implantation

- If pregnancy test +ve→ pelvic USG to evaluate for intrauterine or ectopic pregnancy or ovarian pathology
- If –ve→ CT can be considered to rule out other causes like appendicitis, kidney stones. Or x-ray to rule out intestinal obstruction or perforation

➔ Menopause and hyperthyroidism can have similar symptoms, hence pts with hx suggesting both should be tested with TSH and FSH

➔ ↑ TRH and serotonin, ↓ dopamine (e.g. antipsychotics, TCA, MAOIs), hypothalamic and pituitary tumors→ ↑ prolactin → ↓ GnRH and gonadotropin production→ amenorrhea, galactorrhea

Qid: 12511
ANGIOSARCOMA (breast)
- derived from lining of blood vessels and lymphatics.
- **RF:** localized radiation (eg, breast cancer), chronic lymphedema.
- **Pt:** purpuric masses on the skin 4-8 years following completion of breast cancer therapy.
- **Dx:** biopsy
- **Tx:** surgery but poor prognosis.

Contents

FEMALE REPRODUCTIVE SYSTEM- PEDIATRICS

VAGINAL FOREIGN BODIES

- Common cause of vulvovaginitis in prepubertal children.
- Toilet paper is the most common vaginal foreign body, although small toys and other objects may be seen.
- Presenting symptoms include foul-smelling vaginal discharge, intermittent vaginal bleeding or spotting, and, occasionally, urinary complaints.
- When a vaginal foreign body is suspected, an external examination of the genitalia should be performed with the child in either the knee-to-chest or frog-leg position to minimize discomfort.
- Depending on the age of the child and the size and type of foreign body, sedation or general anesthesia may be required for both the examination and foreign body removal.
- **Small foreign bodies**, such as toilet paper and small toys, can often be removed easily with **a calcium alginate swab or irrigation with warmed fluids** after a topical anesthetic has been applied.
- If these techniques **are unsuccessful or if a large foreign body** is noted, examination under anesthesia may be necessary.
- Bimanual examination should NEVER be performed in prepubertal children

MATERNAL ESTROGEN EFFECTS ON NEWBORNS

Maternal estrogen effects in newborns
• Breast hypertrophy (girls & boys) • Swollen labia • Physiologic leukorrhea (whitish vaginal discharge) • Uterine withdrawal bleeding

- **Female infants <3mo** sometimes develop vaginal spotting or bleeding (odorless cloudy white vaginal discharge mixed with blood)
- **Pathophysiology:** maternal estrogens can cross placenta→ enter fetal blood stream before birth→ pubertal effect on newborn
- Effects disappear as soon as hormone is cleared from circulation→ hence, routine care and reassurance should be provided

PREMATURE THELARCHE

- Assessment of ovarian ultrasound and FSH and LH levels are useful in patients with premature thelarche presenting after infancy.

➔ GnRH stimulation test is for precocious puberty i.e. before the age of 7

Contents

MALE REPRODUCTIVE SYSTEM- IM

PRIAPISM

- Common causes of priapism:

1. Sickle cell disease and leukemia - usually in children or adolescents
2. Perineal or genital trauma - results in laceration of the cavernous artery
3. Neurogenic lesions - such as spinal cord injury, cauda equine compression, etc.
4. Medications - such as trazodone and **prazosin** (most common cause of priapism is prazosin)

IMPOTENCE

- Drugs associated with impotence: most antihypertensives [redacted], non-selective β-blockers e.g. propranolol

ACUTE URINARY RETENTION IN ELDERLY MEN

- Causes: obstruction, neurogenic bladder or detrusor muscle inactivity
- Most common cause in elderly men is BPH or prostatic CA—postvoid dribbling, ↓ stream, urgency, hesitancy, nocturia, and urinary retention
- Achilles tendon reflexes can ↓ or become absent in elderly and is not indication of spinal cord injury--normal
- Spinal cord compression in lumbar region causes lower extremity weakness, bowel/bladder incontinence (rather than retention), ↓ rectal tone, brisk lower extremity DTRs

PROSTATITIS

Overview of prostatitis

	Acute	Chronic
Clinical presentation	• Fever, chills, malaise, myalgia • Pelvic pain, cloudy urine	• Dysuria and ↑ urinary frequency • No symptoms of acute prostatitis • Recurrent urinary tract infection
Diagnosis	• Pyuria, tender prostate • Urine culture positive (usually *E coli*)	• Pyuria with possible tender prostate • Urine culture positive (usually *E coli*)
Treatment	• TPM-SMX or fluoroquinolones	• Fluoroquinolones

E coli = *Escherichia coli*; **TPM-SMX** = trimethoprim-sulfamethoxazole.

- Acute bacterial prostatitis is usually caused by same organisms that cause other infections of urinary tract
- Initial symptoms may resemble cystitis but systemic symptoms are more pronounced in prostatitis

- Even fi leukocyte esterase is positive on dipstick, perform mid-stream urine culture to help direct antibiotic therapy
- Prostate massage to ↑ culture yield has been recommended—painful and may induce bacteremia
- Antibiotic started while awaiting culture results—treatment should be continued for **4-6 wks** in most cases
- Computed tomography scan can be useful to diagnose a **prostatic abscess**, which would be suspected if a patient with acute bacterial prostatitis continues to have fever despite appropriate antibiotic therapy

NON-INFLAMMATORY CHRONIC PROSTATITIS

- Afebrile
- Irritative voiding symptoms i.e. frequency, urgency, hesitancy, interruption of flow.
- **PE:** unremarkable. Mild periprostatic tenderness may be present
- **Urinalysis:** normal.
- Expressed prostatic secretions show a normal number of leukocytes and culture of these secretions is negative for bacteria.
- There is usually no history of past UTI but voiding abnormalities may be present in the past

INFLAMMATORY CHRONIC PROSTATITIS

- Afebrile
- Irritative voiding symptoms like urinary frequency, urgency and suprapubic or perineal discomfort.
- Urinalysis is normal.
- Expressed prostatic secretions show a leukocyte count greater than 10 WBCs/H PF and
- Culture of these secretions is negative.

Chronic prostatitis/chronic pelvic pain syndrome	
Symptoms	• Pain in pelvis, perineum, genitalia • Irritative voiding symptoms (eg, urgency, hesitancy) • Hematospermia, pain with ejaculation
Diagnosis	• No or mild prostate tenderness • Sterile urine culture
Management	• Alpha blockers (eg, tamsulosin) • Antibiotics (eg, ciprofloxacin), especially if history of UTI • 5-alpha-reductase inhibitors (eg, finasteride)

SCREENING FOR PROSTATE CANCER

- USPSTF—does not recommend screening using PSA irrespective to age—states that screening does not saves lives and leads to more tests and treatments that needlessly cause pain, impotence and incontinence in many pts
- American Urological Society and American Cancer Society recommends screening with PSA in conjunction with DRE at age 40 with counselling of risks and benefits of screening. Recommend screening in pts up to age 75 yrs with life expectancy of at least 10 yrs
- As a result of this controversy, screening decisions are left up to individual and physician and determined by discussion of risks and benefits

TESTICULAR CANCER

- After the diagnosis of testicular cancer has been made (hard, palpable, painless testicular mass + suggestive USG)→ initial management: removal of testis and its associated cord, orchiectomy—done through small inguinal incision—procedure is called **high inguinal orchiectomy**
- The testis and abnormal tissue present is then examined under the microscopy to determine the type of cancer→ depending on type, other therapies i.e. additional surgery, radiation therapy or possible chemo may be indicated
- Highest cure rate of all cancers—achieved by combination of surgery and chemo, + radiation in some cases
- Cure can also be achieved in case of cancer spread to other parts of body

- In this tumor, we **kill first and investigate later**—hence biopsy is not the next step—FNAC or transscrotal biopsy are CI due to risk of spillage of cancer cells and spread through blood vessels and lymphatics

Testicular cancer	
Epidemiology	• Age 15-35 • Risk factors: Family history, cryptorchidism
Manifestations	• **Unilateral, painless testicular nodule** • Dull lower abdominal ache • Metastatic symptoms (eg, dyspnea, neck mass, low back pain)
Diagnosis	• Examination: **Firm, ovoid mass** • Tumor markers (AFP, β-hCG) • **Scrotal ultrasound** • Staging imaging (CT scan, chest x-ray)
Treatment	• Radical **orchiectomy** • Chemotherapy • Cure rate ~95%

Educational objective:
Testicular germ cell tumors are common in young men and manifest primarily with a painless testicular mass. However, a minority of patients may have symptoms of metastatic disease, including low back pain (retroperitoneal lymphadenopathy) and dyspnea/cough (pulmonary nodules). Testicular examination showing a firm, ovoid testicular nodule should prompt a scrotal ultrasound and tumor markers to support the diagnosis.

Benign prostatic hyperplasia (BPH)

Comparison of benign prostatic hyperplasia & prostate cancer		
	BPH	**Prostate cancer**
Risk factors	• Age >50	• Age >40, **African American** & family history
Affected part	• **Central** portion (transitional zone)	• Usually **lateral** lobes of prostate but can be anywhere
Examination	• Symmetrically enlarged & smooth prostate • Can have elevated PSA	• Asymmetrically enlarged, **nodules** & firm prostate • Markedly elevated PSA

Medical therapy for benign prostatic hyperplasia	
Alpha-adrenergic antagonists (eg, terazosin, tamsulosin)	• Relax smooth muscle in bladder neck, prostate capsule & prostatic urethra • Usual first-line therapy • **Side effects**: Orthostatic hypotension, dizziness
5-alpha-reductase inhibitors (eg, finasteride, dutasteride)	• Inhibit conversion of testosterone to dihydrotestosterone • Reduce prostate gland size • Effectiveness may take 6-12 months • **Side effects**: Decreased libido, erectile dysfunction
Antimuscarinics (eg, tolterodine)	• Used to treat overactive bladder (urinary frequency, urgency & incontinence) • **Side effects**: Urine retention, dry mouth

- Patients with lower urinary tract symptoms (eg, urinary frequency, nocturia, hesitancy) should have a **urinalysis** to evaluate for hematuria and infection.
- PSA should also be obtained in symptomatic patients to assess the risk for prostate cancer unless predicted life expectancy is <10 years.

QID: 3363
- Anabolic steroid use by a man can produce infertility by suppressing the production of GnRH, LH, and FSH.
- Pt: small testes, gynecomastia & aggressive behavior.
- The exogenous androgen suppresses native testosterone production but is detected as testosterone by current assays, so patients can have normal serum testosterone levels.
- **Summary:** athelete + small testes + low FSH, LH + normal testosterone = steroids

ERECTILE DYSFUNCTION

Common causes of erectile dysfunction	
	Clinical features
Vascular	• Cardiovascular risk factors (eg, hypertension, **smoking**, diabetes) • Abnormal vascular examination (eg, bruits, decreased pulses)
Neurologic	• Neurologic comorbidity (eg, **diabetic neuropathy**, multiple sclerosis, spinal injury/surgery) • Gradual onset, loss of bulbocavernosus reflex
Psychogenic	• Sudden onset • Situational (eg, ED with partner, normal erection during masturbation) • **Normal nonsexual nocturnal erections**
Endocrine	• Additional symptoms due to underlying disorder • Abnormal hormone levels (eg, TSH, prolactin)
Medications	• Onset related to starting medication • Antihypertensives, SSRIs, anti-androgenic medications
Hypogonadism	• Gradual onset • Decreased libido, gynecomastia, testicular atrophy • Low serum testosterone

Adverse effects of phosphodiesterase-5 inhibitors	
Cardiovascular	• **Hypotension** (especially with nitrates, alpha blockers)
Ocular	• Blue discoloration of vision • Nonarteritic anterior ischemic optic neuropathy
Genitourinary	• **Priapism**
Other	• Flushing • Headache • Hearing loss

EPIDIDYMITIS

Acute epididymitis	
Epidemiology	• Age <35: **Sexually transmitted** (chlamydia, gonorrhea) • Age >35: Bladder outlet obstruction (**coliform bacteria**)
Symptoms	• Unilateral testicular **pain** • Epididymal **edema** • Dysuria, frequency (with coliform infection)
Diagnosis	• **Urinalysis**/culture • **NAAT** for chlamydia & gonorrhea
Treatment	• Ceftriaxone/doxycycline (if STI) • Levofloxacin (if coliform bacteria)

Ascending coliform bacteria such as E.coli are the most likely pathogens

Contents

MALE REPRODUCTIVE SYSTEM- PEDIATRICS

CRYPTORCHIDISM

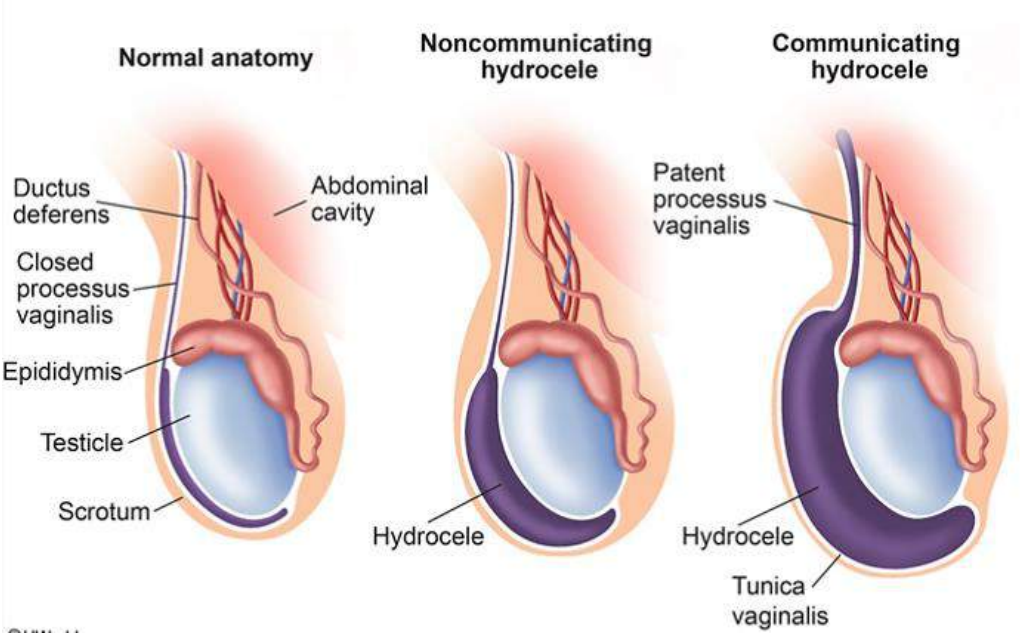
Cryptorchidism	
Risk factors	• Prematurity • Small for gestational age • Low birth weight (<2.5 kg) • In utero exposure to diethylstilbestrol & pesticides • Genetic disorders • Neural tube defects
Clinical features	• Empty, hypoplastic, poorly rugated scrotum or hemiscrotum • +/- Inguinal fullness
Treatment	• Orchiopexy before age 1 year
Complications	• Inguinal hernia • Testicular torsion • Subfertility • Testicular cancer

- Most common congenital anomaly of genitourinary tract
- **U/L:** usually have no other anomaly
- **B/L:** may be one of many manifestations of an endocrinopathy or genetic syndrome
- Regular scrotal exam should be performed on all boys to evaluate testicular location and scrotal appearance
- **Normal scrotum**: thick and rugated and contains palpable testes
- Testicles that have not descended by **age 6 months** are unlikely to descend spontaneously and require surgery
- **Orchiopexy:** almost all pts have associated patent processus vaginalis that is repaired concurrently to prevent **inguinal hernia. Testicular torsion** risk is removed as testis are surgically affixed to scrotal wall. Early surgery improves fertility, but **sperm count and quality remain substandard**. Prepubertal surgery also ↓es but does not eliminate **testicular cancer** risk. Cancer detection also improves as abnormal testicular masses are more easily palpated in scrotum compared to groin and abdomen

HYDROCELE

- **Definition:** Fluid collection within the processus or tunica vaginalis - the peritoneal projection that accompanies the testis during its descent into the scrotum.

- **Communicating hydrocele:** When the processus vaginalis fails to obliterate, peritoneal fluid may accumulate within the processus vaginalis. Frequently reducible but may also ↑ in size with valsalva
- **Non-communicating hydrocele:** A collection of fluid within a tunica vaginalis that has properly obliterated its communication with the peritoneum.
- Hydrocele can be differentiated from other testicular masses by **transillumination**; a hydrocele will transilluminate while other masses will not.
- **Management:** Most hydroceles, both communicating and non-communicating, will **resolve spontaneously by the age of 12 months** and can be safely observed during that period.
- **Communicating hydrocele that fail to resolve in 12 mo:** unlikely to resolve spontaneously→ put the pt at ↑ risk of indirect inguinal hernia→ hence need surgical intervention



Contents

MALE REPRODUCTIVE SYSTEM- SURGERY

PENILE FRACTURE

- Typically not injured in flaccid state by blunt trauma
- Usually injured during erect position mostly during sexual intercourse esp. when woman is on the top
- Snapping sensation and/or sound followed by severe pain—snapping sensation is from tearing of tunica albuginea, which invests the corpus cavernosum
- Hematoma rapidly forms at the site of injury→ bending of the shaft of penis at the site of fracture
- **Treatment** is with an **emergent urethrogram** to assess for urethral injury as well as **emergent surgery** to evacuate the hematoma and mend the torn tunica albuginea.
- Surgical exploration is the treatment of choice for penile fracture, but it should always be preceded by a retrograde urethrogram to rule out a urethral injury. This is important because an occult urethral injury may be exacerbated by placement of a Foley catheter.

VARICOCELE

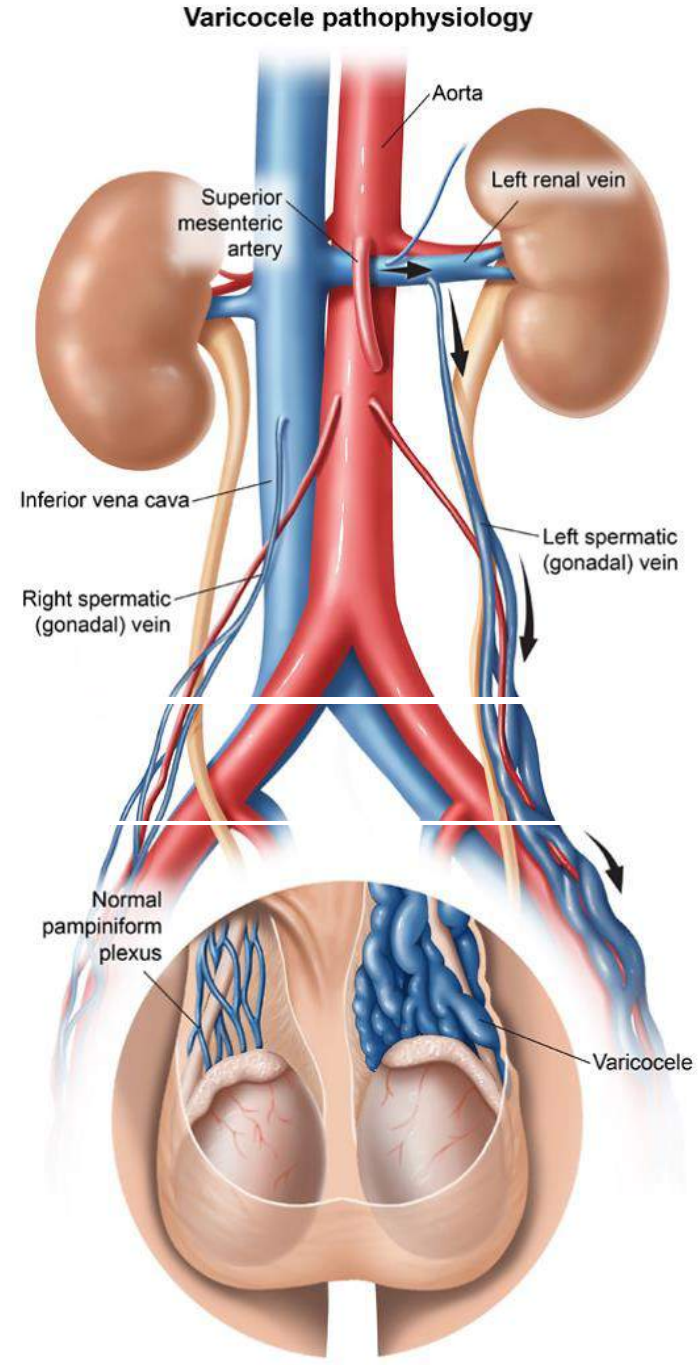
Varicocele	

Clinical presentation	• Soft scrotal mass ("bag of worms")
	  ◦ ↓ In supine position
	  ◦ ↑ With standing/Valsalva maneuvers
	• Subfertility
	• Testicular atrophy

Ultrasound findings	• Retrograde venous flow • Tortuous, anechoic tubules adjacent to testis • Dilation of pampiniform plexus veins
Treatment	• Gonadal vein ligation (boys & young men with testicular atrophy) • Scrotal support & NSAIDs (older men who do not desire additional children)

NSAIDs = nonsteroidal anti-inflammatory drugs.

- 20% of postpubertal males suffer from varicocele—more common on left than right side
- Pts may have no symptoms or dull scrotal ache while standing
- Mass does not transilluminate



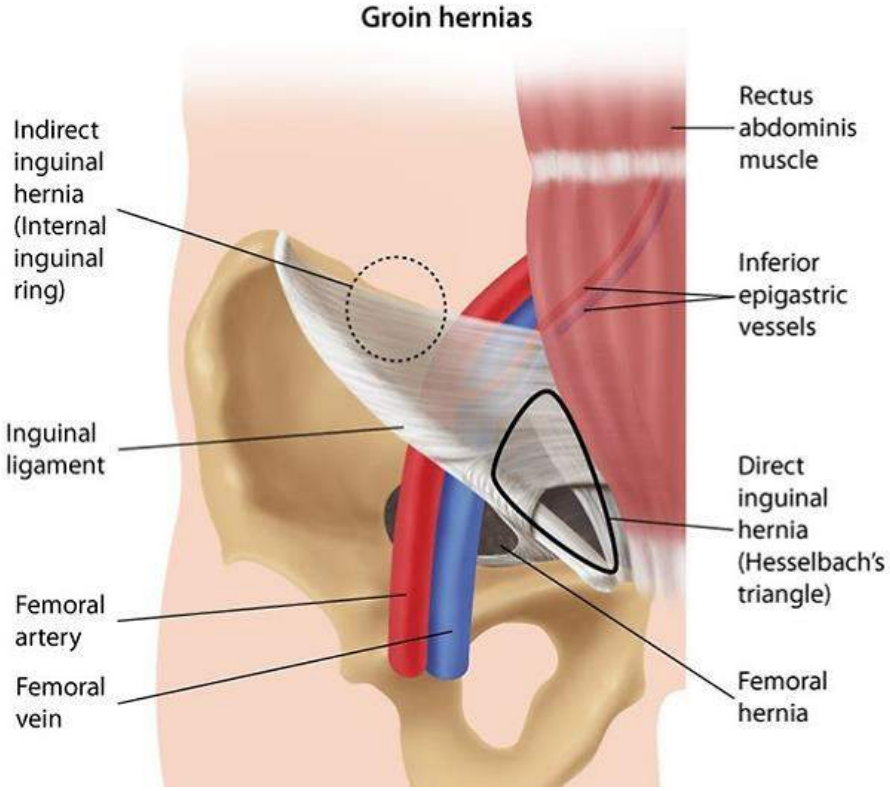
The aorta & superior mesenteric artery compress the left renal vein. The increased pressure in the left renal vein causes retrograde blood flow to testes & dilation of the pampiniform plexus.

SPERMATOCELE

- Painless, fluid-filled cyst of head of the epididymis.
- They are located on the superior pole of the testis and contain nonviable sperm.
- They are distinguishable on physical examination as a mass outside of the testis that does not change with position.

INTESTINAL HERNIAS

- Intestinal hernias can cause painless or painful scrotal masses with a protrusion pattern similar to varicocele (worsens with standing/Valsalva maneuver and regresses when supine).
- Widening of the femoral ring can lead to a femoral hernia. Femoral hernias occur most commonly in older women; this diagnosis is uncommon in men compared to varicocele



➔ Circumcision is the treatment of choice for phimosis, paraphimosis and Zoon's balanitis. It is also associated with a lower risk of squamous cell carcinoma of the penis

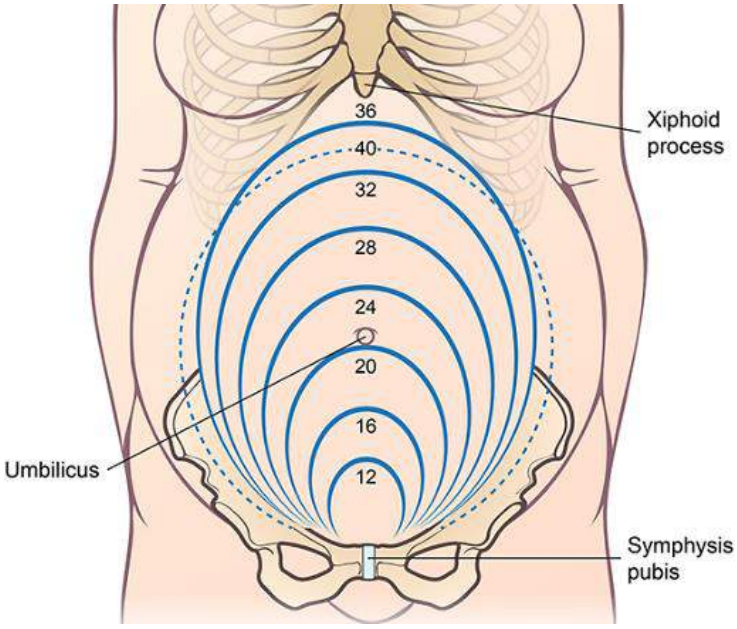
Contents

ULTRASOUND ASSESSMENT OF GESTATIONAL AGE

Ultrasound assessment of gestational age		
Ultrasound parameter	**Gestational age (weeks)**	**Accuracy (days)**
Gestational sac diameter	4.5–6	+/- 5–7
Crown-rump length	7–10	+/- 3
	11–14	+/- 5
Biparietal diameter, head circumference, femur length	14–20	+/- 7
	21–30	+/- 14
	>30	+/- 21–28

Most accurate method of determining gestational age—**estimated gestational age (EGA)** based on 1st trimester USG should not be changed as it is most accurate—becomes less accurate as pregnancy progresses

- If USG during 2nd and 3rd trimester shows discrepancy between EGA (calculated from 1st trimester crown rump length) and fetal measurements, growth problems should be considered (e.g. fetal macrosomia, fetal growth restriction)
- After 20 wks, **fundal height** can be measured in centimeters but vary by +/-3wks in accuracy and can be confounded by leiomyomata and obesity



- **LMP:** in pts with reliable LMP and normal menses, estimated date of delivery and gestational age are based on LMP. LMP assumes cycle of 28 days and fertilization on day 14. If EGA varies > 7 days in 1st trimester and >10 days in 2nd trimester, then USG EGA is used rather than LMP.

NORMAL PHYSIOLOGIC CHANGES IN PREGNANCY

Normal physiological changes during pregnancy		
System	**Clinical finding**	**Mechanism**
Renal/Urinary	↑ Glomerular filtration rate & renal size, ↓ blood urea nitrogen & serum creatinine	↑ Cardiac output & renal blood flow due to progesterone, with ↑ renal excretion
	Urinary frequency, nocturia	↑ Urine output & sodium excretion
	Mild hyponatremia	Hormones reset threshold to ↑ ADH release from pituitary
Heme	Dilutional anemia	↑ Plasma volume & red blood cell mass
	Prothrombotic state	Hormone-mediated ↓ in total protein S antigen & activity; ↑ in fibrinogen & coagulation factors
Cardiovascular	↑ Cardiac output & heart rate	↑ Blood volume, ↓ systemic vascular resistance
Pulmonary	Chronic respiratory alkalosis with metabolic compensation, ↑ PaO_2 & ↓ $PaCO_2$	Progesterone directly stimulates central respiratory centers to ↑ tidal volume & minute ventilation

And ↑ resistance to activated protein C

RENAL AND URINARY CHANGES IN NORMAL PREGNANCY

Renal & urinary changes in normal pregnancy	
Physiologic changes	• ↑ Renal blood flow • ↑ Glomerular filtration rate • ↑ Renal basement membrane permeability
Laboratory findings	• ↓ Serum BUN • ↓ Serum creatinine • ↑ Renal protein excretion

BUN = blood urea nitrogen.

- Renal function gradually ↑es in 1st trimester, reached 40-50% above non-pregnant state by midpregnancy, then remains unchanged till term
- Due to ↑ in renal function during pregnancy, pts on meds that are renally excreted (e.g. gabapentin), require close monitoring and dose adjustments as needed
- Serum creatinine of 1.2 mg/dL may be upper limit in prepregnancy, may be considered renal insufficiency in pregnancy
- Protein excretion of >300—abnormal (>150 abnormal in prepregnancy)—urine dipstick showing trace and 1+ is normal in pregnancy

HEME

- Anemia in pregnancy defined as: Hb <11 g/dl in 1st and 3rd trimester and <10.5 g/dl in 2nd trimester
- Platelet count: usually normal, but often have mildly ↓ (>70,000/mm3)—known as gestational thrombocytopenia

PULMONARY

- Progesterone ↑es significantly during 1st trimester→changes homeostatic set points in medullary resp. centers and also directly stimulates resp. centers→ ↑ ventilation
- Medulla becomes more sensitive to changes in PaCO2→ exaggerated resp. effort
- ↑ minute ventilation→ ↑ PaO2 (100-110 mmHg) to meet metabolic demands of pregnancy—PaCO2 lowers to 27-32 mmHg
- Progesterone ↑es during later stages of pregnancy→↑ pH to 7.40-7.45 with some metabolic compensation with ↓ed serum HCO3

PREGNANCY AND EXERCISE

Pregnancy & exercise	
Absolute contraindications	• Amniotic fluid leak • Cervical incompetence • Multiple gestation • Placenta abruption or previa • Premature labor • Preeclampsia/gestational hypertension • Severe heart or lung disease
Unsafe activities	• Contact sports (eg, basketball, ice hockey, soccer) • High fall risk (eg, downhill skiing, gymnastics, horseback riding) • Scuba diving • Hot yoga

- Encourage exercise in normal, uncomplicated pregnancies to prevent excessive weight gain and improve overall fitness and well-being.
- The American College of Obstetricians and Gynecologists recommends that healthy pregnant women with no contraindications participate in **low-moderate-intensity exercise for >/= 30 minutes, 5-7 days per week**.
- **Perceived exercise intensity is a better gauge** of exertion than heart rate, and patients should be able to **engage in normal conversation during the activity**. Pregnant women should also be advised about **physiologic ligamental laxity** and changes in center-of-balance that can increase propensity for joint injuries and falls.
- Jogging can be done at a **conversational pace**
- Swimming and walking are excellent, low-impact activities for pregnant women

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum	
Risk factors	• Hyperemesis gravidarum in a prior pregnancy • Multifetal gestation • Gestational trophoblastic disease
Clinical features	• Severe, persistent vomiting • Fluid & electrolyte abnormalities, ketonuria • >5% loss of pre-pregnancy weight
Workup	• Orthostatic vital signs • Serum electrolytes, blood urea nitrogen, creatinine • Thyroid function testing • Urinalysis
Treatment	• Dietary modification • Hydration • Ginger • Pyridoxine +/- doxylamine

This is also definition of HG

- It is a severe form of pregnancy induced N/V that complicates approx. 1% pregnancies
- These pts have higher β-hCG levels 2* to ↑ placental mass, esp. at 10-12 wks (when β-hCG levels are higher for all pregnant women)

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

MOLAR PREGNANCY

Molar pregnancy	
Clinical presentation	• Abnormal bleeding +/- passing of hydropic tissue • Uterine enlargement > gestational age • Theca lutein ovarian cysts • Hyperemesis gravidarum • Abnormally high β-hCG levels for gestational age • Hyperthyroidism
Diagnosis	• Ultrasound • Serum β-hCG
Management	• Dilation & suction curettage • Histopathologic confirmation of mole • Serial serum β-hCG levels post evacuation • Contraception

To detect post-molar metastatic gestational trophoblastic dis.

- Complete moles are usually symptomatic due to markedly ↑ β-hCG. Partial moles are less symptomatic due to lower β-hCG
- **Complete mole:** 2 sperms fertilize ovum lacking genetic material
- **Partial mole**: 2 sperms fertilize haploid ovum → triploid karyotype (e.g. 69 XXX, 69 XXY, 69 XYY)
- Benign but may persist despite treatment and become gestational trophoblastic neoplasia
- Theca lutein ovarian cysts resolve spontaneously after treatment of molar pregnancy

MALIGNANT GESTATIONAL TROPHOBLASTIC DISEASE

- Can occur after normal, molar pregnancy or abortion
- All forms present with irregular vaginal bleeding, enlarged uterus and pelvic pain
- Irregular vaginal bleeding 8 wks postpartum is abnormal → suspect GTD
- Malignant GTD can be:
  1. **Invasive gestational trophoblastic neoplasia—** locally invasive
  2. **Choriocarcinoma—**highly metastatic—most commonly to lungs (chest pain, dyspnea, hemoptysis, CXR shows multiple b/l infiltrates of various shapes)
- **Confirmation of diagnosis:** quantitative β-hCG

PRENATAL INFECTIONS

- Assessing maternal health, infections, and exposures is an important part of the **first prenatal visit.**
- A standard set of screening laboratory studies is recommended for every pregnant pt.
- At the first prenatal visit, patients are routinely tested for blood type (A, B, AB, 0), Rh (D) status (positive or negative), and the presence of any red blood cell antibodies (**antibody screen**). Antibody screen is particularly imp in Rh(D) -ve multiparous women
- Identifying STI is particularly imp—most maternal fetal transmissions are preventable with proper treatment
- All pregnant pts should receive screening for:
  - HIV—perform screening at 1st prenatal visit. Repeat screening in 3rd trimester only in high-risk pts

- HBV—HCV screening not recommended unless hx of IVDU, HIV or unexplained liver disease
- Chlamydia trachomatis and Neisseria gonorrhea with nucleic acid amplification test (all high risk sexually active women i.e. </=24 yrs, new or multiple partners, h/o STDs should be screened for gonorrhea→ Rx ↓ risk of PROM, preterm labor, chorioamnionitis)
- Asymptomatic bacteriuria— treatment and screening in 1st trimester as 40% risk of progressing to pyelonephritis

TESTS FOR PREGNANT PATIENTS

Tests for pregnant patients	
All patients	**Specific at-risk patients**
• Cervical cytology (as it fits with patient's routine screening) • Rhesus type & antibody screen • Hematocrit, hemoglobin & mean corpuscular volume • Rubella immunity • Varicella immunity • Urine culture • Syphilis testing • Hepatitis B antigen • Chlamydia testing • HIV test • Influenza vaccine during flu season • Offer genetic screening for cystic fibrosis • Offer Down syndrome testing	• Thyroid function **only** if symptomatic, personal or family history of dysfunction, or associated condition (eg, diabetes) • Tuberculosis for at-risk patients • Toxoplasmosis serology for at-risk patients • Hemoglobin electrophoresis for patients with high-risk ethnic background or mean corpuscular volume <80 fL unrelated to iron deficiency • Lead levels for those at risk based on history

- CDC recommends all pregnant women without CI should receive influenza vaccine during flu season and can be given in any trimester

VACCINES IN WOMEN OF CHILDBEARING POTENTIAL

Vaccines in women of childbearing potential	
Routine vaccines during pregnancy	• Tdap • Inactivated influenza vaccine
Vaccines for special circumstances	• Hepatitis B (if high risk or started series) • Hepatitis A (if high risk) • Pneumococcus during 2nd & 3rd trimesters (if high risk) • *Haemophilus influenzae* (asplenic patients) • Meningococcus (if high risk or age 19-21 living in a college dorm & not vaccinated before age 16) • Anti-D immune globulin (Rh[D]-negative women)
Not recommended during pregnancy	• HPV (halt series if patient found to be pregnant during series & continue after delivery) • MMR (avoid conception for 4 weeks after vaccination) • Varicella (avoid conception for 4 weeks after vaccination) • Smallpox • Live attenuated intranasal influenza vaccine (avoid conception for 4 weeks after vaccination)

HPV = human papillomavirus; **MMR** = measles-mumps-rubella; **Tdap** = tetanus toxoid-reduced diphtheria toxoid-acellular pertussis.

SYPHILIS

Syphilis in pregnancy	
Screening	• **Universal** at **first prenatal visit** • Third trimester & delivery (if high risk)
Serologic tests	• **Nontreponemal** (RPR, VDRL) • **Treponemal** (FTA-ABS)
Treatment	• Intramuscular benzathine **penicillin** G
Pregnancy effects	• Intrauterine fetal demise • Preterm labor
Fetal effects	• Hepatic (**hepatomegaly**, **jaundice**) • Hematologic (hemolytic anemia, ↓ **platelets**) • Musculoskeletal (**abnormalities of the long bones**) • Failure to thrive

Either may be used for screening, but positive test require confirmation with a test from alternate category (as false positives are common)

Usually 1 dose weekly for 3 wks. Desensitization for penicillin allergic pts

FTA-ABS = fluorescent treponemal antibody absorption; **RPR** = rapid plasma reagin.

GROUP B STREPTOCOCCUS INFECTION (GBS)

Preventing neonatal group B *Streptococcus* infection	
Universal screening	• Rectovaginal culture at 35-37 weeks gestation

Indications
For treatment
	• Prior birth to an infant affected with early-onset GBS disease
	• GBS bacteriuria or GBS urinary tract infection anytime during current pregnancy (regardless of treatment)
	• GBS positive within 5 weeks of labor
	• Unknown GBS status PLUS 1 of the following:
	  ○ <37 weeks gestation
	  ○ Intrapartum fever
	  ○ Rupture of amniotic membranes for ≥18 hours

Prophylaxis	First-line treatment = penicillin IV

GBS = group B *Streptococcus*.

i.e. 3-5 wks prior to estimated delivery date. Culture of rectum and vagina—most sensitive screening method of choice

These are exceptions for screening—no need to culture—just treat

If GBS is known to be negative, then no need of antibiotic in PROM

- Prophylaxis should be given 4 hours prior to delivery
- If pt is GBS +ve or unknown, and has to undergo C-sec, prophylaxis is given only if there is rupture of membranes
- Alternatives to penicillin: ampicillin, cefazolin, clindamycin or vancomycin

RUBELLA

- Immunity is evaluated as part of prenatal panel—give MMR postpartum in non-immune women
- Routine vaccination has led to eradication in US
- MMR is given in childhood and to people travelling to US from developing countries
- Women should avoid live vaccines like MMR immediately before and during pregnancy—though not associated with significant fetal harm
- Initially women were advised to avoid conception for 3 mo but now time has been reduced to **28 days**
- Also women who inadvertently receive vaccination during or shortly before pregnancy can be reassured that there is little risk to the fetus and they can proceed with **routine prenatal care** – no need to advise abortion
- **Unvaccinated pregnant women with confirmed rubella exposure**—offer termination of pregnancy→ if pt do not wish termination→ treat with IV immune globulin—benefits unknown
- **Serologic testing for rubella**—standard component of early prenatal care but if vaccination is document, then no need to perform this as it is a proof of immunity

PRENATAL TESTING FOR FETAL ANEUPLOIDY

Prenatal testing for fetal aneuploidy			
Test	**Timing (weeks)**	**Advantages**	**Disadvantages**
First-trimester combined test*	9-13	Noninvasive	Not diagnostic
Second-trimester quadruple screen**	15-20	Noninvasive	Not diagnostic
Chorionic villus sampling	10-13	Definitive karyotypic diagnosis	Pain, vaginal spotting, risk of pregnancy loss
Amniocentesis	15-20	Definitive karyotypic diagnosis	Pain; risk of bleeding & amniotic fluid leak; risk of injury to fetus, placenta, maternal bowel & bladder
Second-trimester ultrasound	18-20	Noninvasive, measures fetal growth, evaluates fetal anatomy, confirms placenta position	Cannot identify all abnormalities; soft markers are ultrasound findings of uncertain significance
Cell-free fetal DNA	≥10	Noninvasive, high sensitivity & specificity for aneuploidy	Not diagnostic

* Pregnancy-associated plasma protein, β-hCG, nuchal translucency.

** Maternal serum α-fetoprotein, estriol, β-hCG, inhibin A.

SECOND TRIMESTER QUADRUPLE SCREENING

Second-trimester quadruple screening				
Diagnosis	**MSAFP**	**β-hCG**	**Estriol**	**Inhibin A**
Trisomy 18	↓	↓	↓	Normal
Trisomy 21	↓	↑	↓	↑
Neural tube or abdominal wall defect	↑	Normal	Normal	Normal

MSAFP = maternal serum α-fetoprotein.

- Pts with abnormal quadruple screen can be tested with cffDNA. USG should be performed to look for fetal anomalies and then confirmed with amniocentesis (USG must be done before amniocentesis to guide needle insertion)

CELL-FREE FETAL DNA

Cell-free fetal DNA testing	
Indications	• Maternal age ≥35 • Abnormal maternal serum screening test • Sonographic findings associated with fetal aneuploidy • Previous pregnancy with fetal aneuploidy • Parental-balanced Robertsonian translocation
Applications	• Screening for trisomy 21, 18, 13 & sex-chromosome aneuploidies • Fetal sex determination

- ~99% sensitivity and specificity for detecting trisomy 21
- >92% sensitivity for trisomy 18
- >80% sensitivity for trisomy 13
- **Normal test:** generally reassuring and ↓ rate of invasive tests
- **Abnormal test:** confirmed by chorionic villus sampling in 1st trimester and amniocentesis in 2nd trimester
- **Pts who do not meet high-risk criteria for cffDNA:** can undergo 1st trimester combined test or 2nd trimester quadruple screen

SECOND TRIMESTER SCREENING

- All pregnant women should have OGTT at 24-28 wks—high risk pts (e.g. marked obesity, FH od DM) may receive earlier

MATERNAL SERUM α-FETOPROTEIN SCREENING

- Major protein produced by fetal yolk sac, liver and GI tract
- MSAFP is measured at 15-20 wks gestation (optimally at 16-18 wks) to screen for fetal anomalies

Maternal serum α-fetoprotein screening	
↑ MSAFP	↓ MSAFP
• Open neural tube defects (eg, anencephaly, open spina bifida) • Ventral wall defects (eg, omphalocele, gastroschisis) • Multiple gestation	• Aneuploidies (eg, trisomy 18 & 21)

- Less commonly ↑ is seen in fetal congenital nephrosis and benign obstructive uropathy
- ↑ MSAFP→ careful USG evaluation—confirm no. of gestations and accurate gestational age as interpretation depends on accurate gestational age

CARDIAC ANOMALIES

- Most fetal congenital cardiac anomalies can be detected by second trimester screening USG

CHORIOAMNIONITIS/INTRAAMNIOTIC INFECTION

Chorioamnionitis (intra-amniotic infection)	
Risk factors	• Prolonged rupture of membranes • Prolonged labor • Internal fetal or uterine monitoring devices • Presence of genital tract pathogens • Nulliparity

Diagnosis	Maternal fever ≥38 C (100.4 F) **PLUS** ≥1 of the following:
	• Maternal
	  ◦ Tachycardia ≥100/min
	  ◦ Uterine tenderness
	  ◦ Malodorous/purulent amniotic fluid or vaginal discharge
	  ◦ White blood cells ≥15,000/μL
	• Fetal tachycardia ≥160/min

Treatment	• Broad-spectrum antibiotics • Delivery
Complications	• Maternal: Uterine atony, postpartum hemorrhage, endometritis • Neonatal: Premature birth, infection, encephalopathy, cerebral palsy, death

i.e. **>18 hours** between time of rupture and birth

IV broad spectrum antibiotics e.g. ampicillin, gentamicin, clindamycin should be used. Give **oxytocin to accelerate labor**. C-sec is reserved for standard obstetrics indications. **Antipyretics—**to ↓ maternal fever which in turn improve fetal tachycardia

- Can also occur in pts with intact membranes
- Usually **polymicrobial (**vaginal or enteric flora) and ascend from vagina, move up the cervical canal in to the uterus and spread through amniotic fluid, amniotic membranes, placenta and uterine decidua
- Amniotic fluid does not need to be purulent or malodorous to make diagnosis
- Tocolysis is contraindicated in this condition regardless of fetal age

ANTEPARTUM FETAL SURVEILLANCE

Antepartum fetal surveillance			
Test	**Description**	**Normal result**	**Abnormal result**
Nonstress test	External fetal heart rate monitoring for 20-40 minutes	Reactive: ≥2 accelerations >2 in 20 min of at least 15 beats/min amplitude and lasting >/=15 sec each	• Nonreactive: <2 accelerations • Recurrent variable or late decelerations
Biophysical profile	Nonstress test plus ultrasound assessment of the following: • Amniotic fluid volume • Fetal breathing movement • Fetal movement • Fetal tone 2 points per category if normal & 0 points if abnormal (maximum 10/10)	8 or 10 points	• Equivocal: 6 points • Abnormal: 0, 2, or 4 points • Oligohydramnios
Contraction stress test	External fetal heart rate monitoring during spontaneous or induced (eg, oxytocin, nipple stimulation) uterine contractions	No late or recurrent variable decelerations	Late decelerations with >50% of contractions
Doppler sonography of the umbilical artery	Evaluation of umbilical artery flow in fetal intrauterine growth restriction only	High-velocity diastolic flow in umbilical artery	Decreased, absent, or reversed end-diastolic flow

- Antepartum fetal surveillance is performed in pregnancies with high risk fetal demise due to:
  - Maternal factors: HTN, DM
  - Fetal factors: post term pregnancy, IUGR
- Most common surveillance modality: BPP. Pts with gestational HTN need weekly BPP starting at 32 wks
- ↓ **fetal movements:** subjective and non-specific symptom that may be benign (e.g. normal fetal sleep cycle) or ominous (e.g. CNS hypoxia)→ needs assessment with above tests starting from non-stress test

NON-STRESS TEST

Nonstress test	
Reactive	• Baseline of 110-160/min • Moderate variability (6-25/min) • ≥2 accelerations in 20 minutes, each peaking ≥15/min above baseline & lasting ≥15 seconds
Nonreactive	• Does not meet criteria for reactivity

- To assess fetal status and identify fetuses at risk of adverse outcomes. Usually performed in high-risk pregnancies with maternal or fetal comorbidities (e.g. Grave's disease, fetal growth restriction) starting at 32-34 wks gestation or when there is a loss of perception of fetal movement in any pregnancy
- During an NST, heart rate of a well-oxygenated fetus ↑es with fetal movement (accelerations) (HR is measured while monitoring for spontaneous movement)
- **Reactive NST:**
  - **High negative predictive value** to rule out fetal acidemia
  - Fetal heart rate accelerations are the product of the fetal sympathetic nervous system, which matures at **26-28 weeks—extremely premature do not demonstrate accelerations**
- **Non-reactive NST:**
  - Most common cause of non-reactive test is **fetal sleep cycle** (fetal sleep can last for 40 min. typical NST is performed for 20 min, but in cases of non-reactive, perform for 40-120 min to ensure fetal activity is captured outside sleep); vibroacoustic stimulation is used to awaken the fetus and allow timely test
  - Fetal hypoxia due to placental insufficiency and fetal cardiac or neurologic abnormalities
  - High false positive rate and low positive predictive value—cannot rule in fetal acidemia
  - Need further evaluation with **biophysical profile (BPP) or contraction stress test (CST):**
    - Both are equivalent in assessing fetal status and are selected based on available resources and relevant contraindications
    - BPP performed if labor is contraindicated
    - Perform C-sec in pt with placenta previa with these tests abnormal

BIOPHYSICAL PROFILE

Biophysical profile*	
Component	**Normal finding**
1. Nonstress test	Reactive fetal heart rate monitoring
2. Amniotic fluid volume	Single fluid pocket ≥2 x 1 cm or amniotic fluid index >5
3. Fetal movements	≥3 general body movements
4. Fetal tone	≥1 episodes of flexion/extension of fetal limbs or spine
5. Fetal breathing movements	≥1 breathing episode for ≥30 seconds

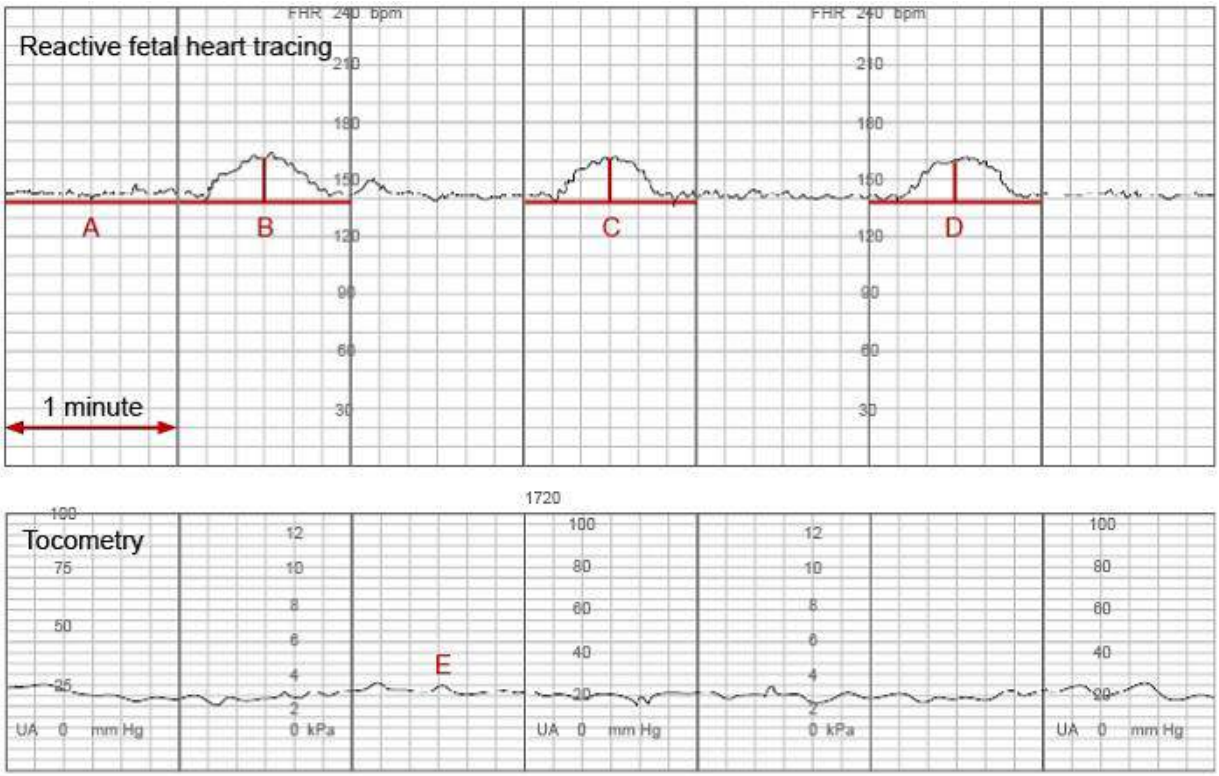
Maximum score = 10; 0 = abnormal; 2 = normal for each component

*Performed continuous observation for ≥30 minutes

- **BPP** is performed to assess fetal oxygenation
- **Score 0-4** indicate **fetal hypoxia** due to **placental dysfunction (**placental insufficiency)→ prompt delivery due to high likelihood of fetal demise
- **Score 6/10**→ equivocal and should be repeated in 24hours
- **Risk factors for placental insufficiency:** advanced maternal age, **tobacco use, HTN** and **DM**
- **BPP is normal in:** fetal malpresentation (causes fetal growth restriction or chronic fetal hypoxia but not abnormal BPP), anterior placental location

CONTRACTION STRESS TEST

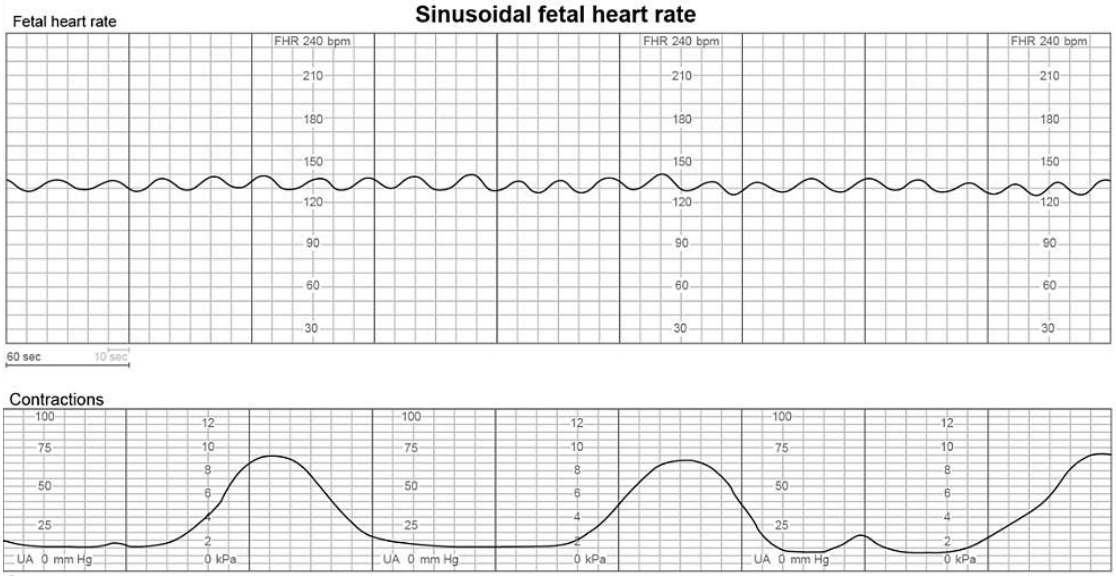
- Oxytocin infusion or nipple stimulation sufficient to cause 3 contractions every 10 min and the effect these contractions have on HR is noted.
- If late decelerations occur at each contraction→ test is positive and delivery usually indicated
- **Contraindications:** same as contraindications to labor (e.g. placenta previa, prior myomectomy)

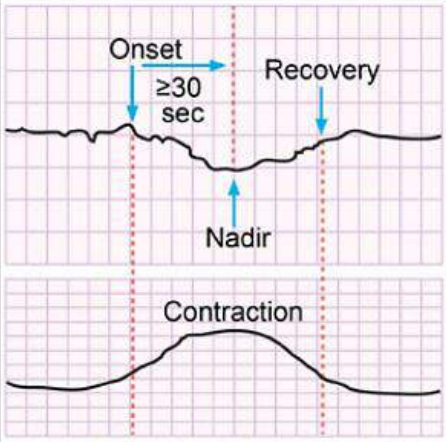
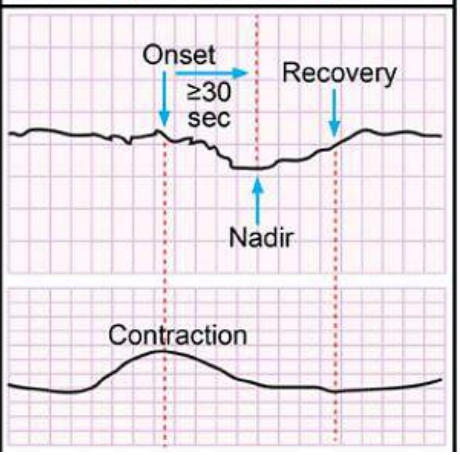
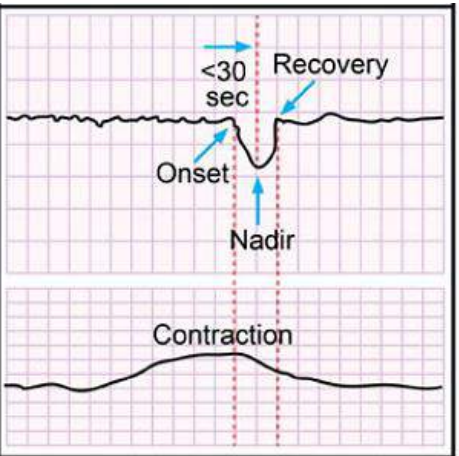


A: Baseline 140 beats per minute (bpm) (normal 110-160 bpm) with moderate variability (average amplitude 6-25 bpm)
B, C, D: Positive accelerations (peaks ≥15 bpm above baseline for ≥ 15 seconds)
E: No uterine contractions

INTRAPARTUM FETAL HEART RATE MONITORING

- Normal baseline heart rate: 110-160 beats/minute with moderate variability (average amplitude 6-25/min)—maintained by fetal brain's autonomic control to heart
- **Tachycardia**: FHR > 160 beats/min. Common causes: chorioamnionitis, maternal fever, maternal hyperthyroidism, medication use (e.g. terbutaline), abruptio placenta
- **Fetal anemia** causes sinusoidal FHR tracing—smooth, undulating waveform with no variability



Intrapartum fetal heart rate monitoring		
Early	**Relationship to contraction** • Symmetric to contraction • Nadir of deceleration corresponds to peak of contraction • Gradual (≥30 sec from onset to nadir) **Etiology** • Fetal head compression • Can be normal fetal tracing	
Late	**Relationship to contraction** • Delayed compared to contraction • Nadir of deceleration occurs after peak of contraction • Gradual (≥30 sec from onset to nadir) **Etiology** • Uteroplacental insufficiency	
Variable	**Relationship to contraction** • Can be but not necessarily associated with contractions • Abrupt (<30 sec from onset to nadir) • Decrease ≥15/min; duration ≥15 sec but <2 min **Etiology** • Cord compression • Oligohydramnios • Cord prolapse	

EARLY DECELERATIONS

- Fetal head compression→ stimulates vagus nerve→ ↓es fetal heart rate
- Occurs when anterior fontanel is in close contact with cervix (cervix >/=5cm dilated and station 0)
- No treatment needed if normal baseline rate, moderate variability, no late or variable decelerations present as does not indicate fetal hypoxemia

LATE DECELERATIONS

- E.g. placental calcification→ uteroplacental insufficiency → contraction→ transient fetal hypoxemia → late deceleration (it is fetal reflex to transient hypoxemia)

VARIABLE DECELERATIONS

- Abrupt fetal heart rate (FHR) ↓ to a nadir followed by rapid return to baseline
- Duration and depth of each deceleration can be quite variable

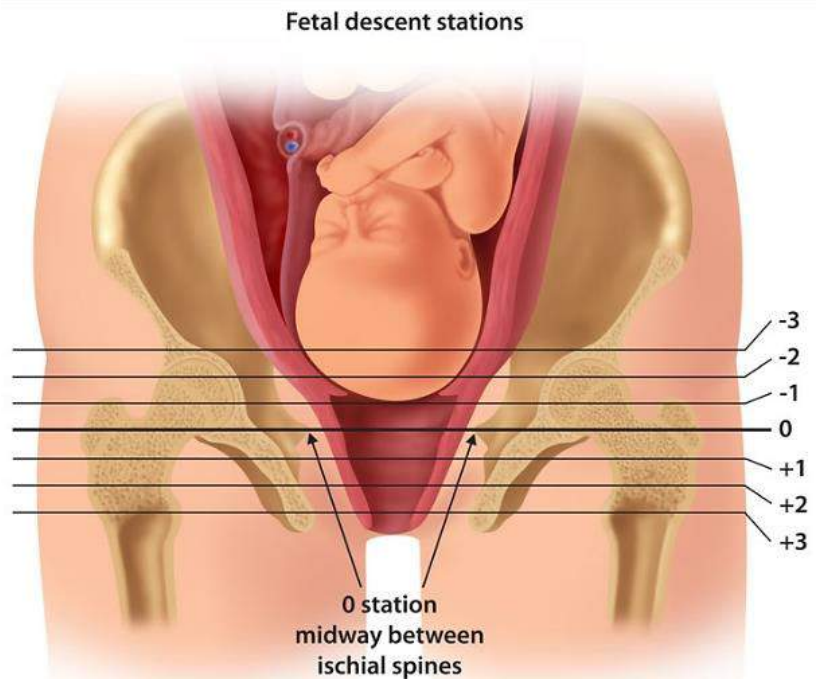
Cord compression:

- Amniotomy (artificial rupture of membranes) → release of amniotic fluid → mechanical compression and occlusion of umbilical artery, particularly during contractions→ ↑ in fetal systemic vascular resistance and BP→ fetal baroreceptor activation→ ↓ fetal pulse→ ↓ BP
- Cord compression can impede fetal blood flow
- **Intermittent variable decelerations** (associated with <50% of contractions)— well tolerated by the fetus— do not typically cause fetal hypoxia→ require **close observation without intervention**
- **Recurrent variable decelerations** occur with >50% of contractions— **require treatment**, as fetal acidosis can develop with increasing frequency and severity of decelerations.
  - **Maternal repositioning** (e.g. left lateral position)—1st line—may ↓ cord compression and improve blood flow to placenta
  - **Amnioinfusion—**2nd line if above fails—as cord compression may result from amniotomy and loss of amniotic fluid, hence, instillation of saline into amniotic sac may ↓ cord compression and variable decelerations
  - Instrumental vaginal delivery (eg, forceps, vacuum) would be indicated to expedite delivery if the patient is fully (10 cm) dilated
  - DO NOT use oxytocin as it can ↑ contraction strength and frequency and worsen variable decelerations

Nuchal cord

- Cord around neck
- Associated with recurrent variable decelerations (abrupt decreases in FHR below the baseline of varying depth and duration) but not adverse fetal outcomes. It is a common finding on ultrasound and at delivery

FETAL DESCENT STATIONS



ANTEPARTUM BLEEDING

Differential diagnosis of antepartum bleeding	
Etiology	**Common clinical features**
Normal labor	Intermittent pain with contractions, small amount of blood-tinged mucus ("bloody show")
Placental abruption	Sudden-onset vaginal bleeding, abdominal pain, hypertonic/tender uterus, tachysystole (frequent uterine contractions)
Placenta previa	Painless vaginal bleeding, ultrasound with placenta covering cervical os
Uterine rupture	Sudden-onset vaginal bleeding, constant abdominal pain, cessation of uterine contractions, loss of fetal station, fetal deterioration
Vasa previa	Painless vaginal bleeding that occurs with rupture of membranes, fetal deterioration (sinusoidal tracing or bradycardia)

>/=5 contractions in 10 minutes

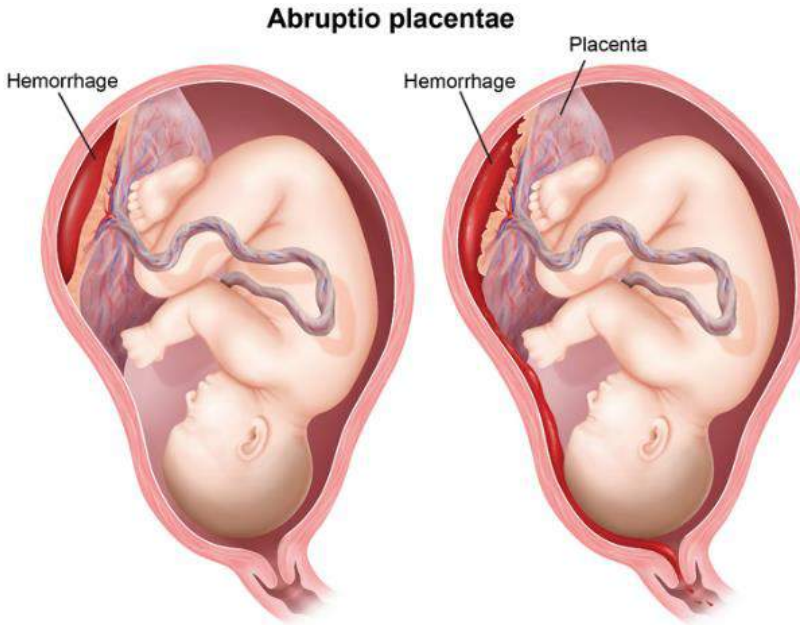
- **Evaluation of antepartum bleeding:**
  1. Speculum exam to confirm and quantify bleeding and to inspect for lesions, lacerations, and cervical dilation

2. Transvaginal USG—best imaging modality to evaluate placentation

ABRUPTIO PLACENTAE

Placental abruption	
Risk factors	• Maternal hypertension or preeclampsia/eclampsia • Abdominal trauma • Prior placental abruption • Cocaine & tobacco use
Clinical presentation	• Sudden-onset vaginal bleeding (80%) • Abdominal or back pain • High-frequency, low-intensity contractions • Hypertonic, tender uterus
Diagnosis	• Primarily by clinical presentation • Ultrasound (not required for diagnosis) to rule out placenta previa; may show retroplacental hematoma

- **Premature detachment of placenta** from uterus as a result of rupture of maternal decidual vessels
- Bleeding at decidual-placental interface will **sometimes be self-limited and clinically insignificant**
- **More severe cases**: bleeding persist and dissect the placenta off the decidua→ progress→ **uterus becomes distended and tender and bleeding becomes apparent** → significant bleeding → can cause **hypovolemic shock and DIC** (— due to tissue factor released by decidual bleeding— larger the area of detachment, larger the risk of complications). Pts can appear stable until about 20% blood is lost due to physiologic hypervolemia in pregnancy
- Blood may have uterotonic effect→ unusually frequent but regular contractions
- Very large separation→ fetal hypoxia and preterm delivery→ FHR abnormalities (e.g. loss of variability) and fetal demise
- **Management of hemorrhagic shock:**
  1. **1st step:** aggressive fluid resuscitation with crystalloids
  2. **Place pt in left lateral decubitus position (**if pt is stable) to displace uterus off aortocaval vessels and maximize cardiac output
  3. **Blood transfusion** – for persistent bleeding and/or hypotension unresponsive to fluid resuscitation—CBC should be repeated after administration of IV fluids to determine if transfusion of crossmatched blood is appropriate

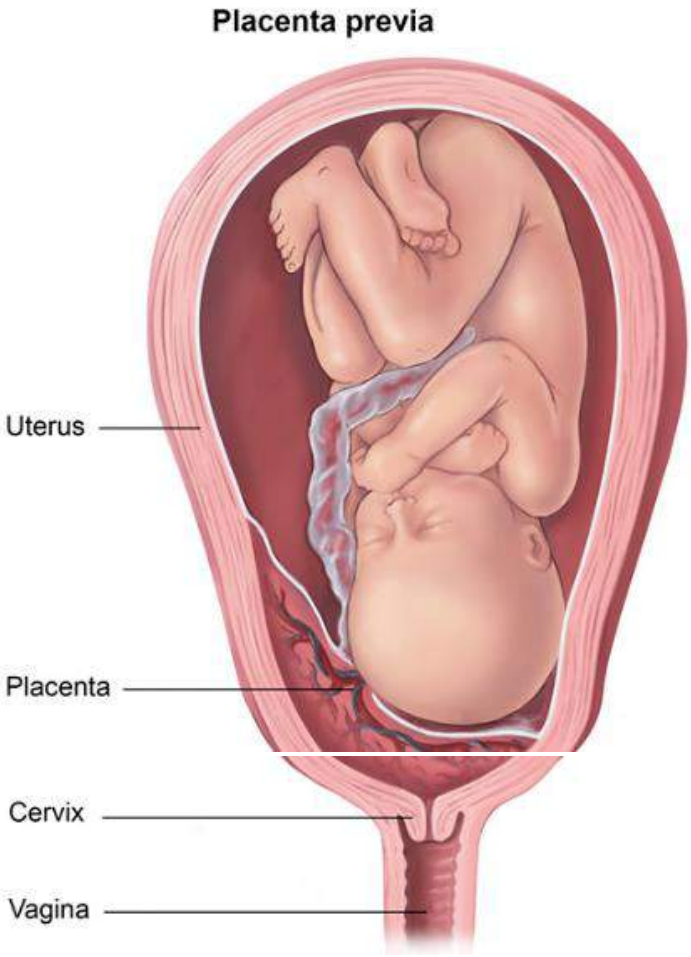


Concealed bleeding **Visible bleeding**

PLACENTA PREVIA

Placenta previa	
Risk factors	• Prior placenta previa • Prior cesarean section or other uterine surgery • Multiparity • Advanced maternal age • Smoking
Clinical features	• Painless third-trimester bleeding
Diagnosis/ management	• Transabdominal followed by transvaginal sonography • **NO** intercourse or digital vaginal examination

- Usually diagnosed during prenatal USG at 18-20 wks—occurs when placenta implants over internal cervical os. Should a follow-up USG show resolution of placenta previa, plan can be modified accordingly and pelvic rest restriction can be lifted
- Fetal heart tracing usually unaffected as bleeding is maternal in origin
- **Management:**
  - Speculum exam and transvaginal USG—both do not penetrate cervix and are safe
  - **Requires C. section** at 36-37 wks (late preterm/ early term) due to risk of hemorrhage from placenta and implantation site during labor and because cervical changes and uterine contraction can cause partial placental detachment
- **Contraindications due to risk of antepartum hemorrhage:**
  - Vaginal delivery contraindicated (placenta > 2cm from internal cervical os is not CI for vaginal delivery)

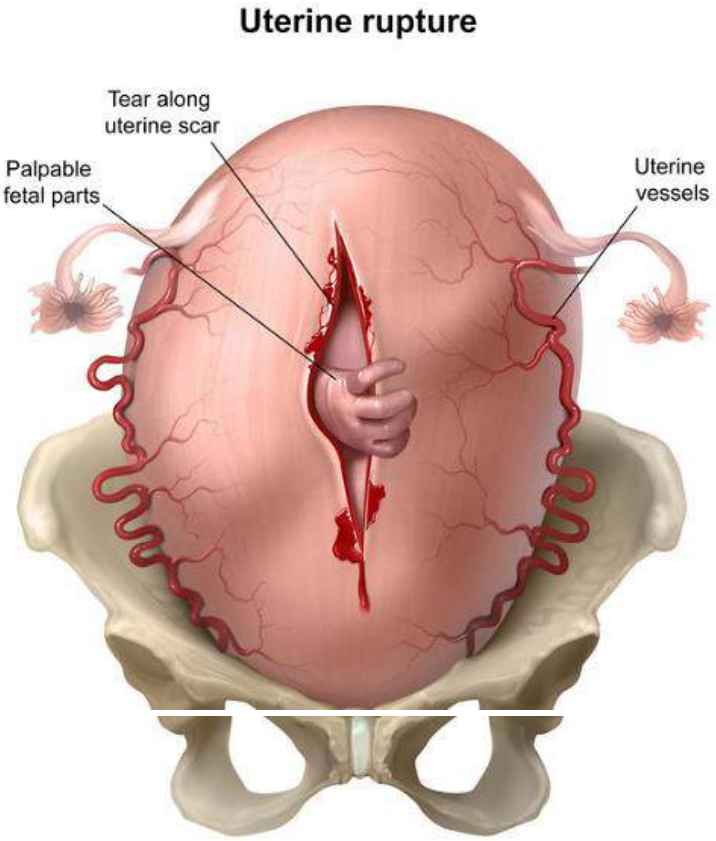


UTERINE RUPTURE

Uterine rupture	
Risk factors	• Prior uterine surgery (eg, cesarean delivery, myomectomy) • Induction of labor/prolonged labor • Congenital uterine anomalies • Fetal macrosomia
Clinical presentation	• Vaginal bleeding • Intra-abdominal bleeding (hypotension, tachycardia) • Fetal heart decelerations (fetal distress) • Loss of fetal station • Palpation of fetal parts on abdominal examination • Loss of intrauterine pressure

- **C/F**: often presents with focal, **intense abdominal pain** prior to rupture that is relieved by rupture but resumes shortly after in a diffuse distribution
  - Hyperventilation, agitation and tachycardia—signs of imminent rupture
  - Loss of fetal station—pathognomonic
  - In pts with intrauterine catheter, loss of pressure may be observed but many have contractions despite rupture

- **Prevention of fetal and maternal exsanguination:** emergency laparotomy to confirm diagnosis and expedite delivery



UTERINE SURGICAL HISTORY AND VAGINAL BIRTH

Uterine surgical history & vaginal birth	
Surgery	**Trial of labor contraindicated?**
Low transverse cesarean delivery (horizontal incision)	No
Classical cesarean delivery (vertical incision)	Yes
Abdominal myomectomy with uterine cavity entry	Yes
Abdominal myomectomy without uterine cavity entry	No

↑ Risk of uterine rupture

Or extensive myomectomy

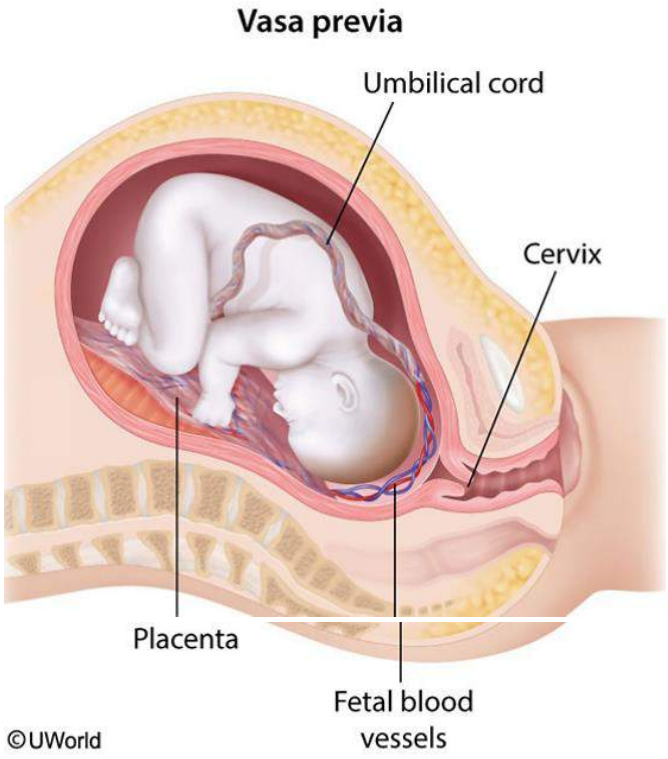
- **Pts with h/o classical cesarean delivery or extensive myomectomy or myomectomy with uterine cavity entry**

- Plan cesarean delivery 36-37 wks
- If present in labor→ perform urgent laparotomy followed by hysterotomy (for fetus delivery if unruptured) or uterine repair (if rupture occurred)

VASA PREVIA

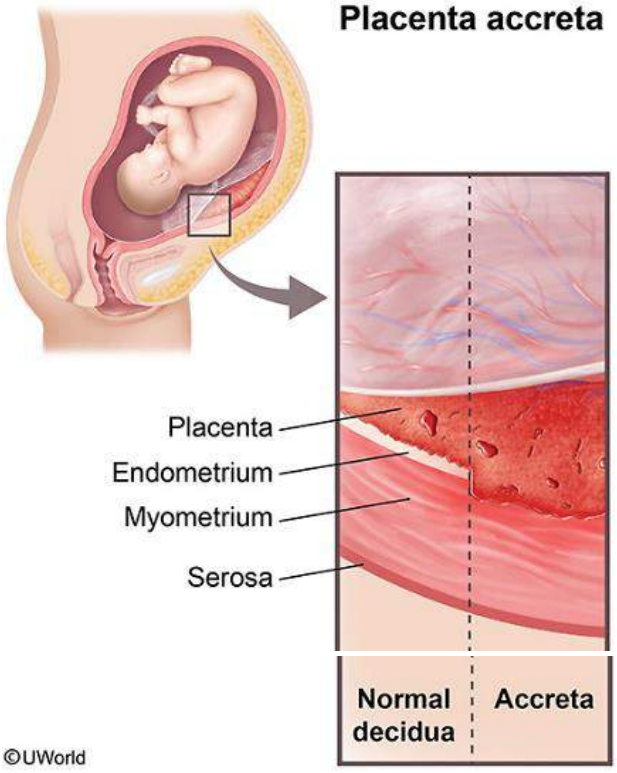
- Fetal vessels traverse internal cervical os in amniotic membrane→ vulnerable to injury during amniotomy→ painless bleeding and fetal heart rate abnormalities immediately after amniotomy
- **Risk factor:** 2nd trimester USG showing placenta previa that resolves by 3rd trimester—may involve involution of placental parenchyma covering internal os without involution of associated blood vessels
- **FHR:** typically show tachycardia, followed by bradycardia and ultimately **sinusoidal pattern**
- **Emergency C-section:** if found during labor— due to significant risk of fetal death by **exsanguination**
- **Dx:** gold standard of diagnosis: antenatal abdominal and transvaginal **Doppler USG**—dx often missed in 20% cases→ if diagnosed prenatally→ offer **cesarean delivery** prior to onset of labor

→ **Bleeding in placenta previa is maternal in origin and in vasa previa, it is fetal in origin—hence the reason for rapid deterioration of fetus**



PLACENTA ACCRETA

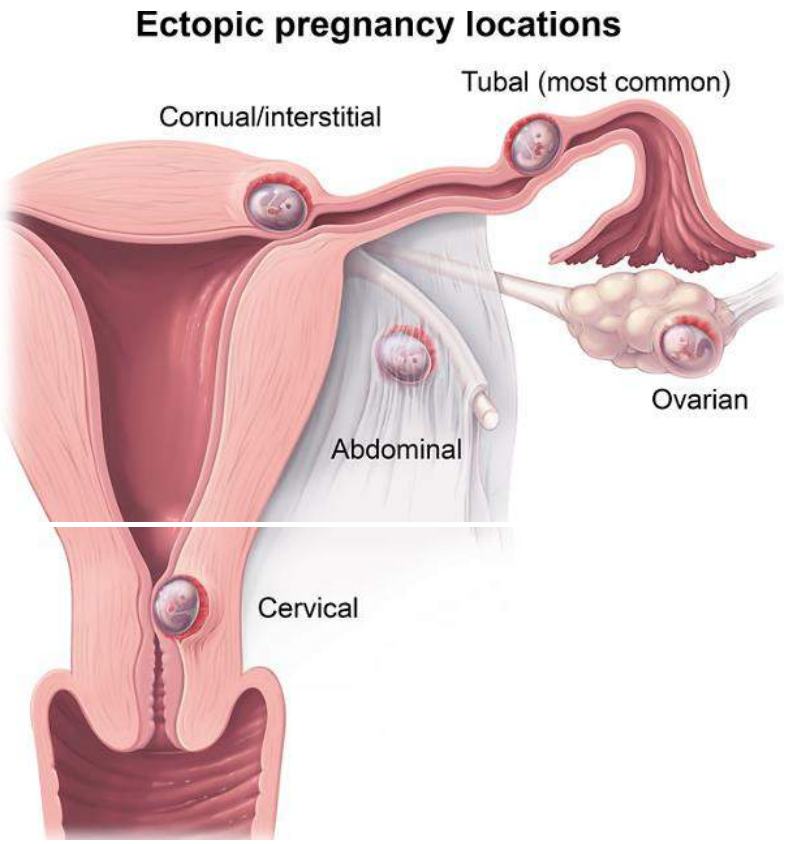
- **Risk factors:** h/o cesarean delivery, myomectomy, or h/o dilatation and curettage, maternal age >35
- **Antenatal ultrasound**: an irregular or absent myometrial-placental interface and intraplacental villous lakes—typically diagnosed antenatally
- **Antenatally diagnosed placenta accreta:** delivered by planned cesarean hysterectomy
- **Undiagnosed**: difficulty with placenta delivery→ does not detach from uterus→ cord avulsion and necessitates manual extraction→ **placental adherence** and **massive hemorrhage**



ECTOPIC PREGNANCY

Ectopic pregnancy	
Risk factors	• Previous ectopic pregnancy • Previous pelvic/tubal surgery • Pelvic inflammatory disease
Clinical features	• Abdominal pain, amenorrhea, vaginal bleeding • Hypovolemic shock in ruptured ectopic pregnancy • Cervical motion, adnexal &/or abdominal tenderness • +/- Palpable adnexal mass
Diagnosis	• Positive hCG • Transvaginal ultrasound showing adnexal mass, empty uterus
Management	• Stable: Methotrexate • Unstable: Surgery

Most ectopic pregnancies are caused by prior chlamydia and/or gonorrhea infections which damage uterine tubes—most are asymptomatic



CORNUAL/INTERSTITIAL ECTOPIC PREGNANCY

- Rare type
- Specific risk factors for corneal type: uterine anomalies (e.g. bicornuate “heart shaped” uterus) and in vitro fertilization
- Can cause life-threatening hemorrhage due to abundant blood supply from uterine and ovarian arteries

LABOR

NORMAL LABOR

Stages of labor		
Stage	**Definition**	
1	**Latent**	0-6 cm cervical dilation
	Active	6-10 cm (complete) cervical dilation
2	10 cm (complete) cervical dilation to delivery	
3	Delivery of baby to expulsion of placenta	

- Abnormal progress with stages 1 and 2 can be described as **protracted** (slower than expected progress) or **arrested** (unlikely to make progress)

ARRESTED LABOR

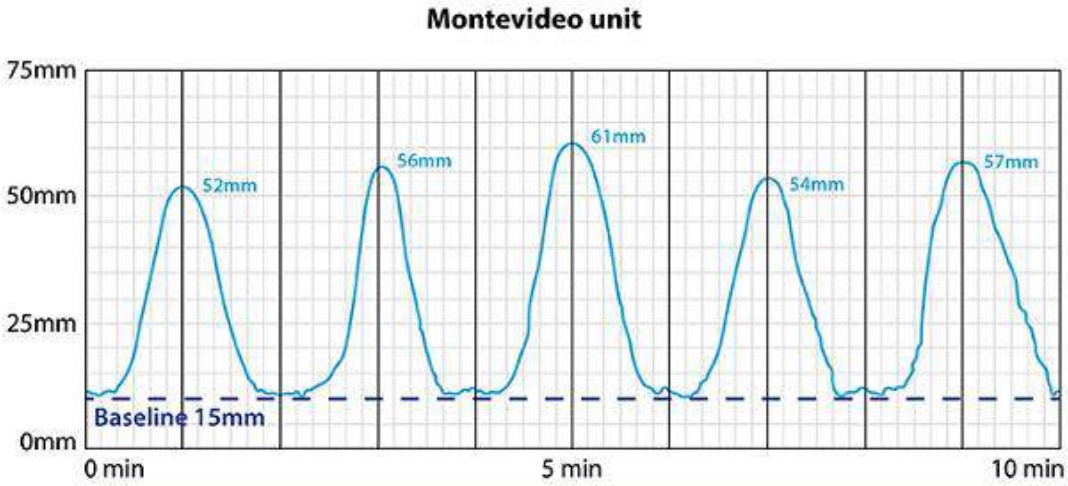
- **Arrest of labor** in the **first stage** is diagnosed when dilation is **>/=6 cm with ruptured membranes** and **1 of the following**
- No cervical change for **>/=4 hours** despite **adequate contractions**

OR

- No cervical change for **>/= 6 hours** with **inadequate contractions**
- In case of arrest of labor→ C. section should be performed

ADEQUATE CONTRACTIONS

- Contractions summing to >/=200 Montevideo units for >/=2 hours



- Montevideo unit = # of uterine contractions in 10 minutes x contraction strength
- Contraction strength = peak mmHg - baseline mmHg using internal pressure catheter
- Adequate labor = 200 Montevideo units

FALSE VS. LATENT LABOR

False labor vs. latent labor		
Contractions	**False labor**	**Latent labor**
Timing	Irregular, infrequent	Regular, increasing frequency
Strength	Weak	Increasing intensity
Pain	None to mild	Yes
Cervical change	No	Yes

- **Labor:** regular, painful uterine contractions that cause cervical dilation and effacement. Normal uterine contraction during labor: every 2-3 minutes, lasting 45-55 sec and intrauterine pressure of 50mmHg
- **False labor:** ultimately resolves with no cervical dilation. E.g. Braxton Hick's contractions → reassure and discharge with routine prenatal care
- **Preterm labor:** Important to differentiate between false preterm labor and latent preterm labor (based on table above).
- **Precipitous labor** – fetal delivery that occurs within 3 hours of the initiation of contractions. The most significant risk factor for precipitous labor is multiparity. It is spontaneous and not caused by oxytocin infusion

OXYTOCIN

Oxytocin	
Indications	• Induction or augmentation of labor • Prevention & management of postpartum hemorrhage
Adverse effects	• Hyponatremia • Hypotension • Tachysystole

- Oxytocin can enhance ADH release→ SIADH→ hyponatremia
- All uterotonic drugs used for induction of labor can cause **tachysytole (**>/=5 contractions in 10 min averaged over 30-min period). Can also cause tetanic contractions (intense or prolonged)—particularly at higher doses
  - Although many fetuses tolerate tachysystole with no adverse outcome, fetal heart rate tracing abnormalities are more common with tachysystole due to insufficient uterine relaxation between contractions, causing placental spiral artery constriction, a decrease in placental blood flow, and fetal hypoxia. Consequently, tachysystole is associated with an increased risk for cesarean delivery, low umbilical cord pH, and neonatal ICU admission.
- Rupture of the unscarred uterus can occur, particularly in patients exposed to high doses of oxytocin, but is associated with uterine anomalies, multiple gestation, and abnormal placentation

EPIDRUAL ANESTHESIA

- Important modality for pain relief in labor
- Continuous epidural analgesia involves infusion of a low concentration of a local anesthetic into the epidural space at the **L2-L5 level**, blocking nerves responsible for labor pain.
- **Side effects:**
  - **Hypotension:** 10% pts suffer from hypotension—easily treated and prevented. **MOA:** sympathetic nerves responsible for vascular tone are blocked→ vasodilation (venous pooling)→ ↓ venous return to right side of heart→↓ CO→ if persistent and untreated→ placental hypoperfusion → fetal acidosis
    - **Prevention:** aggressive IV fluid volume expansion prior to epidural placement
    - **Rx:** left uterine displacement (positioning patient on the left side) to improve venous return, additional intravenous fluid bolus, or vasopressor administration.
  - **Depression of cervical spinal cord and brainstem activity:** Occurs when local anesthesia ascends toward the head, also known as a "**high spinal" or "total spinal,"** a dangerous complication of

epidural anesthesia. It may happen with intrathecal injection or overdose of the anesthetic. First signs include hypotension, bradycardia, and respiratory difficulty, and later, diaphragmatic paralysis and possibly cardiopulmonary arrest

- **Leakage of cerebral spinal fluid** may occur if the dura is inadvertently punctured during epidural placement→ leakage of spinal fluid and is known as a "**wet tap** "→ postural headaches that are worse with sitting up and improved with lying down after delivery

PRETERM LABOR

Preterm labor	
Risk factors	• Prior spontaneous preterm delivery • Multiple gestation • Short cervical length • Cervical surgery (eg, cold knife conization) • Cigarette use
Screening & prevention	• Cervical length measurement by TVUS • Progesterone administration • Cerclage placement

Or prior prePROM (PPROM)

Maternal age >40, obesity, in vitro fertilization

TVUS = transvaginal ultrasound.

Preterm labor	
Gestational age (weeks)	**Management**
34 0/7 to 36 6/7	• +/- Betamethasone • Penicillin if GBS positive or unknown
32 0/7 to 33 6/7	• Betamethasone • Tocolytics • Penicillin if GBS positive or unknown
<32	• Betamethasone • Tocolytics • Magnesium sulfate • Penicillin if GBS positive or unknown

Given at <37 wks to those who are expected to deliver in next 7 days

Tocolytics: indomethacin or nifedipine

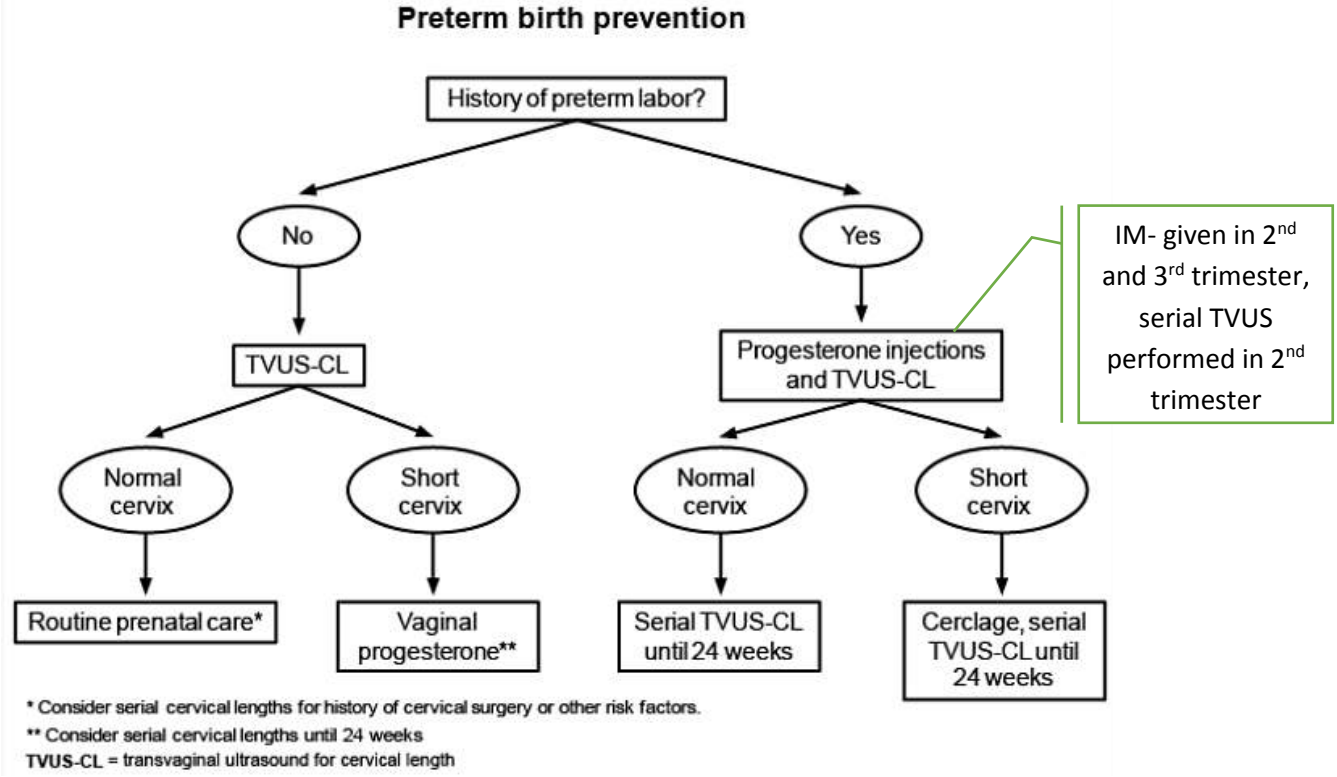
MgSO4: lower the risk of neonatal neurological morbidities (e.g. cerebral palsy)—it has weak tocolytic effect as well but given mainly for **fetal neuroprotection** who are expected to deliver in next 24 hrs. Can be given with indomethacin but not nifedipine

GBS = group B *Streptococcus*.

- Refers to **regular contractions at <37 wks of gestation** that cause **cervical dilatation and/or effacement**
- **Risk factors:** maternal age >40
- **Tocolysis**—*not given >/=34 wks* as its risks ↑es more than that of preterm labor:
  - Indomethacin→ oligohydramnios, closure of the ductus arteriosus
  - Nifedipine→ maternal hypotension/tachycardia
- **Nifedipine**: 1st line tocolytic but when given with MgSO4, can suppress muscular contractility and cause respiratory depression

- **Predictors of preterm labor:**
  - **Shortened cervix** as measured by **transvaginal ultrasound** during 2nd trimester—strong predictor (TVUS is the first step in evaluating risk of preterm labor)
  - **Positive fetal fibronectin test—** Fetal fibronectin (FFN) in vaginal secretions is usually low from 22-33 weeks gestation, and an elevated FFN concentration during this period is associated with an increased risk of preterm delivery. Before and after 22-33 weeks gestation, FFN is normally high and therefore not a useful test

PREVENTION OF PRETERM LABOR



- **Progesterone**— During pregnancy, progesterone maintains uterine quiescence and protects the amniotic membranes against premature rupture. Supplementation with exogenous progesterone **decreases the rate of preterm delivery** in patients with **short cervixes or with a history of preterm birth**. No tocolytic effect and has no effect if pt is already in labor
- **Cerclage**: procedure of placing suture or synthetic tape to reinforce cervix—performed in pts with h/o 2nd trimester deliveries and short cervical length (<2.5cm)

PREMATURE RUPTURE OF MEMBRANES (PROM)

PRETERM PREMATURE RUPTURE OF MEMBRANES

- When membranes rupture before term
- **Dx**: clinical
- **C/F:** amniotic fluid may be noted in vagina, or seen leaking from cervix when Valsalva or slight fundal pressure is applied
- **If PPROM diagnosed→** amniotic fluid sampling for fetal lung indices is mandatory, USG to detect fetal anomalies, determine gestational age and measure amniotic volume
- **PPROM** (24-34 wks), L/S ratio <2.0→ **steroid injection** to accelerate lung maturity. Glucocorticoids are not given beyond 34 wks in PPROM

- **Long term tocolysis** not indicated as ↑ risk of chorioamnionitis
- **Short term tocolysis** may be given to delay labor long enough for glucocorticoids to be given to promote fetal lung maturity—usually given prior to 32 wks, often used between 32-34 wks and almost never used beyond 34 wks. Not used if chorioamnionitis present (same is the case with steroids)

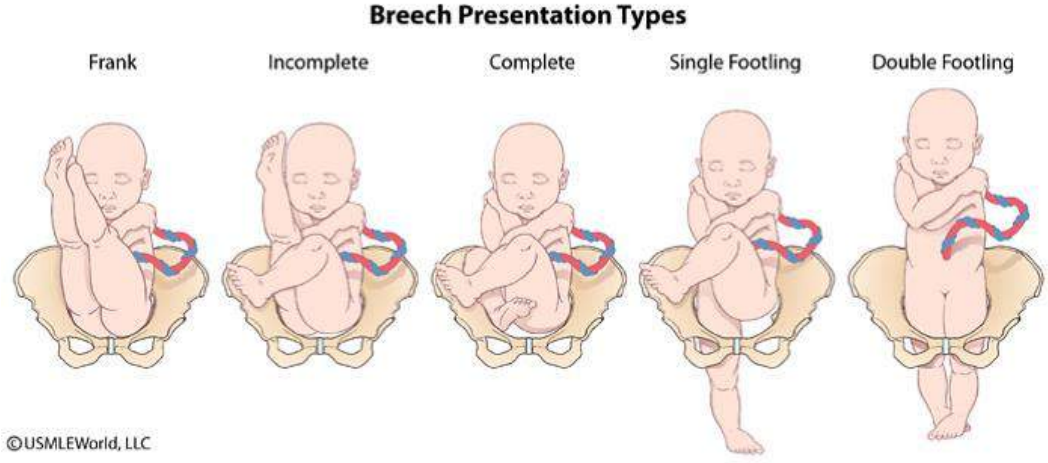
CESAREAN DELIVERY

- **Indications:**
  - Fetal distress indicated by deceleration
  - Loss of FHR variability (occurs in fetal academia)
  - Breech presentation
  - Multiple prior cesarean deliveries

BREECH PRESENTATION

- Breech presentation occurs when the buttocks or lower extremities of the fetus present first into the maternal pelvis.
- Approx. 25% of fetuses </=28wks of gestation are in breech presentation
- By 37 wks→ 4% are breech
- **Risk factors:** prematurity, multiparity, multiple gestation, uterine anomalies, fetal anomalies, and abnormal placentation.
- **Dx:** when head is palpated in fundus or fetal presenting part is not palpable on pelvic exam→ should always be confirmed by **transabdominal USG**
- **Management:**
  - Vaginal delivery of singleton breech fetus is generally CI due to ↑ incidence of birth asphyxia and trauma→ if no CI to vaginal delivery (e.g. placenta previa, active herpes lesion) or ECV→ must offer ECV to avoid C. sec at >/=37 wks
  - If pt refuses ECV, or ECV fails or CI to ECV or vaginal delivery→ perform C. sec at 39 wks

TYPES OF BREECH PRESENTATIONS



EXTERNAL CEPHALIC VERSION

- Maneuver to convert a breech into a vertex presentation for delivery.
- It can be performed **between 37 weeks gestation and the onset of labor** and has been shown to reduce the rate of cesarean deliveries.
- Document fetal well-being by non-stress test and there should be no contraindication to vaginal delivery

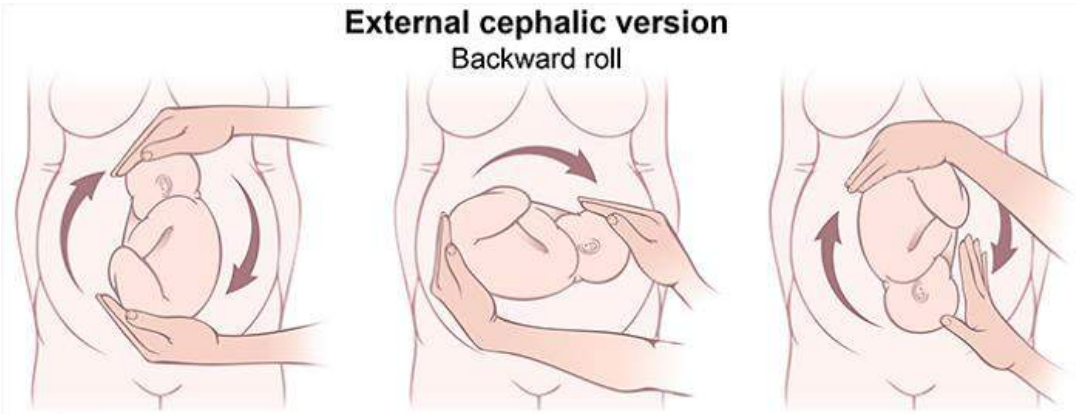
- It has potential to cause fetal distress, perform only when arrangements have been made for a back-up emergency C-section

Contraindications to external cephalic version

- Indications for cesarean delivery regardless of fetal lie (eg, failure to progress during labor, non-reassuring fetal status)
- Placental abnormalities (eg, placenta previa or abruption)
- Oligohydramnios
- Ruptured membranes
- Hyperextended fetal head
- Fetal or uterine anomaly
- Multiple gestation

Incomplete breech, estimated fetal weight >4kg [8.8 lb]→ perform C-sec.

- Abnormal fetal heart tracing



INTERNAL PODALIC VERSION

- Performed in twin delivery to convert the second twin from a transverse/oblique presentation to a breech presentation for subsequent delivery. Breech delivery of a second twin has a lower risk of asphyxia than cesarean delivery and is not contraindicated

Breech extraction of the second twin

Place hand in uterus, grab fetal foot

Deliver baby, feet first

PRETERM BREECH PRESENTATION

- >/=34 wks of gestation but </=37 wks→ active labor and breech presentation→ Tocolysis (at >/=34 wks) and vaginal delivery (for singleton breech presentation) contraindicated due to ↑ risk of fetal asphyxia and fetal injury, external cephalic version is CI in active labor→ perform C. section

TRANSVERSE LIE

- **Risk factors**: prematurity, uterine anomalies, placenta previa, multiple gestations
- **PE:** fetal head near mother's side and/or absence of fetal presenting part during digital cervical exam→ confirm with **USG**
- Most convert to either breech or vertex (more common) presentation spontaneously→ repeat USG at or around 37 wks to determine delivery management
  - If converts to vertex→ trial of labor (TOL)
  - Remain in traverse lie or converts to breech→ ECV (if not CI)→ successful→ trial of labor→ unsuccessful ECV or ECV CI→ C. sec

TERMINATION OF PREGNANCY

SPONTANEOUS ABORTION (SAB)

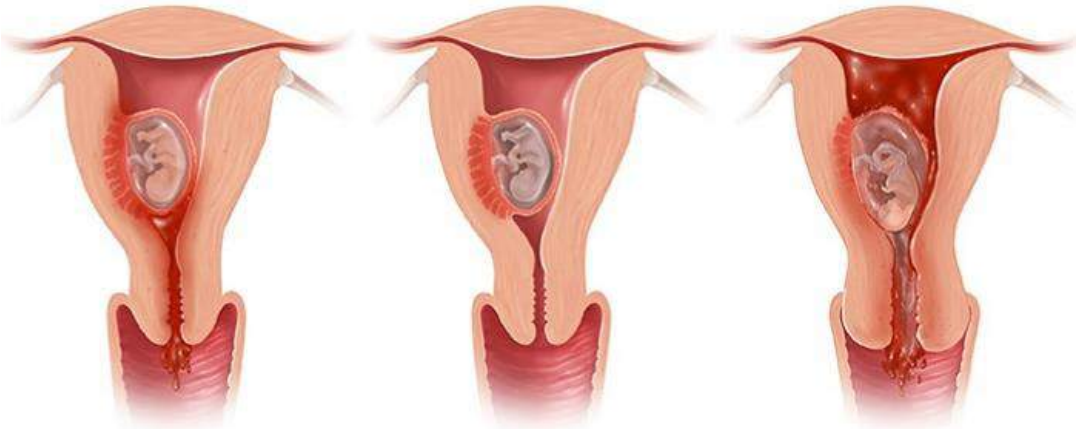
- **Definition:** fetal loss before the 20th week of gestation
- **Risk factors:** 50% are caused by chromosomal abnormalities, increased maternal age (especially age >35 as associated with ↑ chromosomal abnormalities), drugs (e.g., alcohol, smoking), previous spontaneous abortion, infections (e.g. Chlamydia trachomatis, Listeria monocytogenes), poorly controlled diabetes
- **Evaluation:**
  1. Pelvic examination for cervix and vaginal bleeding
  2. Assessment of fetal heart tones
  3. **Transvaginal ultrasound** to document the presence of intrauterine products of conception and to attempt to **visualize motion of the fetal heart (**absent fetal heart movements on USG is the most significant indicator of fetal loss)
  4. **Quantitative β-hCG** measurements are usually done after the pelvic ultrasound to compare with prior baseline readings—single β-hCG not useful as it is usually elevated after SAB—however, can be helpful in cases with non-diagnostic USG or suspected ectopic pregnancy—**serial β-hCG measurements** with ↓ing level suggest likely SAB. Serum β-hCG will become undetectable by 4-6 wks after abortion

5. **Coagulation studies –** sometimes retained products of conception (POC) cause coagulopathy

Classification of spontaneous abortion			
Type	**Clinical presentation**	**Cervix**	**Ultrasound findings**
Missed	• Variable presentation from no symptoms to light vaginal bleeding • Pregnancy symptoms may decrease	Closed	Nonviable fetus
Inevitable	• Vaginal bleeding, uterine cramps • Possible intrauterine fetus with heartbeat	Open	Fetus with possible heartbeat
Incomplete	• Vaginal bleeding with passage of large clots or tissue • Uterine cramps • Products of conception often visualized in dilated cervical os	Open	Products of conception often in cervix
Threatened	• Variable amount of vaginal bleeding • Pregnancy can proceed to viable birth	Closed	Viable pregnancy
Septic	• Fever, malaise, signs of sepsis • Foul-smelling vaginal discharge, cervical motion & uterine tenderness • Rarely occurs after spontaneous abortion • Usually with induced abortions, can be life-threatening	Usually open	Usually retained products of conception

USG: ruptured or collapsed gestational sac

Types of miscarriages



Threatened

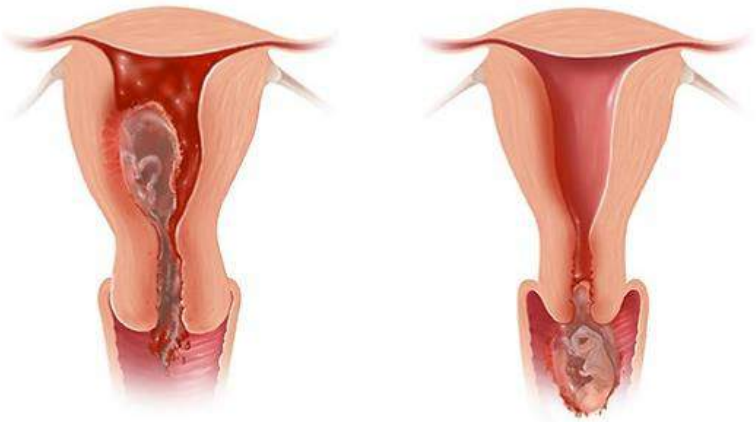
- Vaginal bleeding
- Closed cervical os
- Fetal cardiac activity

Missed

- No vaginal bleeding
- Closed cervical os
- No fetal cardiac activity or empty sac

Inevitable

- Vaginal bleeding
- Dilated cervical os
- Products of conception may be seen or felt at or above cervical os



Incomplete

- Vaginal bleeding
- Dilated cervical os
- Some products of conception expelled & some remain

Complete

- Vaginal bleeding or none
- Closed cervical os
- Products of conception completely expelled

MANAGEMENT OF SPONTANEOUS ABORTION

Management of spontaneous abortion	
Type	**Management**
Threatened	Expectant management until 1 of the following: • Symptom resolution • Progression to inevitable, incomplete, or missed abortion
Incomplete, inevitable, or missed	• Hemodynamically unstable, heavy bleeding: Surgical evacuation (eg, dilation & suction curettage) • Hemodynamically stable, mild bleeding: Expectant management, prostaglandins, or surgical evacuation
Septic	• Blood & endometrial cultures • Broad-spectrum antibiotics • Surgical evacuation of uterine contents

- Appropriate treatment should ensure complete elimination of POC—can be done: surgically, medically or expectantly
- **Surgical**: for unstable, heavy bleeding, low Hb, intrauterine sepsis, or who do not desire medical or expectant. Antibiotic prophylaxis is given to prevent postabortal endometritis
- **Medical**: who do not want surgery and do not want to wait for spontaneous expulsion
- **Expectant**: who are willing to wait and do not want above two—keep pt at home and regular clinical follow-up and TVUS to ensure complete natural evacuation
- All three methods are effective, surgery achieves more complete evacuation
- **Repeat USG after medical or expectant** to confirm absence of retained POC
- **Hospitalization and bed rest—**not indicated in 1st trimester spontaneous or threatened abortion
- **Oxytocin infusion—**not used in 1st trimester (used in late 2nd or 3rd trimester)

THREATENED ABORTION

- 1st step is to ascertain presence or absence of fetus an whether alive or not—with USG→ if alive→ management is reassurance and USG repeat 1 wk later
- Bed rest and abstaining from intercourse generally recommended to prevent couple from guilt if fetus is actually lost—otherwise no evidence of benefit of this intervention on outcome

SEPTIC ABORTION

Septic abortion	
Risk factors	**Retained products of conception from:** • Elective abortion with non-sterile technique outside of health care setting • Missed, incomplete, or inevitable abortion (rare)
Clinical presentation	• Fever, chills, lower abdominal pain, bloody or purulent vaginal discharge • Boggy & tender uterus with dilated cervix • **Pelvic ultrasound:** Retained products of conception, increased vascularity, echogenic material in the cavity, thick endometrial stripe
Management	• Blood & endometrial cultures • Intravenous fluids & broad-spectrum antibiotics • Surgical evacuation of uterus (suction curettage) • Hysterectomy if no response to antibiotics, development of abscess, or signs of clostridial infection
Complications	• Salpingitis • Peritonitis • Septic shock

Cervical motion tenderness

Closely observe afterwards as pt can still develop sepsis after surgery

- Medical emergency and can progress to death

ELECTIVE ABORTION

- Misoprostol is a synthetic prostaglandin approved for use with mifepristone to terminate pregnancies of <49 days gestation

INTRAUTERINE FETAL DEMISE (IUFD)

- Death of a fetus in utero after 20 wks of gestation and before the onset of labor
- Suspected when pt reports disappearance of fetal movements, ↓ or stagnation in uterine size or when fetal heart sounds are no longer heard
- **Risk factors:** hypertensive disorders, diabetes mellitus, placental and cord complications, antiphospholipid syndrome, congenital anomalies and fetal infections such as the TORCH infections or listeriosis, smoking > 10 cigarettes/day. Cause unknown in 50% cases
- β-hCG may continue to be elevated due to ongoing placental production of that hormone
- **Real time USG**—more reliable tool for confirming the diagnosis—demonstrates absence of fetal movement and fetal cardiac activity (if fetal heart tones present on USG, go for NST)
- **Monitoring the coagulation profile**: done after USG confirm IUFD, as IUFD can cause maternal consumptive coagulopathy and DIC.
  - Retention of dead fetus→ gradual release of tissue factor (called thromboplastin) from placenta to maternal circulation→chronic consumptive coagulopathy

- Fibrinogen levels are normally high in pregnancy—low normal level may be early sign of coagulopathy esp. with fall in platelet count, ↑ in PT and PTT or + fibrin split products
- Any **suspected coagulation derangement**→ delivery without delay
- **All coagulation parameters normal:** management depends on pt's preference:
  - **Watchful expectancy**—usually 80% cases deliver in 2-3 wks—higher risk of complications like chorioamnionitis, DIC (hence serial fibrinogen level testing performed), emotionally disturbing for most
  - **Induction of labor**—usually preferred by pts
- **DIC, hemorrhage or coagulation profile markedly abnormal**→ fresh frozen plasma

- It is important to **try to find the cause of fetal demise** after first episode in order to prevent, if possible, a recurrence of same issue in any subsequent pregnancies→ **autopsy** of fetus and placenta should be performed

STILLBIRTH DELIVERY OPTIONS

Stillbirth delivery options	
2nd trimester	• Dilation & curettage (up to 24 weeks) • Induction of labor • Spontaneous vaginal delivery
3rd trimester	• Induction of labor +/- cervical ripening agents • Spontaneous vaginal delivery • Repeat cesarean upon maternal request if patient has a history of prior cesarean delivery

- Vaginal delivery is preferred even in pts with prior C. sec
- Cervical ripening, if needed, is done with misoprotol or transcervical Foley bulb (preferred in pts with prior C. sec as prostaglandins ↑ risk of uterine rupture)

LATE TERM AND POSTTERM PREGNANCY COMPLICATIONS

Late-term and postterm pregnancy complications	
Fetal	**Maternal**
• Oligohydramnios • Meconium aspiration • Stillbirth • Macrosomia • Convulsions	• Cesarean delivery • Infection • Postpartum hemorrhage • Perineal trauma

- **Late-term:** pregnancy at 41 wks or beyond (41 wks to 41 wks and 6 days)→ **consider induction of labor**
- **Post-term:** pregnancy >/=42 wks gestation→ **recommend induction of labor** to prevent complications
- Antepartum fetal testing with **biophysical profile frequently** started at 41 wks to assess fetal well-being
- Late-term and post-term pregnancies are at risk of **uteroplacental insufficiency**

- May show **late decelerations and oligohydramnios** on BPP

- **Oligohydramnios** (single deepest vertical pocket of amniotic fluid </=2cm or an amniotic fluid index of </=5cm (**normal AFI= 5-25**) on transabdominal ultrasound) is a common complication of prolonged pregnancies.
  - Aging placenta→ ↓ fetal perfusion→ ↓ renal perfusion→ ↓ urinary output from fetus→ oligohydramnios
  - It is an **indication for delivery** even if antepartum fetal testing is normal

FETAL GROWTH RESTRICTION

Causes of fetal growth restriction (weight <10th percentile)	
Asymmetric (maternal factors)	• Vascular disease (hypertension, preeclampsia, diabetes) • Antiphospholipid antibody syndrome • Autoimmune disease (systemic lupus erythematosus) • Cyanotic cardiac disease • Substance abuse (tobacco, alcohol, cocaine)
Symmetric (fetal factors)	• Genetic disorders (aneuploidy) • Congenital heart disease • Intrauterine infection (malaria, cytomegalovirus, rubella, toxoplasmosis, varicella) • Congenital anomalies e.g. gastroschisis

CMV- most common in developed countries- no Sx in mother

- **Asymmetric growth restriction:** from conditions that impair blood flow to placenta—can be caused by any maternal vascular disease, malnutrition. Blood shifts from abdominal viscera to vital organs (like brain), hence, asymmetric growth (weight is affected more than height and head size)
- **Symmetric growth restrictions:** genetic defects or insults during 1st or 2nd trimester (before 28 wks gestation)→ entire fetus is affected—if no anatomic anomaly on USG or ↓ risk of chromosomal anomaly→ suspect intrauterine infection early in pregnancy (height, weight and head circumference equally affected)
- **FGR infants** are at ↑ risk of intrauterine demise, neonatal morbidity and mortality including **hypoxia**, **perinatal asphyxia, meconium aspiration, hypothermia** (↓subQ fat), **hypoglycemia** (due to ↓ glycogen stores in infants 2.6 kg, managed with early and frequent feeds—hyperglycemia in very low birth weight infants due to ↓ insulin), **hypocalcemia** (↓ transfer of calcium across placenta), **polycythemia** (due to ↑ erythropoietin cox of hypoxia). More prone to cognitive delay in childhood, obesity, DM type 2, coronary artery disease and stroke in adulthood

SHOULDER DYSTOCIA

- **Risk factors**: infant large for gestational age (birth weight >4 kg)
- Shoulder dystocia and its complications are usually unpredictable and unpreventable. Prophylactic cesarean delivery is not routinely recommended for suspected fetal macrosomia because the rate of shoulder dystocia and associated complications is not significantly different in cesarean versus vaginal deliveries.

Risk factors for fetal macrosomia (Weight >4kg)	
Maternal	• Advanced age • Diabetes • Excessive weight gain during pregnancy or pre-existing obesity • Multiparity
Fetal	• African-American or Hispanic ethnicity • Male sex • Post-term pregnancy

Complications of shoulder dystocia	
Fractured clavicle	• Clavicular crepitus/bony irregularity • Decreased Moro reflex due to pain on affected side • Intact biceps & grasp reflexes
Fractured humerus	• Upper-arm crepitus/bony irregularity • Decreased Moro reflex due to pain on affected side • Intact biceps & grasp reflexes

Erb-Duchenne palsy	• Decreased Moro & biceps reflexes on affected side
	• "Waiter's tip"
	  • Extended elbow
	  • Pronated forearm
	  • Flexed wrist & fingers
	• Intact grasp reflex

Klumpke palsy	• "Claw hand"
	  • Extended wrist
	  • Hyperextended metacarpophalangeal joints
	  • Flexed interphalangeal joints
	  • Absent grasp reflex
	• Horner syndrome (ptosis, miosis)
	• Intact Moro & biceps reflexes

Perinatal asphyxia	• Variable presentation depending on duration of hypoxia • Altered mental status (eg, irritability, lethargy), respiratory or feeding difficulties, poor tone, seizure

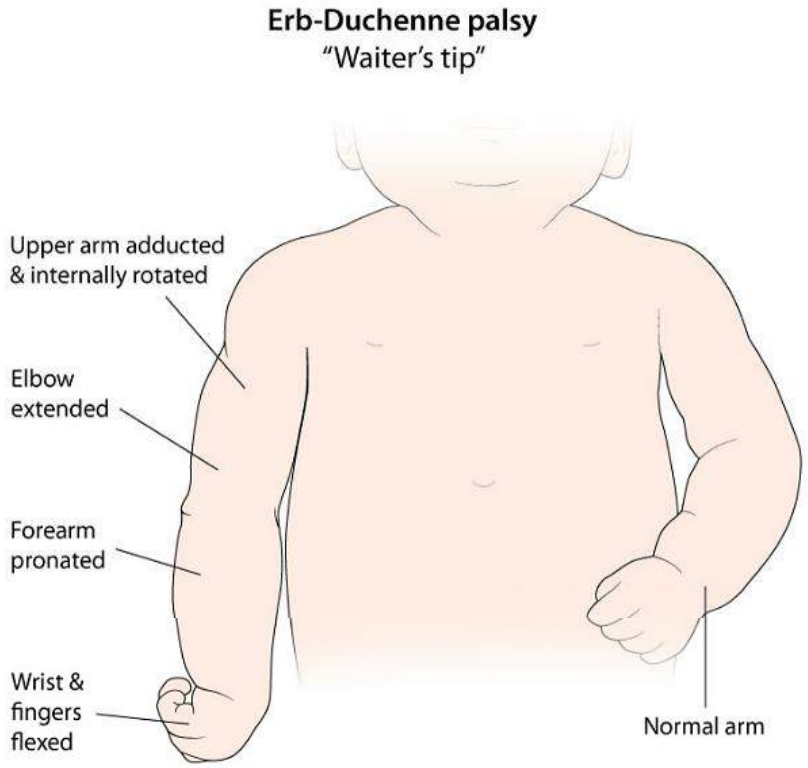
FRACTURED CLAVICLE

Neonatal displaced clavicular fracture	
Risk factors	• Fetal macrosomia (maternal diabetes, post-term pregnancy) • Instrumental delivery (vacuum or forceps) • Shoulder dystocia
Clinical features	• Crying/pain with passive motion of affected extremity • Crepitus over clavicle • Asymmetric Moro reflex
Diagnosis	• X-ray
Treatment	• Reassurance • Gentle handling • Analgesics • Place affected arm in a long-sleeved garment & pin sleeve to chest with elbow flexed at 90 degrees

- Usually heal spontaneously and quickly without long-term sequelae
- Healing usually occurs in 7-10 days

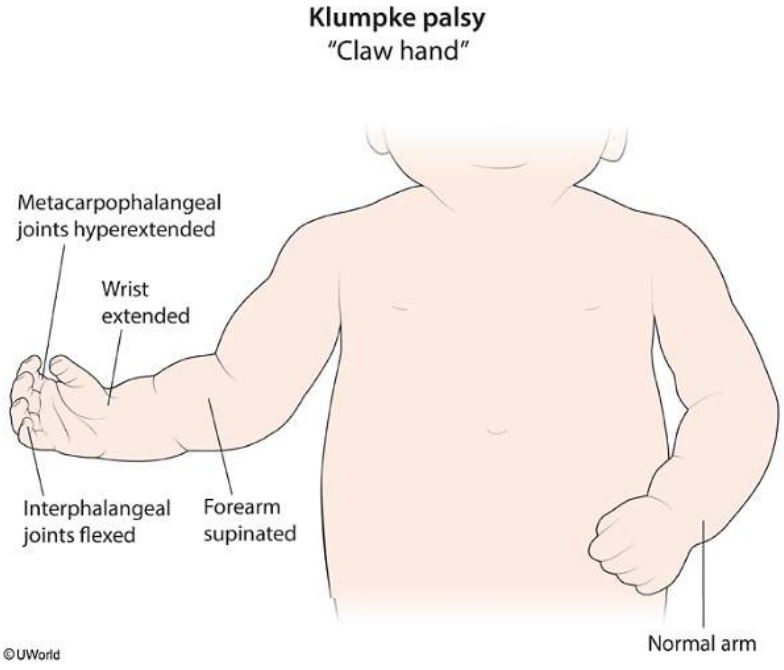
ERB-DUCHENNE PALSY

- Most common type of brachial plexus injury
- Injury to upper trunk of brachial plexus—C5-C6 and sometimes C7
- **Weakness** of the deltoid and infraspinatus muscles (innervated by C5), biceps (innervated by C6), and wrist/finger extensors (innervated by C7)
- **Treatment** involves gentle massage and physical therapy to prevent contractures.
- **Prognosis** depends on whether damage resulted from mild nerve stretching or compression as opposed to severe rupture or avulsion. Fortunately, **up to 80% of patients have spontaneous recovery within 3 months.**
  - No improvement by 3-6 mo→ surgical intervention can be considered but not necessarily curative

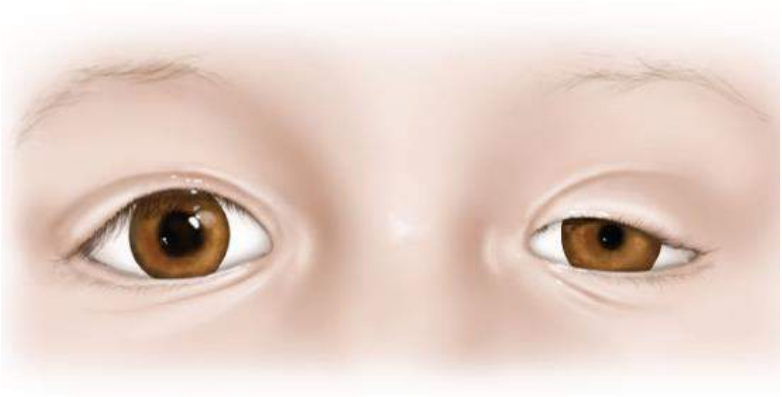


KLUMPKE PALSY

- Excessive traction on C8-T1 → rare complication of **hand paralysis**
- Sometimes there is associated damage to sympathetic fibers that run along C8-T1→ipsilateral **ptosis and miosis (Horner syndrome)**
- **Prognosis:** depends on whether damage was due to nerve stretching or compression as opposed to avulsion. Horner syndrome also portends suboptimal outcome
- **Rx:** controversial—involves gentle massages and **physical therapy to prevent contractures.** In most cases function returns within a few months. If no improvement by age 3-9 mo→ consider surgical intervention



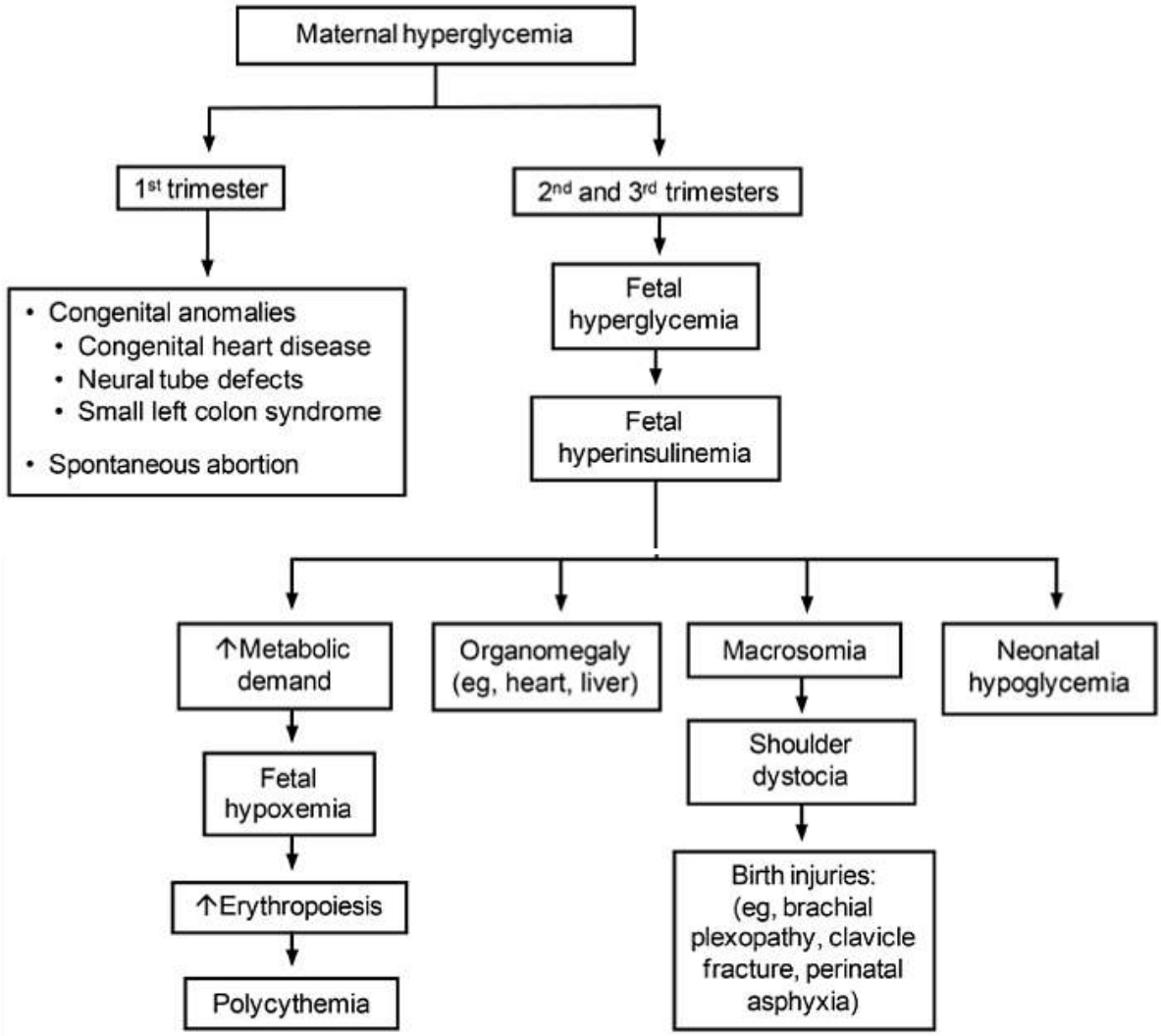
Horner syndrome



Normal eye Ptosis, miosis

FETAL AND NEONATAL COMPLICATIONS FROM MATERNAL DIABETES

Fetal and neonatal complications from maternal diabetes mellitus



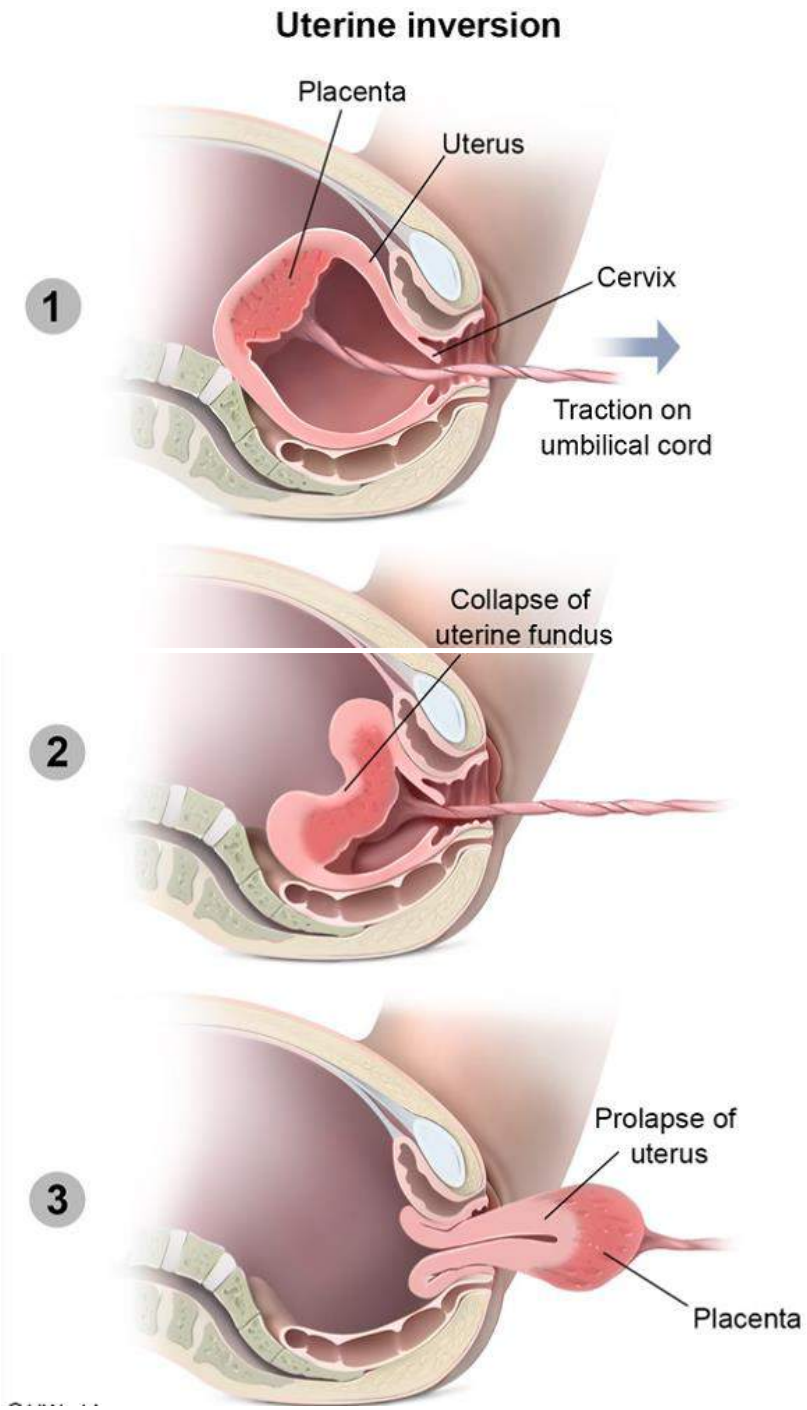
- Combination of hyperinsulinemia, major anabolic hormone and hyperglycemia → disproportionate growth (higher chest-to-head and shoulder-to-head ratio) , visceromegaly and fat accumulation→ ↑ risk of shoulder dystocia (occur in 1/3rd of infants of diabetic mothers)
- **Prevention of complications:** dietary modification, insulin and/or oral hypoglycemics

POSTPARTUM HEMORRHAGE

UTERINE INVERSION

Uterine inversion	
Pathophysiology	• Excessive fundal pressure • Excessive umbilical cord traction
Presentation	• Lower abdominal pain • Round mass protruding through cervix • Uterine fundus not palpable transabdominally • Hemorrhage shock
Management	• Aggressive fluid replacement • Manual replacement of the uterus • Placental removal and uterotonic drugs after uterine replacement

- Uncommon but **potentially fatal** cause of postpartum hemorrhage
- **Risk factors:** nulliparity, fetal macrosomia, placenta accreta, rapid labor and delivery
- **Immediate manual replacement of uterus:** place the hand in vagina and push along the axis of vagina towards cervix→ if delayed→ can cause uterine edema and cervix contraction around inverted uterus, making it difficult
- Placenta should not be removed before replacement as can cause massive hemorrhage
- **Uterine atony**—common after replacement and placenta removal → uterotonic drugs (e.g. oxytocin, misoprostol) given **after replacement** and placenta removal to prevent further hemorrhage and recurrence of prolapse. Uterine relaxation is necessary for replacement hence given after replacement
- Uterine relaxants (eg, nitroglycerine, terbutaline) can be administered to aid in the replacement of the uterus if the initial attempt is unsuccessful→ but preferable without this as can exacerbate uterine atony
- Laparotomy—if manual replacement fails



UTERINE ATONY

- Hemostasis **after placental delivery** is achieved by clotting and by compression of placental site blood vessels by myometrial contraction → failure of either → postpartum hemorrhage (PPH).
- Primary PPH occurs <24 hours delivery

Postpartum uterine atony	
Risk factors	• Uterine fatigue from prolonged or induced labor • Chorioamnionitis • Uterine over-distension (multiple gestation, polyhydramnios) • Retained placenta
Clinical features	• Most common cause of postpartum hemorrhage • Enlarged, soft, boggy, poorly contracted uterus
Treatment	• Bimanual uterine massage • Intravenous fluids, oxygen • Uterotonic medications (eg, oxytocin, methylergonovine, carboprost, misoprostol)

- Uterus becomes unresponsive to oxytocin from oxytocin receptor saturation
- Operative (e.g. forceps-assisted) vaginal delivery/precipitous delivery
- Hypertensive disorders

- Management begins with assessment of vital signs, IV fluids to maintain systolic BP and often transfusion of appropriate blood products
- **Uterotonic drugs:**
  - **Oxytocin:** 1st line and give IV—2nd drug can be added if this and massage don't work
  - **Methylergonovine:** causes smooth muscle constriction, uterine contraction, and vasoconstriction.
    - Can cause HTN
    - CI in hypertensive pts
  - **Carboprost:** synthetic prostaglandin that stimulates uterine contraction.
    - Can cause bronchoconstriction
    - CI in asthma
- **Hysterectomy:** last resort but should not be delayed in unstable pts with massive hemorrhage to prevent death
-

POSTPARTUM PERIOD

Postpartum period	
Normal findings	• Transient rigors/chills • Peripheral edema • Lochia rubra • Uterine contraction & involution • Breast engorgement
Routine care	• Rooming-in/lactation support • Serial examination for uterine atony/bleeding • Perineal care • Voiding trial • Pain management

- Normal postpartum period is characterized by several physiologic processes that can be mistaken for signs of pathology

TRANSIENT RIGORS AND CHILLS

- Occurs immediately after delivery of placenta
- Thought to be due to thermal imbalance

LOCHIA

- During the **first few days** after delivery**, lochia rubra** occurs, which is a **red or reddish-brown vaginal** discharge (the normal shedding of the uterine decidua and blood). Small blood clots may also be present
- After **3-4 days**, the discharge becomes **thin and pink or brown colored (lochia serosa**)
- After **2-3 weeks,** the discharge becomes **white or yellow (lochia alba)**
- Heavy bleeding that soaks >2 pads per hour is considered excessive

UTERUS CONTRACTS

- Becomes **firm and globular** with fundus typically 1-2 cm above or below umbilicus

POSTPARTUM URINARY RETENTION

Postpartum urinary retention	
Risk factors	• Nulliparity • Prolonged labor • Perineal injury • Regional analgesia • Cesarean delivery • Instrumental vaginal delivery
Clinical features	• Inability to void • Sensation of bladder fullness • Dribbling of urine or small-volume voids
Management	• Analgesics • Encourage ambulation • Urinary catheterization

Reassure that it is temporary and reversible

- Common after delivery
- Regional anesthesia→ ↓ motor and sensory impulses of sacral spinal cord→ suppression of micturition reflex and/or ↓ in bladder tone (↓ detrusor tone), pudendal nerve palsy from injury, or periurethral swelling
- **Dx:** inability to void by 6hours after vaginal delivery or 6 hours after removal of indwelling catheter after C. sec. Bladder catheterization more accurate than bladder USG→ >/=150 mL of urine confirms diagnosis

POSTPARTUM ENDOMETRITIS

- Suspect puerperal infection if**: fever >/=38*C (100.4*F) outside the first 24 hours postpartum (**known as postpartum fever). Temp. of 37.9*C (100.2*F) after delivery is considered normal
- Endometritis is the most common cause of puerperal fever on 2nd and 3rd day postpartum
- **Causative organism:** polymicrobial caused by a combination of gram +ve, gram –ve, aerobic and anaerobic and occasionally other organisms like Chlamydia and Mycoplasma. Commonly isolated organisms include group B streptococci, group D streptococci, Staphylococcus epidermidis, Escherichia

coli, Neisseria gonorrhoeae, Gardnerella vaginalis, Bacteroides fragilis, peptostreptococci and peptococci.

- **Risk factors** for endometritis include, but not limited to:
  - Prolonged rupture of membranes (>24 hours)
  - Prolonged labor (>12 hours)
  - C. section
  - Use of intrauterine pressure catheters or fetal scalp electrodes
- **C/F of postpartum endometritis:**
  - Fever
  - Uterine tenderness
  - Foul smelling lochia (normal lochia, i.e. vaginal discharge occurs after pregnancy but resolves in 2 wks and never foul smelling)
  - Leukocytosis
- **Rx:**
  - Most appropriate therapy: IV clindamycin + IV aminoglycoside such as gentamicin

RECTOVAGINAL DELIVERY

- Obstetric injury is the most common cause of rectovaginal fistula (RVF), which may present with in the first 2 weeks postpartum. RVFs occur most often after third- or fourth-degree laceration, inadequate wound repair or wound breakdown, and infection. In less industrialized countries, RVFs occur due to poor intrapartum care and a prolonged second stage of labor, which causes ischemic pressure necrosis of the rectovaginal septum from fetal head compression.
- RVF presents with incontinence of flatus or fecal material through the vagina, causing a malodorous brown/tan discharge. Diagnosis is usually confirmed by visual examination showing dark red, velvety rectal mucosa on the posterior vaginal wall. If an RVF is suspected but not clearly visible, anoscopy may help visualize the opening. Definitive treatment is surgical repair of the fistulous tract.

HYPERTENSION IN PREGNANCY

- To diagnose HTN during pregnancy, BP should be ↑ed on two separate occasions taken at least 4 hours apart
- Pregnancy→ marked systemic vasodilation that lowers the blood pressure by 5- 10 mm Hg from baseline during the first trimester— returns to pre-pregnancy levels during the third trimester

Hypertensive disorders of pregnancy	
Chronic hypertension	• Systolic pressure **≥140 mm Hg** &/or diastolic pressure **≥90 mm Hg** prior to conception or 20 weeks gestation
Gestational hypertension	• New-onset elevated blood pressure at ≥20 weeks gestation • No proteinuria or end-organ damage
Preeclampsia	• New-onset elevated blood pressure at ≥20 weeks gestation **AND** • Proteinuria **OR** signs of end-organ damage
Eclampsia	• Preeclampsia **AND** • New-onset grand mal seizures
Chronic hypertension with superimposed preeclampsia	Chronic hypertension **AND** 1 of the following: • New-onset proteinuria or worsening of existing proteinuria at ≥20 weeks gestation • Sudden worsening of hypertension • Signs of end-organ damage

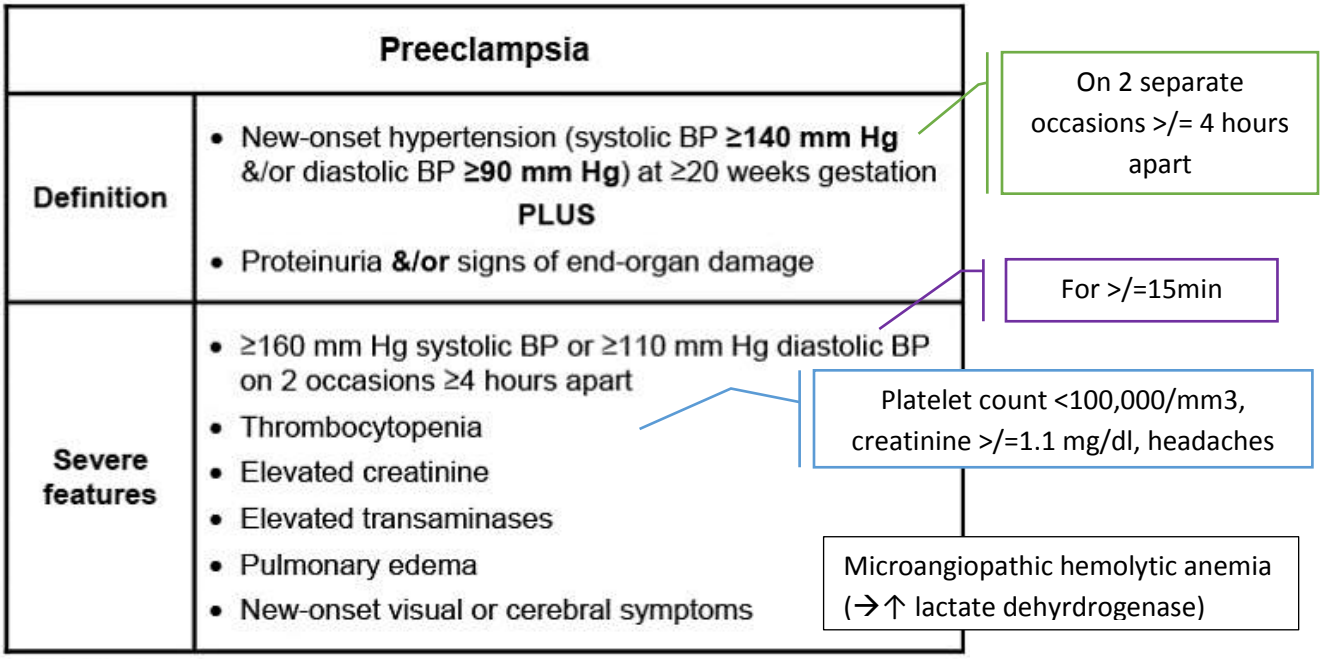
Pregnancy-related risks due to hypertension	
Maternal	• Superimposed preeclampsia • Postpartum hemorrhage • Gestational diabetes • Abruptio placentae • Cesarean delivery
Fetal	• Fetal growth restriction • Perinatal mortality • Preterm delivery • Oligohydramnios

- The risk of preterm labor and other complications may be due to ↑ systemic vascular resistance and arterial stiffness leading to placental dysfunction. May also be due to expedited preterm delivery due to unstable maternal or fetal complications

GESTATIONAL HYPERTENSION

- New-onset HTN at >/=20 wks gestation with no proteinuria or end-organ damage
- Methyldopa is used for chronic HTN in pregnancy

PRE-ECLAMPSIA



BP = blood pressure.

- **Risk factors**: maternal age <18 or >40, multiple gestation, nulliparity, preexisting DM, chronic kidney disease and prior preeclampsia
- If proteinuria is detected on urine dipstick (>/=1+), which has a high false positive and false negative during pregnancy, must be confirmed either by **urine protein/creatinine ratio** or **24-hours urine collection for total protein** (gold standard) to quantify the proteinuria—Dx is confirmed if **urine protein/creatinine ratio >0.3** or **a 24 hour urine collection gives total protein excretion of > 300 mg/24hr**
- **Complications:**
  - **Maternal complications:** although all pts are at risk of eclamptic seizures, hepatic rupture and DIC, hemorrhagic or ischemic stroke, pulmonary edema and myocardial ischemia, those with severe symptoms are at ↑ed risk
  - **Fetal complications:** can cause disruption of blood flow through uterine arteries or lead to abruptio placentae, oligohydramnios, **fetal growth restriction/ low birth weight** even if delivered at term due to chronic uteroplacental insufficiency

TREATMENT OF PRE-ECLAMPSIA

- Initial goal is to **stabilize mother** by administering anti-hypertensive meds

Treatment of preeclampsia	
Drug	**Indication**
Hydralazine IV, labetalol IV, or nifedipine PO	Lower blood pressure acutely to decrease stroke risk
Magnesium sulfate IV or IM	Prevent or treat eclamptic seizures

IM = intramuscular; **IV** = intravenous; **PO** = by mouth.

- **Labetalol:** β-blocker and α-blocker—cannot be given to pt with ↓ pulse as it can further ↓ causing dizziness or lightheadedness
- **Hydralazine:** vasodilator and can be given to pt with low pulse
- **Oral nifedipine:** CCB—cannot be given to pt with emesis
- **Loop diuretics (e.**g. furosemide): typically used in pts of preeclampsia with pulmonary edema (e.g. crackles, dyspnea)

ECLAMPSIA

Eclampsia (severe preeclampsia + seizures)	
Clinical features	• Hypertension • Proteinuria • Severe headaches • Visual disturbances • Right upper quadrant or epigastric pain • 3-4 minutes of tonic-clonic seizure, usually self-limited
Management	• Administer magnesium sulfate • Administer antihypertensive agent • Deliver the fetus

After stabilization of pt. with above 2

- As seizure lasts for 3-4 minutes and self-limited, hence, treatment is directed at **prevention of further seizure**
- If MgSO4 does not control seizure, then diazepam or phenytoin would be indicated as 2nd line
- Approx. 10% pregnancy related maternal mortality is due to eclampsia—from abruptio placenta, DIC and cardiopulmonary arrest

MgSO4 toxicity:

Magnesium toxicity	
Clinical features	• Mild: Nausea, flushing, headache, hyporeflexia • Moderate: Areflexia, hypocalcemia, somnolence • Severe: Respiratory paralysis, cardiac arrest
Treatment	• Stop magnesium therapy • Give IV calcium gluconate bolus

IV = intravenous.

- Mg is solely excreted by kidneys
- Renal insufficiency—risk factor for Mg toxicity→ pt with ↑ creatinine may need lower dose and close observation.
- Mg levels should be checked after initiation of infusion and infusion rate adjusted accordingly in all pts
- Concomitant use of calcium channel blocker and Mg can potentiate hypotension

HELLP SYNDROME

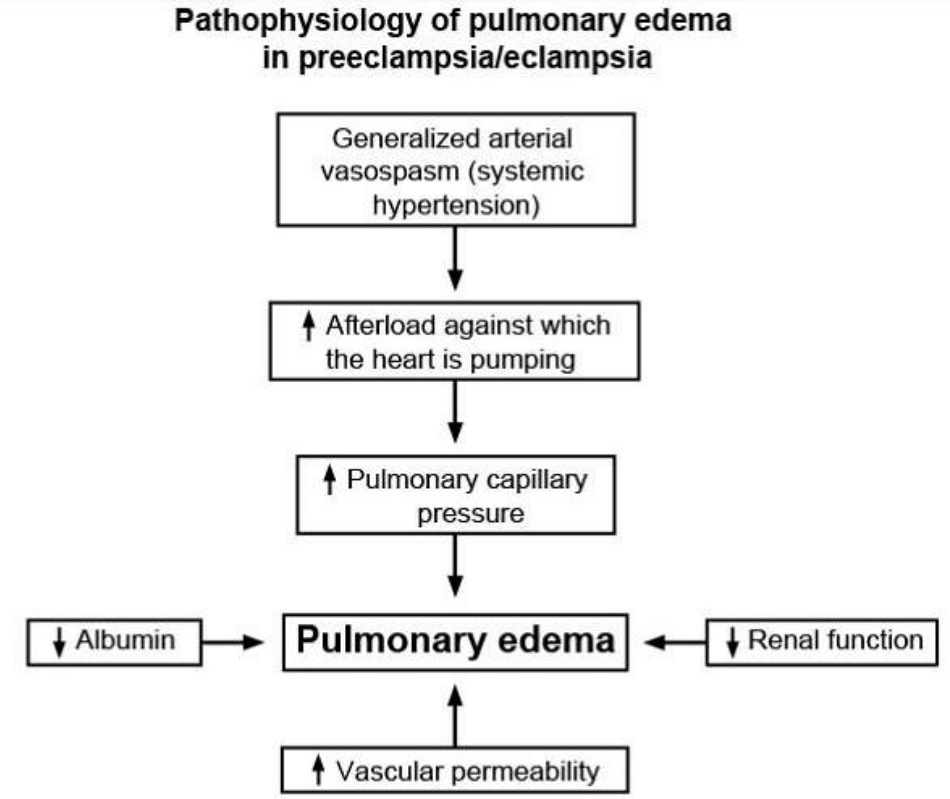
- Life threatening pregnancy complication that may be severe pre-eclampsia
- Abnormal placentation→ systemic inflammation→ activation of coagulation cascade and complement cascade→ **circulating platelets are rapidly consumed**, and **microangiopathic hemolytic anemia (MAHA)** is particularly detrimental to liver→ hepatocellular necrosis (centriobular necrosis), hematoma formation and thrombi in portal capillary system→ ↑ LFTs, liver swelling and distention of hepatic capsule (Glisson capsule)→right upper quadrant or epigastric pain
- MAHA→ indirect hyperbilirubinemia and RBC fragments on blood smear.
- Can also cause ARDS

HELLP syndrome	
Clinical features	• Preeclampsia • Nausea/vomiting • Right upper quadrant abdominal pain
Laboratory findings	• Microangiopathic hemolytic anemia • Elevated liver enzymes • Low platelet count
Treatment	• Delivery • Magnesium for seizure prophylaxis • Antihypertensive drugs

- **Rx**: 1st stabilize pt with antihypertensives and/or magnesium prophylaxis for seizure. Once stabilized→ **only definitive treatment is delivery.**

- Coagulation disturbances recover spontaneously after delivery. Prophylactic platelet transfusion considered if:
  - Platelet count <20,000/mm3 or
  - If platelet count <40,000/mm3 and C-section to be done
- Delivery should occur **promptly at >/=34 wks** or at any gestational age with **abnormal fetal testing** or **severe or worsening maternal status**

PULMONARY EDEMA IN PRE-ECLAMPSIA OR ECLAMPSIA



- **C/F:** sudden-onset dyspnea, hypoxia, and crackles
- Rare, life-threatening complication
- **Rx:** supplemental oxygen, fluid restriction and diuresis in severe cases. Fluid restriction and diuresis must be used with caution as plasma-volume is effectively ↓ed through third-spacing and placental perfusion can be compromised

ACUTE FATTY LIVER OF PREGNANCY

- Acute fatty liver of pregnancy (AFLP) is characterized by nausea, vomiting, abdominal pain, and significant elevations of liver markers in the third trimester.
- Many features of AFLP overlap with those of HELLP syndrome, but patients with AFLP are more likely to have additional extrahepatic complications such as leukocytosis, hypoglycemia, and acute kidney injury

CAUSES OF HYPERANDROGENISM IN PREGNANCY

Causes of hyperandrogenism in pregnancy		
Diagnosis	**Maternal clinical features**	**Fetal virilization**
Luteoma	• Yellow or yellow-brown masses (often with areas of hemorrhage) of large lutein cells • Solid ovarian masses on ultrasound (50% are bilateral) • Regress spontaneously after delivery	High risk
Theca luteum cyst	• Bilateral ovarian cysts on ultrasound • Associated with molar pregnancy & multiple gestation • Regress spontaneously after delivery	Low risk
Krukenberg tumor	• Bilateral solid ovarian masses on ultrasound • Metastases from primary GI tract cancer	High risk

- Hyperandrogenism in pregnancy is usually caused by ovarian masses

LUTEOMA

- More common in African-American
- Most are asymptomatic—~30% symptomatic: new onset **hirsuitism and acne** due to ↑ testosterone, dihydrotestosterone and androstendione
- **Dx:** USG—gold standard—masses are typically 6-10 cm in diameter
- **Management:**
  - Clinical monitoring and USG as regress after delivery—also monitor size as rarely can cause mass effect (e.g. hydrocephalus, obstructive labor) and ovarian torsion
  - Inform pt that symptomatic luteoma can cause virilization of female fetus
  - Surgery indicated only in mass effects and torsion

KRUKENBERG TUMOR

- Unintentional weight loss, abdominal pain and other complain
- Biopsy and surgery indicated if malignancy is suspected

LUPUS NEPHRITIS

- Must be distinguished from preeclampsia as both can mimic each other as corticosteroids can aggravate lupus

- ANA titers may be weakly positive in normal pregnancy but markedly raised in lupus nephritis
- Lupus nephritis shows RBC casts along with proteinuria
- If proteinuria persists after pregnancy→ renal biopsy to diagnose lupus nephritis

MEDICINES CONTRAINDICATED IN PREGNANCY

LITHIUM

- Use in 1st trimester→ ↑ risk of congenital heart defect, classically Ebstein's anomaly
- In pts with stable bipolar disorder→ slowly taper lithium as abrupt discontinuation may cause relapse

ISOTRETINOIN

- Associated with many congenital abnormalities: craniofacial dysmorphism, heart defects, and deafness.
- It must not be taken by women of **reproductive age unless two effective forms of contraception** have been used for **at least 1 month prior to initiating treatment.** Contraception must be continued during treatment, and for **1 month after isotretinoin** is discontinued.
- In addition, patients **must have a pregnancy test the week before beginning treatment,** and should have **periodic pregnancy tests during therapy,** to make sure the patient is not pregnant

➔ There is no known effect of inhaled betamethasone and albuterol

ACE INHIBITORS

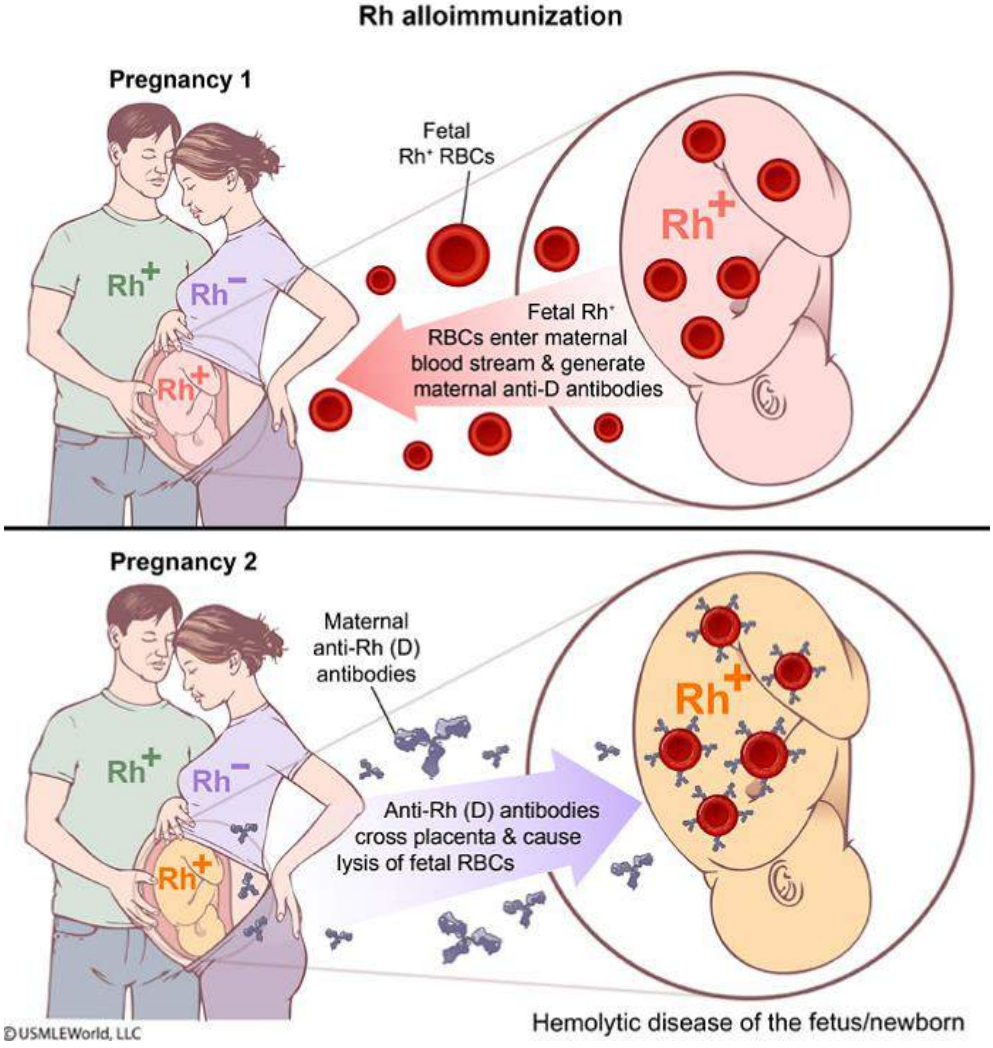
- Can cause fetal growth restriction, renal failure, pulmonary hypoplasia, oligohydramnios, and skeletal abnormalities if administered in the second or third trimester

HEMOLYTIC DISEASE OF NEWBORN

INDICATIONS FOR PROPHYLACTIC ANTI-D IMMUNE GLOBULIN ADMINISTRATION FOR AN UNSENSITIZED Rh-NEGATIVE PREGNANT PATIENT

Indications for prophylactic anti-D immune globulin administration for an unsensitized Rh-negative pregnant patient*
• At 28-32 weeks gestation • Within 72 hours of delivery of an Rh-positive infant or a spontaneous, threatened, or induced abortion • Ectopic pregnancy • Hydatidiform molar pregnancy • Chorionic villus sampling, amniocentesis • Abdominal trauma • 2nd & 3rd trimester bleeding • External cephalic version
*Antepartum prophylaxis is not needed if the father is known to be Rh negative.

- If the pt is already sensitized (i.e. ↑ antibody titers) → anti-D immune globulin not helpful→ close fetal monitoring for hemolytic disease required
- The initial timing of 28-32 weeks is selected because the half-life of anti-D immune globulin is about 6 weeks, which would cover any potential future exposure to fetal red blood cells through most of the third trimester



CHILDREN BORN TO ANOREXIC MOTHER

- Even if the pt has corrected eating disorder—she is at ↑ed risk of pregnancy complications due to chronic nutritional def.
- Pt with current or past anorexia are at higher risk of giving birth to infants that are:
  1. Premature
  2. Small for gestational age (due to IUGR) or both
  3. Miscarriage
  4. Hyperemesis gravidarum
  5. C. sec
  6. Postpartum depression (not postpartum psychosis)
- Children born to anorexic mothers often suffer from poor growth and intellectual disability
- Complications in mother in general:

1. Osteoporosis

2. Elevated cholesterol and carotene levels
3. Cardiac arrhythmias (prolonged QT interval)
4. Euthyroid sick syndrome
5. Hypothalamic-pituitary axis dysfunction resulting in anovulation, amenorrhea, and estrogen deficiency
6. Hyponatremia secondary to excess water drinking is often the only electrolyte abnormality, but the presence of other electrolyte abnormalities indicates purging behavior

BREASTFEEDING

- Exclusive form of nutrition for <6mo infants
- **Benefits to infants**—protection against:
  - Necrotizing enterocolitis
  - Diarrheal illnesses
  - Otitis media
  - Respiratory tract infections
  - UTIs
- **Benefits to mother:**
  - ↓ postpartum bleeding
  - More rapid uterine involution
  - ↓ menstrual blood loss
  - ↑ child spacing
  - Earlier return to pre-pregnancy weight
  - ↓ risk of breast and ovarian cancer

CONTRAINDICATIONS TO BREASTFEEDING

Contraindications to breastfeeding	
Maternal	• Active untreated tuberculosis (mothers may start breastfeeding 2 weeks after anti-tuberculin therapy) • Maternal HIV infection (in developed countries where formula is readily available) • Herpetic breast lesions • Varicella infection <5 days before or 2 days after delivery • Chemotherapy or ongoing radiation therapy • Active abuse of alcohol or drugs
Infant	• Galactosemia

Active substance use

- Until pt can demonstrate that she has been off illicit drugs consistently, she should not breastfeed

Alcohol use and abuse

- Mother with alcohol abuse should be advised against breastfeeding

- Occasional maternal alcohol use is not absolute contraindication
- Counsel mother to limit alcohol use to an occasional drink and should not breastfeed for at least 2-3 hours after intake

Smoking

- Not an absolute contraindication to feeding
- Women should be strongly encouraged to quit as it ↑es the risk of **SIDS** and the development of **respiratory allergies** in infants

Influenza

- Women with H1N1 or other strains should be separated from infant while febrile but encouraged to pump

Hepatitis B and C

- Contrary to previous teaching, HCV is not a contraindication to breastfeeding
- Although HCV RNA is detectable in maternal colostrum, transmission of hep C via breastfeeding has never been documented.
- It is **strongly recommended that mothers with both hepatitis B and C breastfeed** whenever possible However, they should be strongly counseled to abstain if their nipples are cracked or bleeding

COMMON PROBLEMS RELATED TO LACTATION

Common problems related to lactation	
Diagnosis	**Clinical features**
Engorgement	Bilateral, symmetric fullness, tenderness & warmth
Nipple injury	Abrasion, bruising, cracking &/or blistering from poor latch
Plugged duct	Focal tenderness & firmness &/or erythema; no fever
Galactocele	Subareolar, mobile, well-circumscribed, nontender mass; no fever
Mastitis	Tenderness/erythema + fever
Abscess	Symptoms of mastitis + fluctuant mass

BREAST ENGORGEMENT

- Can occur 3-5 days after delivery, when colostrum is replaced by milk
- Can occur any time during breastfeeding due to milk accumulation with inadequate drainage, particularly common early in postpartum period when milk production is robust. Intrapartum IV fluid administration can also cause breast edema and exacerbate pain
- Can occur due to rapid cessation of breastfeeding

- **PE: without erythema and fever (**mastitis causes erythema and fever)
- **Management:** lactation suppression if breastfeeding is stopped—accomplished as follows:
  - Wear comfortable, supportive bra—tight bra can cause inadvertent nipple stimulation
  - Avoid nipple stimulation and manipulation
  - Apply ice packs to breast and **NSAIDS**—to ↓ inflammation and pain
  - Breast binding: NOT recommended→ ↑ risk of mastitis, plugged ducts and ↑ pain
  - Medications are also not recommended
  - Engorgement itself leads to events that cause cessation of lactation due to negative inhibition of prolactin release
- **Management** if breastfeeding is to be continued:
  - Cool compresses
  - Acetaminophen and NSAIDS may be used for symptom control
  - Pt should feel improvement in symptoms as regular feeding or pumping is established

LACTATIONAL MASTITIS

Lactational mastitis	
Pathogenesis	Skin flora (eg, *Staphylococcus aureus*) enters ducts through nipple & multiplies in stagnant milk

Risk factors	• Past history of mastitis
	• Engorgement & inadequate milk drainage due to:
	  ◦ Sudden increase in sleep duration
	  ◦ Replacing nursing with formula or pumped breast milk
	  ◦ Weaning
	  ◦ Pressure on the duct (tight bra or clothing, prone sleeping)
	  ◦ Cracked or clogged nipple pore
	  ◦ Poor latch

Clinical presentation	• Fever • Firm, red, tender, swollen quadrant of unilateral breast • +/- Myalgia, chills, malaise
Treatment	• Analgesia • Frequent breastfeeding or pumping • Antibiotics

- Bacteria is also transmitted by infants nasopharynx
- **Direct feeding with both breasts** is the best way to completely drain the milk ducts
- Encourage to nurse infant **every 2-3-hours—**it is safe for infant to consume milk as they are already colonized by bacteria
- **Preferred empiric therapy:**
  - **Methicillin sensitive S. aureus:** dicloxacillin or cephalexin
  - **If MRSA risk factors exist (**e.g. recent antibiotic therapy, residence in long-term care facility, incarceration): clindamycin, TMP-SMX, or vancomycin

BREAST ABSCESS

- Untreated or severe mastitis can lead to formation of breast abscess
- **C/F:** features of mastitis along with a **fluctuant, tender, palpable mass**
- **Dx:** clinical—USG may be required to differentiate severe mastitis from an abscess if a mass is deep within the tissue.
- **Rx:** needle aspiration of breast abscess under ultrasound guidance and antibiotics (e.g. dicloxacillin, cephalexin) for surrounding mastitis—1st line treatment. Continue breastfeeding
- Abscesses not responsive to needle aspiration and antibiotics, suspected necrotic material, and large (>/=5cm) pus collections→**incision and drainage (eg, surgical drainage) with packing** are recommended. Surgical drainage may be required if the overlying skin is thin with imminent abscess rupture.

POINTERS

- ➔ PID is uncommon after first trimester and cervical mucus and decidua seals off and protects uterus from pathogens (e.g. Chlamydia and Gonorrhea) during pregnancy
- ➔ Any systemic infection can trigger preterm labor even if it does not originate from reproductive tract
- ➔ Lead exposure occurs in pts living in home built before 1960
- ➔ Calcium gluconate is used as antidote to magnesium toxicity
- ➔ Lower back pain in 3rd trimester of pregnancy is common – due to ↑ in **lumbar lordosis and relaxation of ligaments supporting the sacroiliac** and other joints of pelvic girdle due to hormonal factors—dull pain and ↑es in intensity by the end of the day
- ➔ Alkaline phosphatase is normally ↑ed in pregnancy
- ➔ USG showing thin endometrial stripe is normal—represent empty uterus with no retained products of conception
- ➔ Labor should be allowed to proceed in patients where the fetus has been diagnosed with a severe congenital anomaly incompatible with life.
- ➔ Cesarean delivery after maternal trauma is indicated for fetal rescue in case of imminent maternal death, to assist with maternal cardiopulmonary resuscitation or due to a category 3 tracing.
- ➔ Fibroids commonly degenerate during pregnancy when they outgrow their blood supply--. Intense, constant abdominal pain with no bleeding
- ➔ Terbutaline—tocolytic—given if there is uterine contraction abnormality like tachysystole (>/=5 contractions in 10 min) or tetanic contractions (lasting > 2min) causing fetal heart rate abnormality

Contents

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions		
	Immunology	**Examples**
Type I (immediate)	IgE-mediated	• Anaphylaxis • Urticaria
Type II (cytotoxic)	IgG & IgM autoantibody-mediated	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	Antibody-antigen complex deposition	• Serum sickness • Poststreptococcal glomerulonephritis • Lupus nephritis
Type IV (delayed type)	T cell- & macrophage-mediated	• Contact dermatitis • Tuberculin skin test

SKIN CONDITIONS AND ASSOCIATED DISEASES

Skin conditions & associated diseases	
Skin conditions	**Important associated conditions**
• Acanthosis nigricans	• Insulin resistance • Gastrointestinal malignancy
• Multiple skin tags	• Insulin resistance • Pregnancy • Crohn disease (perianal)
• Porphyria cutanea tarda • Cutaneous leukocytoclastic vasculitis (palpable purpura) secondary to cryoglobulinemia	• Hepatitis C
• Dermatitis herpetiformis	• Celiac disease
• Sudden-onset severe psoriasis • Recurrent herpes zoster • Disseminated molluscum contagiosum	• HIV infection
• Severe seborrheic dermatitis	• HIV infection • Parkinson disease
• Explosive onset of multiple itchy seborrheic keratoses	• Gastrointestinal malignancy
• Pyoderma gangrenosum	• Inflammatory bowel disease

Or genitourinary malignancy

PIGMENTATION DISORDERS

VITILIGO

- Specific form of leukoderma
- Peaks in 20-30s

Depigmentation has predilection for acral areas and body orifices

- Pale whitish papules with hyperpigmented borders
- **Etiopathology:** autoimmune destruction of melanocytes
- Slowly progressive. Few experience spontaneous remission

PIEBALDISM

- Inherited absence of melanocytes
- Usually noticed at birth

Vitiligo	
Clinical manifestations	• Depigmented macules on acral areas & extensor surfaces; face commonly affected • Lesions may be symmetrical, dermatomal, or unilateral
Clinical course	• Most cases progress gradually • Repigmentation is spontaneous in 10%-20% of cases • Increased incidence of other autoimmune disorders (eg, lupus, thyroid disease, pernicious anemia, Addison disease)
Treatment	• **Limited disease:** Topical corticosteroids • **Extensive/unresponsive disease:** Oral corticosteroids, topical calcineurin inhibitors, PUVA

PUVA = psoralen + ultraviolet A light.

- Confined to head and trunk

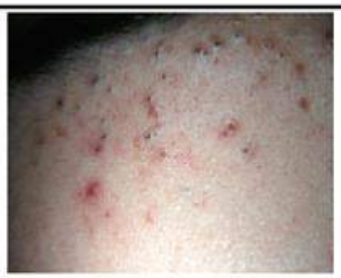
MONGOLIAN SPOTS

- Mongolian spot—congenital dermal melanocytosis—blue-grey macule on patient's sacrum and buttocks.
- Benign birthmarks prevalent in African, Asian, Hispanic and Native Americans
- Usually fade spontaneously during 1st decade
- It is imp. For physicians to document Mongolian spots as they can be mistaken for bruise—raise concern for coagulopathy and abuse
- Skeletal survey is imp in suspected abuse but bruises are tender and more varied in color

COMMON SKIN DISORDERS

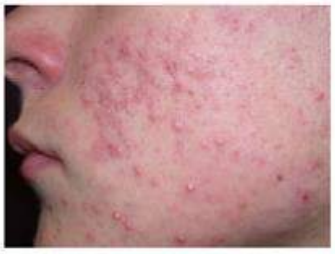
ACNE VULGARIS

Treatment of acne vulgaris



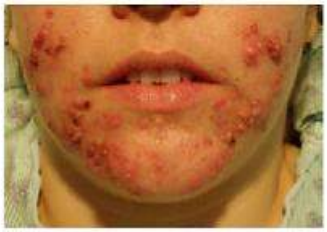
Comedonal acne

- Closed or open comedones on forehead, nose & chin
- May progress to inflammatory pustules or nodules
- Treatment: **Topical retinoids**; salicylic, azelaic, or glycolic acid



Inflammatory acne

- Inflamed papules (<5 mm) & pustules; erythema
- Treatment:
  - Mild: Topical retinoids + benzoyl peroxide
  - Moderate: Add topical **antibiotics** (eg, erythromycin, clindamycin)
  - Severe: Add oral antibiotics



Nodular (cystic) acne

- Large (>5 mm) nodules that can appear cystic
- Nodules may merge to form sinus tracts with possible scarring
- Treatment:
  - Moderate: Topical retinoid + benzoyl peroxide + topical antibiotics
  - Severe: Add oral antibiotics
  - Unresponsive severe: **Oral isotretinoin**

These organic acids are added to retinoids if only retinoids rx fails. Benzoyl peroxide is added if inflammatory features develop

- **Factors contributing to acne vulgaris:** include increased sebum production, follicular hyperkeratinization, bacterial colonization (Propionibacterium acnes), and, in some cases, an inflammatory response

- **S/E of benzoyl peroxide:** can cause photosensitivity reaction but less severe than tetracyclines. Common S/E are irritation, contact dermatitis, dryness, erythema, peeling and stinging

STEROID-INDUCED ACNE OR STEROID INDUCED FOLLICULITIS

- Characterized by monomorphous pink papules on face, trunk and extremities and absence of comedones

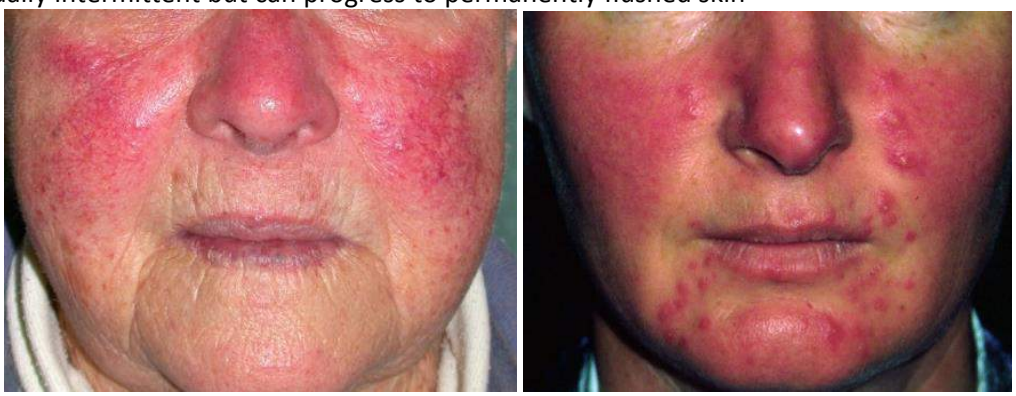
ACNE ROSACEA

Rosacea	
Erythemato-telangiectatic	• Persistent facial erythema/flushing • Telangiectasias
Papulopustular	• Papules & pustules on central face
Ocular	• Conjunctival hyperemia • Lid margin telangiectasias
Treatment	• Avoidance of triggers (eg, alcohol, spicy foods) • Sun protection • Gentle cleansers & emollients • Topical metronidazole for papulopustular type • Laser or topical brimonidine (vasoconstrictive α-2 agonist) for erythematotelangiectatic type

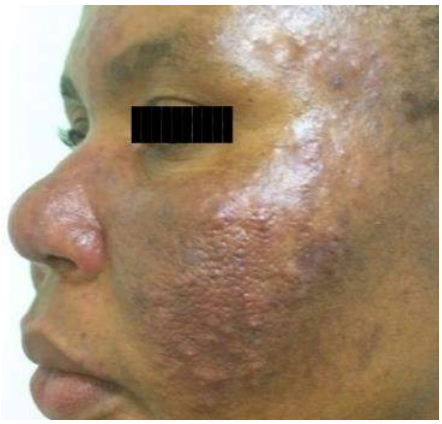
In nose and medial cheeks including nasolabial folds (central face), edema, roughness or scaling (tissue hyperplasia) and burning discomfort

Other triggers: hot drinks, heat, emotion and other causes of rapid body temp. changes

- Typically occur in fair-skinned individuals >30yrs
- Phymatous is another type of rosacea
- **Etiology:** unknown— may be due to chronic inflammatory response to cutaneous micro-organisms, UV light damage or vasomotor dysfunction
- Sx usually intermittent but can progress to permanently flushed skin



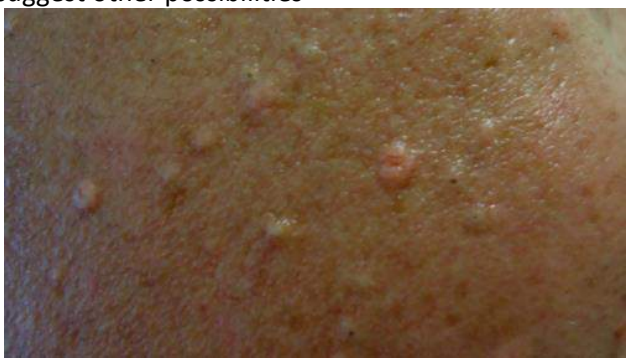
Erythemato-telangiectatic type



Papulopustular type

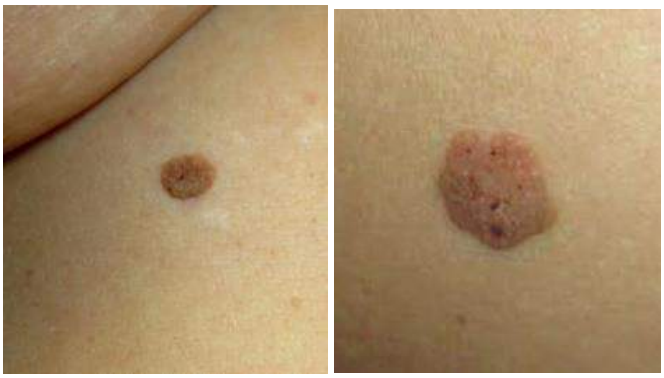
SEBACEOUS HYPERPLASIA

- Common skin disorder characterized by small pale/yellow papules at the central face.
- Lesions are stable in size and appearance;
- Noticeable growth→ suggest other possibilities

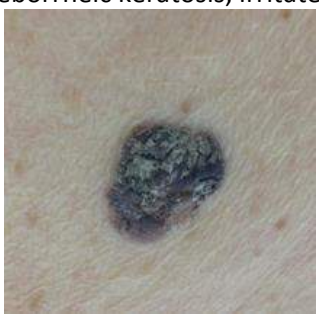


SEBORRHEIC KERATOSIS

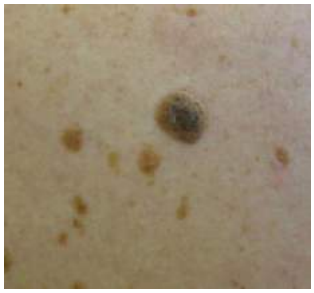
- More common with advancing age
- No sex predilection
- Mostly asymptomatic— can be pruritic or tender, esp. in locations that come into contact with clothing or jewelry.
- Benign growths
- **Common locations**: many locations but favors the face and trunk. Do not occur on the palms and soles.
- **Characteristics:**
  - Characteristic waxy, "stuck on," warty, and well-circumscribed appearance.
  - Some are flat and lie just above the surface of the normal surrounding skin.
  - Scaling on the surface may be present.
  - Colors vary from pink/white to pale brown to dark brown or black.
  - The natural history is slow enlargement with increasing thickness.
- **Dx:** mainly on clinical appearance. Biopsy is rarely required in difficult cases.
- **Management:**
  - No therapy unless the lesions become irritated or the patient desires them removed for cosmetic reasons.
  - **Treatment options**: removal by snip/shave excision, cryosurgery, and electrodessication
- Sudden onset of multiple seborrheic keratoses may indicate an occult internal malignancy (Leser-Trelat sign)



Seborrheic keratosis, irritated



Seborrheic keratosis



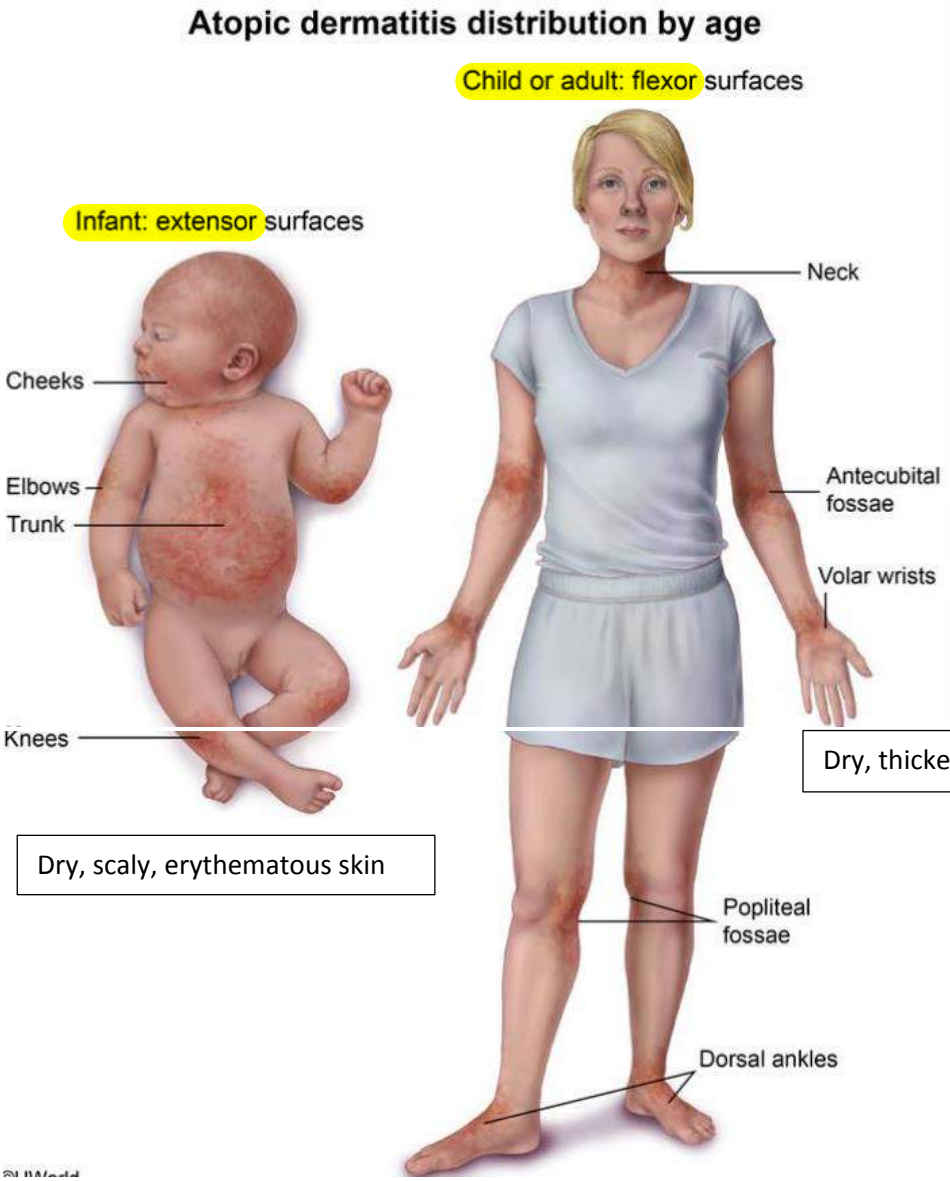
Leser-Trelat sign

ECZEMA/ATOPIC DERMATITIS

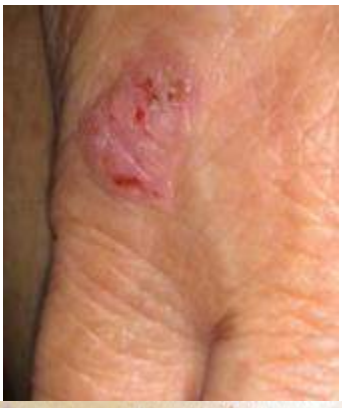
Atopic dermatitis (eczema)	
Risk factors	• Low humidity • Relatives with eczema, allergies, or asthma
Clinical features	• **Infant:** Itchy, red, scaly, crusted lesions on extensor surfaces, trunk, cheeks & scalp • **Child/adult**: Lichenified plaques in flexural creases
Treatment	Topical emollients +/- steroid ointment
Complications	• Eczema herpeticum • Cellulitis/abscess • Discomfort interfering with daily activities & sleep

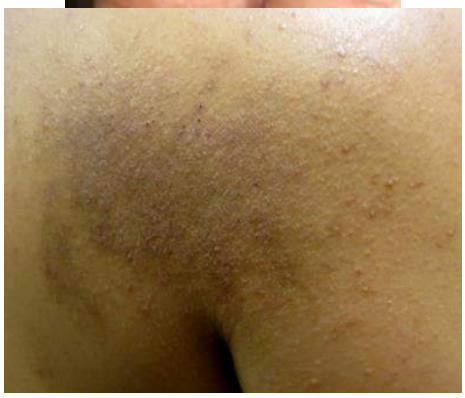
Severe lesions may have serous exudates and crusting

- **Pathogenesis:** epidermal dysfunction due to improper synthesis of stratum corneum components→ allergen enters disrupted skin→ inflammatory response
- **Risk factors:** excessive bathing, dry environments, stress, overheating, and irritating detergents can trigger flares
- **Rx:** trigger avoidance, frequent application of thick, bland emollients, and use hypoallergic cleansers for bathing and laundary



- Eczema in adults usually presents as erythematous plaques with thickened skin, lichenification (increased skin markings), and fibrotic papules with excoriation. The rash is usually pruritic and commonly involves the neck, antecubital fossa, popliteal fossa, face, wrists, and forearms.





Chronic

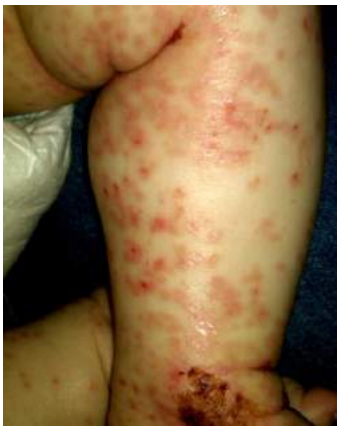
- Inflammation and excoriation→ ↑ risk of superimposed bacterial, viral and fungal infections

INFECTIOUS COMPLIACTIONS OF ATOPIC DERMATITIS

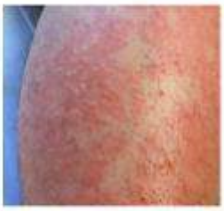
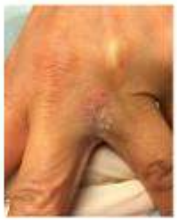
Infectious complications of atopic dermatitis		
Diagnosis	**Pathogen**	**Presentation**
Impetigo	*Staphylococcus aureus* *Streptococcus pyogenes*	Painful, non-pruritic pustules with honey-crusted adherent coating
Eczema herpeticum	Herpes simplex type 1	Painful vesicular rash with "punched-out" erosions & hemorrhagic crusting
Molluscum contagiosum	Poxvirus	Flesh-colored papules with central umbilication
Tinea corporis	*Trichophyton rubrum*	Pruritic circular patch with central clearing & raised, scaly border

ECZEMA HERPETICUM

- Lesions can be localized or disseminated
- Fever, irritability and LAD is common
- Can be fatal in infants
- Systemic acyclovir—give asap



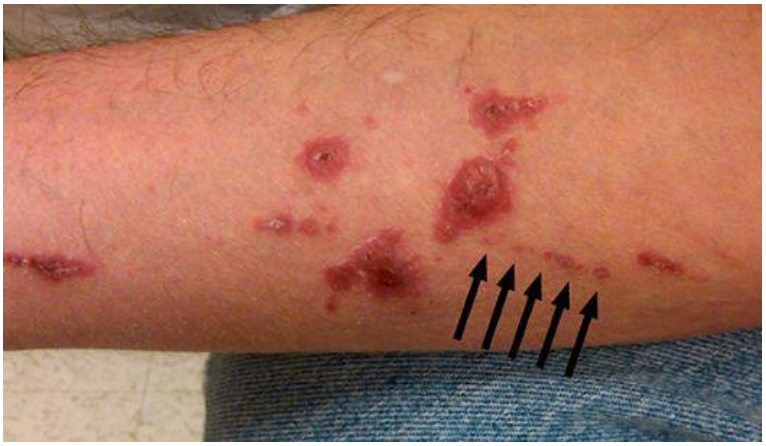
CONTACT DERMATITIS

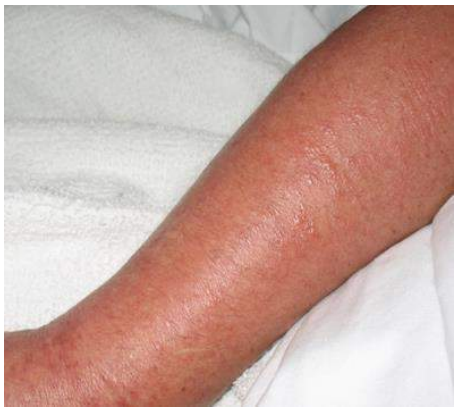
Contact dermatitis		
	Allergic 	**Irritant** 
Pathophysiology	Type IV hypersensitivity	Physical or chemical irritation
Triggers	• Poison oak/ivy/sumac • Nickel • Rubber/latex • Leather dyes • Medications	• Soaps/detergents • Chemicals • Acid/alkali
Appearance	• Primarily on exposed skin, well demarcated • Erythema • Papules/vesicles • Chronic lichenification	• Commonly on hands • Erythema • Fissures

ALLERGIC CONTACT DERMATITIS

- Toxicodendron (formerly Rhus) (poison ivy/oak/sumac)—grow as small shrubs or vines→ produce urushiol, a highly allergenic resin—most common in undeveloped and wooded areas but be present urban and suburban areas not properly maintained
- Rash appears days after exposure—frequently form linear streaks where skin has brushed against plant leaves

- Diffuse or atypical can occur after exposure to contaminated cloth, pets and smoke from burning plants
- **Management**:
  - Typically resolve within 1-3wks
  - **Prevention:** allergen avoidance (long-sleeved shirts, pants)
  - **Rx:** ↓ post-exposure spread (e.g. remove exposed clothes, wash fingernails) and topical/oral steroids
- **Metals that can cause ACD:** nickel, chromium, cobalt, beryllium and zinc. Copper causes greenish discoloration of skin and not ACD. Metal→ sweat→ forms metal ions→ HS reaction. Gold, silver, platinum and titanium do not cause ACD
- Most pts respond to low to mid potency topical corticosteroids and elimination of exposure to allergen





Acute allergic contact dermatitis

IRRITANT CONTACT DERMATITIS

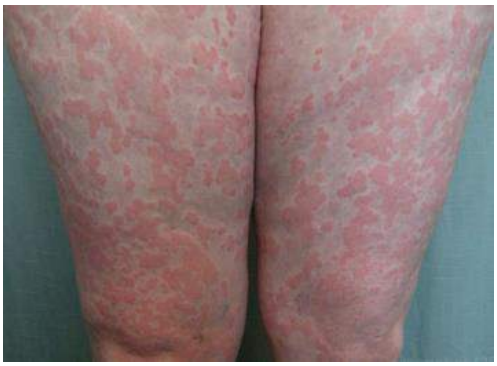
- It is non-immunologically mediated but can resemble allergic contact dermatitis with pruritis, erythema, local swelling and vesicles
- Sx can develop acutely but are often chronic, leading to excoriations, hyperkeratosis, and fissuring of involved skin
- **Management:**
  - Emollients and use of protective barriers often relieve symptoms
  - Identification and avoidance of offending agent—essential but difficult to figure out
  - Dx is usually clinical but if initial measures do not clear rash→ perform biopsy

URTICARIA

Clinical features of acute urticaria	
Clinical presentation	• Well-circumscribed, raised erythematous plaques • Lesions can be oval, round, or serpiginous up to several centimeters in diameter • Intense pruritus • Lesions can worsen over minutes to hours, then resolve within 24 hours
Acute **Etiologies**	• Infections (viral, bacterial, parasitic) • IgE mediated (antibiotics, insect bites, latex, food, blood products) • Direct mast cell activation (narcotics, muscle relaxers, radiocontrast medium) • NSAIDs • Idiopathic (up to 50% of patients)

NSAID = nonsteroidal antiinflammatory drug.

- Acute urticaria last <6wks and chronic lasts >6wks
- **Etiology of chronic urticaria:** physical stimuli (eg, cold temperature, skin pressure), serum sickness, or systemic disorders (eg, autoimmune disease, vasculitis, malignancy)
- **Pathophysiology:**
  - Due to mast cell activation in superficial dermis→ ↑ release of inflammatory mediators (e.g. histamine)→ pruritis and localized swelling in upper layers of skin
  - Mast cell activation in deeper layers and subcutaneous tissue (e.g. hands, face and buttocks)→ can cause angioedema→ can occur with or without urticaria—typically presents as non-pitting and non-pruritic edematous swelling involving subcutaneous tissues, abdominal organs, or the upper airway.



SERUM SICKNESS LIKE REACTION

- Type III HS reaction

Serum sickness-like reaction	
Etiology	Antibiotics (β-lactams, sulfa) most common
Clinical features	• Fever, urticaria & polyarthralgia 1-2 weeks after first exposure • Headache, edema, lymphadenopathy & splenomegaly less common
Treatment	• Remove/avoid offending agent • Steroids for severe cases

No mucosal involvement

Usually resolves symptoms in 48 hours

Although not a true allergic reaction, still avoid to prevent recurrence

- Labs: non-specific hypocomplementemia and elevated inflammatory markers (ESR, CRP)—consistent with any type III HS reaction

BLUE NEVI

- Smooth-surfaced, dome-shaped melanocytic papules that develop from macules and tend to be less than 1cm in diameter. They have a blue color due to the depth of the melanin in the skin.

MELANOCYTIC NEVI

- Melanocytic nevi are common benign lesions found in the integument of most individuals. They typically obey the ABCDE rules.

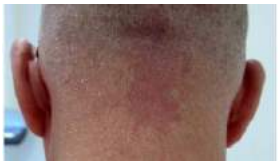
LENTIGO SIMPLEX

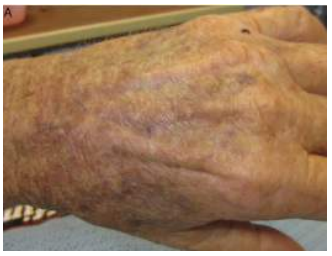
- Lentigo simplex is clinically characterized by a round or oval macule with even pigmentation
- They are the result of intraepidermal melanocyte hyperplasia

ACROCHORDON

- Skin tags
- Flesh-colored or pedunculated papules
- Occur in regions subjected to friction like neck, axillae, and inner thigh

Nevus simplex (eg, macular stain, salmon patch, stork bite, angel kiss)
- **blanchable,** pink-red patches that most commonly occur on the eyelid, glabella, and midline of the nape of the neck.
- They are typically present at birth and fade spontaneously by age 1-2, although **neck** lesions may persist with no sequelae.





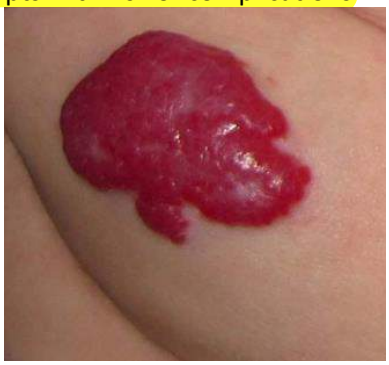
SENILE PURPURA (solar or actinic purpura)

- Non-inflammatory disorder
- Common in elderly, but can also be seen in middle aged with ↑ sun exposure
- Due to loss of elastic fiber in perivascular CT
- Minor abrasions that normally stretch skin in younger pt, can cause rupture of superficial BV in elderly→ ecchymosis in vulnerable areas like dorsum of hand and forearms→ residual brownish discoloration from hemosiderin
- ↑ incidence in pts on anticoagulants, corticosteroids and NSAIDS
- Usually not dangerous and no need of further investigation if all labs are normal
- Severe senile purpura→ pts may require extra wound care following even minor lacerations

VASCULAR TUMORS OF SKIN

STRAWBERRY (SUPERFICIAL INFANTILE) HEMANGIOMA

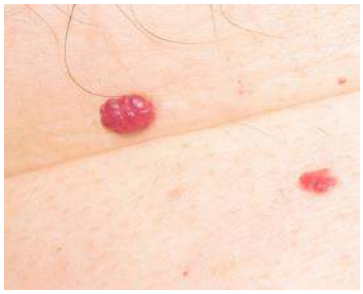
- Most common benign vascular tumor of children
- Composed of capillaries separated by connective tissue—superficial, well demarcated and lanch with pressure
- Can occur in deep tissues and viscera e.g. liver
- Appear during the first days to weeks of birth
- Initially grow rapidly during 1-2 yrs and then frequently regress spontaneously by age 5-8, usually with minimal consequence
- Bright red when near the epidermis and more violaceous when deeper
- Minority can be disfiguring, ulcerating, disabling (e.g. strabismus from eyelid hemangioma), or life threatening e.g. tracheal lesions
- **Management:** beta blockers for pts with risk of complications



CHERRY ANGIOMA OR SENILE HEMANGIOMA

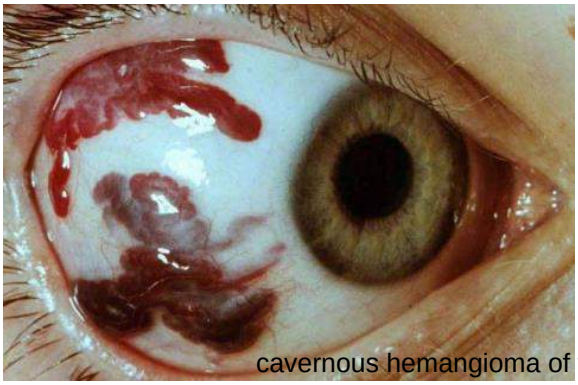
- Most common benign vascular tumor in adults
- Typically 1st seen in 3rd or 4th decade of life—no. ↑es with age

- **Appearance:** sharply circumscribed areas of congested capillaries and post-capillary venules in the papillary dermis.
- Always cutaneous and not found in mucosa and deep tissues
- Do not regress spontaneously and may bleed if disrupted
- **Rx**: not needed other than cosmetic reasons



CAVERNOUS HEMANGIOMA OR CAVERNOUS MALFORMATIONS

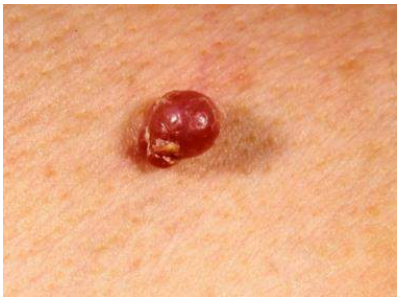
- Consist of dilated vascular spaces with thin-walled endothelial cells.
- **C/F:** soft blue, compressible masses growing up to a few centimeters.
- **Locations:** May appear on the skin, mucosa, deep tissues, and viscera.
- Cavernous hemangiomas of the brain and viscera are associated with von Hippel-Lindau disease



cavernous hemangioma of the conjunctiva

PYOGENIC GRANULOMA

- Benign vascular skin tumor
- **Presents as** a small red papule that grows rapidly over weeks or months to a pedunculated or sessile shiny mass.
- **Common locations:** lip and oral mucosa and can bleed with minor trauma.

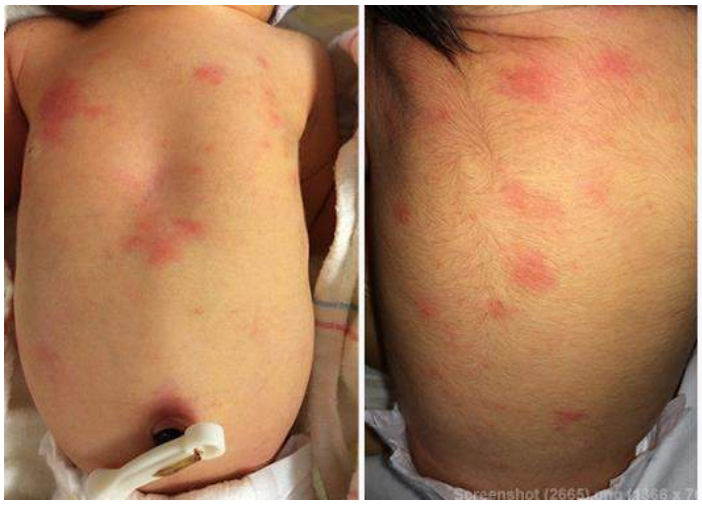


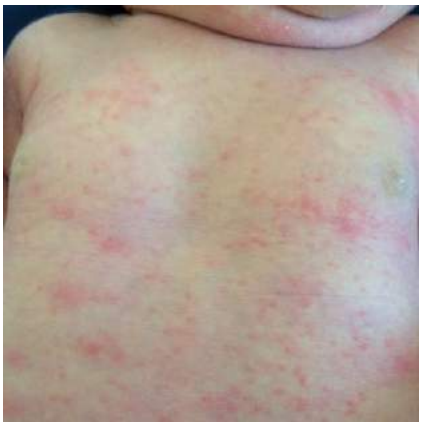
COMMON NEONATAL RASHES

Neonatal rashes		
Diagnosis	**Clinical presentation**	**Treatment**
Erythema toxicum neonatorum	Asymptomatic, scattered erythematous macules, papules & pustules throughout the body	None
Neonatal HSV	Three patterns • Vesicular clusters on skin, eyes & mucous membranes • Central nervous system infection • Fulminant, disseminated multi-organ disease	Acyclovir
Neonatal varicella	Fever; ranges from vesicular clusters on skin to fulminant, disseminated disease	Acyclovir
Staphylococcal scalded skin syndrome	Fever, irritability & diffuse erythema followed by blistering & exfoliation, positive Nikolsky's sign	Oxacillin, nafcillin, or vancomycin

ERYTHEMA TOXICUM NEONATORUM

- Benign and evanescent
- Appears in 1st 2 wks of life—common in full term infants
- Rash can change appearance— spares palms and soles
- Etiology unknown
- Reassure parents—as it resolves without sequel
- Workup is rarely necessary—if presentation is atypical, skin biopsy with a sterile pustule and numerous eosinophils support ETN





SKIN INFECTIONS

BACTERIAL INFECTIONS

IMPETIGO

Impetigo		
Type	**Non-bullous**	**Bullous**
Microbiology	• *Staphylococcus aureus* • Group *A Streptococcus (S pyogenes)*	• *S aureus*
Clinical features	• Painful non-pruritic pustules • Honey-crusted lesions	• Rapidly enlarging flaccid bullae with yellow fluid • Collarette of scale at periphery of ruptured lesions
Treatment	• Limited skin involvement: Topical antibiotics (eg, mupirocin) • Extensive skin involvement: Oral antibiotics (eg, cephalexin, dicloxacillin, clindamycin)	

Nonbullous impetigo	
Microbiology	• *Staphylococcus aureus* • Group A beta-hemolytic *Streptococcus (S pyogenes)*
Clinical features	• Painful non-itchy pustules & honey-crusted lesions
Treatment	• Topical antibiotics (eg, mupirocin)
Complications	• Poststreptococcal glomerulonephritis

- Common pediatric infection→ contagious→ thorough hand washing prevents spread
- Starts with erythematous papules→ rapidly evolve into painful pustules→ over a course of week, rupture→ honey-crusted exudates
- Systemic Sx like fever typically absent. Local LAD may be present
- **Predisposing factors**: warm and humid climate, poverty/crowding, poor personal hygiene, and pre-existing skin trauma/inflammation (eg, insect bite, eczema, abrasion). Colonization with staphylococci or streptococci is also a risk factor→↑ risk of superinfection
- Extensive bullous impetigo is an additional indication for oral antibiotics.

ERYSIPELAS AND CELLULITIS

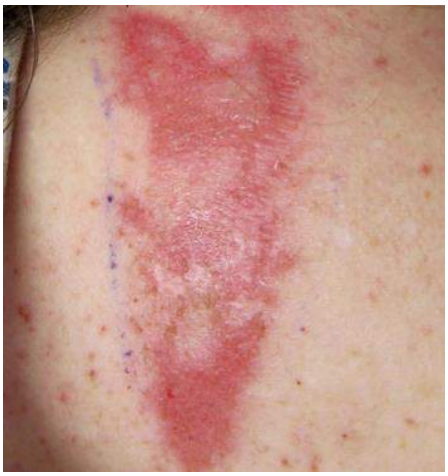
Common skin infections		
Infection	**Organism**	**Manifestations**
Erysipelas	• *Streptococcus pyogenes*	• **Superficial** dermis & lymphatics • Raised, sharply **demarcated edges** • **Rapid** spread & onset • **Fever** early in course
Cellulitis (nonpurulent)	• *S pyogenes* • MSSA	• **Deep** dermis & subcutaneous fat • **Flat edges** with poor demarcation • **Indolent** (over days) • Localized (fever later in course)
Cellulitis (purulent)	• MSSA • MRSA	• Purulent drainage • Folliculitis: Infected hair follicle • Furuncles: Folliculitis → dermis → abscess • Carbuncle: Multiple furuncles

ERYSIPELAS

- Infection limited to epidermis and superficial dermis
- Begins as a small erythematous patch→ progresses to a red, indurated, tense, and shiny plaque.
- The presence of a raised, sharply demarcated margin is a classic feature.
- Overlying skin streaking and regional LAD indicate lymphatic involvement

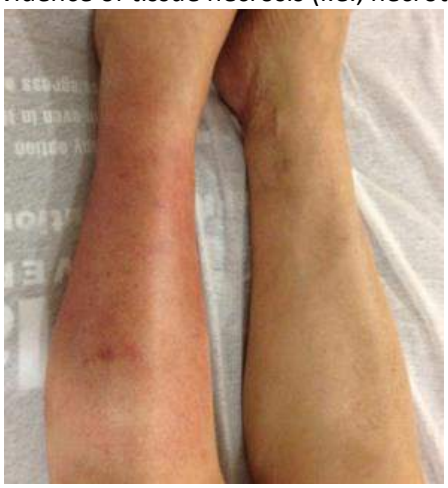
Tx:
1. oral Amoxicillin
2. IV Ceftriaxone (used in most pts)

- These patients usually have fever and chills.



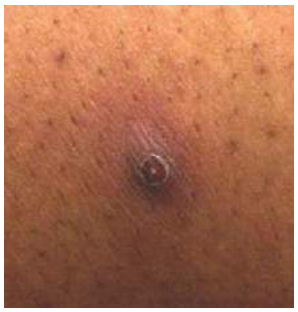
CELLULITIS

- Infection of skin and subcutaneous tissue
- **Risk factors:** obesity, venous insufficiency and disruption of skin (e.g. Tinea pedis infection). Chronic fungal foot infection can serve as a nidus of bacterial cellulitis → eradicate in pts with recurrent cellulitis
- **Pathophysiology:** disrupted skin barrier→ bacteria enters→ invade dermis (erythema, edema) and may reach lymphatics (steaking, regional LAD)
- **Sx**: local and systemic
  - **Local Sx:** generalized swelling which is erythematous, warm, tender and less- well demarcated than erysipelas
  - **Systemic Sx:** fever may or may not be present. Signs of toxicity like high grade fever with chills and rigors, fatigue, hypotension, malaise and confusion—may or may not be present
- **Rx:**
  - **Mild cellulitis without systemic Sx:** oral dicloxacillin
  - **Severe cellulitis with extensive involvement, rapidly progressing infection or signs of systemic involvement (e.g. hypotension, tachycardia):** IV nafcillin or cefazolin are DOC. In areas with high prevalence of MRSA, vancomycin can be used as 1st line agent.
  - Surgical drainage is reserved for patients with abscesses (more common with staphylococcal cellulitis) or those with evidence of tissue necrosis (i.e., necrotizing fasciitis)



Furuncle

- Skin abscess due to S. aureus infection
- Presents as a painful pustule or nodule, typically draining purulent material



ORBITAL CELLULITIS VS PRESEPTAL CELLULITIS

Symptom/Sign	Preseptal Cellulitis	Orbital Cellulitis
Eyelid edema	+	+
Eyelid erythema	+	+
Eyelid tenderness	+	+
Fever	+/-	+/-
Leukocytosis	+/-	+/-
Ophthalmoplegia	-	+
Pain with extraocular movements	-	+
Proptosis	-	+/-
Vision impairment	-	+/-

- Both may have overlapping features but clinical consequences are very different
- Both types of cellulitis can result from local trauma (e.g., insect bite, wound) or by extension from another source of infection (e.g., sinusitis, dental abscess)

PRESEPTAL CELLULITIS

- Mild infection of eyelid anterior to orbital septum
- **Rx:** Can be treated with outpatient oral antibiotics

ORBITAL CELLULITIS

- Serious infection posterior to orbital septum
- Most commonly identified organisms: S. aureus, S. pneumoniae, and other streptococci—bacterial sinusitis most common predisposing factor due to prevalence, proximity of sinuses to orbital space and valveless orbital venous system

- **Rx:** inpatient treatment with IV antibiotics and monitor closely for complications
- **Complications:** Dangerous complications due to valveless ophthalmic venous system: abscess within orbit or brain, subperiosteal abscess, blindness or **cavernous venous sinus thrombosis** (headache is most common early manifestation and can become unbearable, periorbital edema, exophthalmos and chemosis, fundoscopy shows papilledema, and dilated tortuous retinal veins. Usually begins U/l but within 24-48 hours, spread to other eye. Signs of CN III, IV, V and VI present)
- Diagnosis unclear→ perform CT scan to help identity inflammation or abscesses within orbit and to determine whether infection has spread posterior to orbital septum and to detect abscesses requiring surgery

NECROTIZING FASCIITIS

Features of necrotizing fasciitis	
Microbiology	• *Streptococcus pyogenes* (group A streptococci) • *Staphylococcus aureus* • *Clostridium perfringens* • Polymicrobial
Pathogenesis	• Bacteria spread rapidly through subcutaneous tissue & deep fascia, undermining the skin • Most commonly involves extremities & perineal region
Clinical manifestations	• Often antecedent history of minor trauma • Erythema of overlying skin • Swelling & edema • Pain **out of proportion** to examination findings • Systemic symptoms (eg, **fever & hypotension**)
Treatment	• Requires **surgical debridement** & broad-spectrum antibiotics

- **Crepitus** can be felt because of air produced by bacteria in tissue
- Necrotizing fasciitis can also result from peripheral vascular dis. Like diabetes.
- Group A strep is most frequently cultured from lesions but it is usually polymicrobial
- Pain usually precedes systemic symptoms
- Untreated lesion can lead to rapid discoloration of affected area, purulent discharge, bullae and necrosis.
- Imaging reveals extent of tissue involvement and air in tissue. Treatment should be started asap without further imaging if there is high suspicion
- High morbidity and mortality even with treatment because of rapid spread
- **Pyomyositis:** has similar systemic findings but it is confined to one muscle group and less rapid spread. No air on imaging

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

- Syndrome of acute exfoliation of skin
- **Cause:** exfoliative-toxin producing strains of **Staphylococcus aureus**→ toxin targets desmoglein 1 in superficial dermis

- **C/F:**
  - **Prodrome:** fever, irritability, skin tenderness→
  - Erythema starts on face→ generalizes within 24-48 hours→
  - Superficial flaccid bullae (+ve Nikolsky—fragile bullae, when unroofed, reveal moist erythematous base) with flexural accentuation and perioral crusting→
  - Scaling, desquamation, extensive exfoliation of skin continue for about 5 days. Whole process usually resolves within 1-2 wks
  - The skin is tender and warm, with a sandpaper-like, diffuse erythematous rash
  - **Other features**: facial edema, perioral crusting, and dehydration
- **Common age group:**
  - Most common in infancy and rarely occurs beyond 5 years of age→ ↓ mortality
  - Adults with renal disease or immunocompromised may also be affected → ↑ mortality
- **Management:**
  - Culture of intact bullae→ sterile as dis. is toxin mediated
  - Eliminate any inciting focus of infection with appropriate anti-staphylococcal antibiotics
  - Supportive wound care of all denuded areas

SCARLET FEVER

- **Cause:** group A β-hemolytic streptococcus that produce erythrogenic exotoxin
- **Mode of transmission and age of distribution:** same as that for streptococcal pharyngitis
- **May follow:** streptococcal pharyngitis, tonsillitis, wound infections, burns or streptococcal skin infection
- **Incubation period:** begins acutely after incubation period of 1-7 days
- **Disease progression:**
  - Prodrome: fever, headache, vomiting, chills, toxicity, abdominal pain, pharyngitis
  - Within 12-48 hours: fine, pink blanching papular rash (rough, sandpaper like) appear on neck, axillae, upper trunk and groin
  - Within 24 hours: rash generalizes
  - Towards the end of 1st week: desquamation begins in the face, progresses down the trunk and finally extends to hand and feet
- **PE:**
  - **Characteristic of rash:** punctate or finely papular texture which is sometimes palpable, hence "sandpaper like"
  - Pharynx is typically swollen, erythematous, and possibly covered with gray-white exudates, strawberry tongue
  - Cheeks extremely red and area around moth appears pale—"circumoral pallor"
- **Rx:** penicillin V (drug of choice). Erythromycin, clindamycin, and 1st generation cephalosporins—good alternatives for penicillin allergic pts

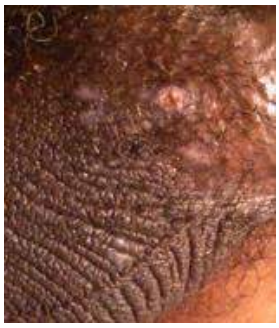
FELON

- Tailors can develop felon due to needle injuries.
- It is important to distinguish felon from whitlow.
- Felon is a bacterial infection of the distal volar space, characterized by a tense abscess (non-purulent vesicle in whitlow) and intense throbbing pain.
- Incision and drainage with appropriate antibiotic (e.g., cephalosporins) is the treatment of choice.

CONDYLOMATA LATA

- Manifestation of secondary syphilis

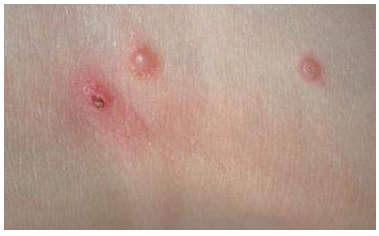
- Characterized by flattened pink or gray velvety papules
- These are seen most commonly at the mucous membranes and moist skin of the genital organs, perineum, and mouth



VIRAL INFECTIONS

MOLLUSCUM CONTAGIOSUM

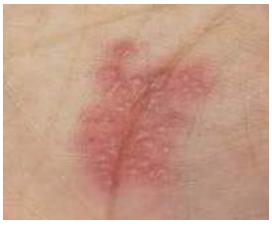
- **Cause:** poxvirus
- **Transmission:**
  - Skin-to-skin contact or via
  - Contaminated fomites→ subsequent autoinoculation to additional sites.
  - Sexual contact
- **Affected pts:** more common in children but adolescents and adults may also be affected
- **Characteristics:** small, pruritic, skin colored papules with umbilicated centers
  - **In children:** commonly on extremities, face or trunk—can occur anywhere except palms and soles
  - **In adults:** sexual transmission may lead to lesions on lower trunk and anogenital region
  - Pts with **impaired cellular immunity** (e.g. HIV infection)→ may have prolonged course with widely distributed papules, facial involvement, large lesions (>10mm) and lesion count numbering in hundreds → consider **HIV testing** 💬
  - Lesions may be widely scattered and may occur in a linear pattern due to spread of infection to adjacent area due to scratching
- **Dx:** primarily clinical based on clinical appearance of lesions
- **Management:**
  - Self-limited usually in 6-12 months
  - Rx with curettage, cryotherapy, or topical agents (e.g. podophyllotoxins)—may be considered to prevent further spread, ↓ symptoms, or improve cosmesis



HERPETIC WHITLOW

- Systemic symptoms may also be present like fever and LAD
- Self-limiting; however, oral acyclovir and topical bacitracin may be used to prevent secondary infection

- adult infections are acquired from contact with genital herpetic lesions or infected orotracheal secretions.
- grouped vesicles on an erythematous base.
- Tingling, burning, and **pain** are common.
- resolve spontaneously within 2-3 weeks.



SHINGLES

- Usually present with a rash that starts as erythematous papules and evolves into vesicles or bullae, with subsequent crusting in 7-10 days
- The rash is usually limited to 1 or 2 dermatomes
- Mostly pain precedes the rash
- **Rx:** antivirals (e.g. acyclovir, famcyclovir or valacyclovir)-- ↓ duration of sx and incidence of post-herpetic neuralgia

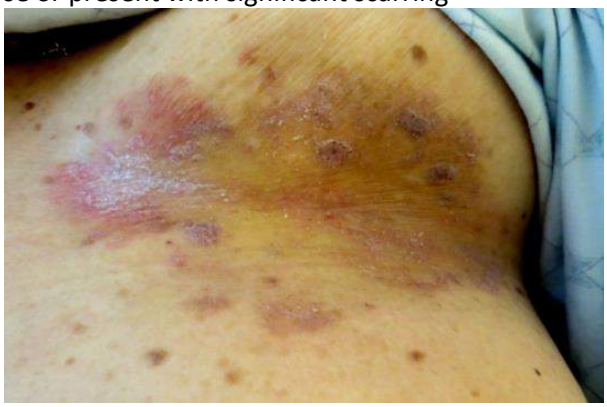
CONDYLOMATA ACCUMINATA (anogenital warts)

- Caused by HPV—most common STD in US
- **C/F:** characteristic lesions are verrucous, papilliform, and either pink or skin-colored.
  - Usually asymptomatic but may have itching or burning
  - Systemic sx absent
- **Dx:**
  - Clinical
  - Biopsy in atypical cases
- **HPV infection (**esp. serotypes 16 and 18)—associated with ↑ risk of SCC of anus, genital organs and throat
- ↑ risk of other STDs, esp. HIV→ offer HIV testing
- **Management:**
  - Usually self-limited in most cases. If specific Rx is required, treatment options include:
    1. Chemical or physical agents (eg, trichloroacetic acid, podophyllin)
    2. Immune therapy (eg, imiquimod)
    3. Surgery (eg, cryosurgery, excision, laser treatment)

FUNGAL INFECTIONS

INTERTRIGO

- Due to infection with **Candida species** and presents as well-defined, erythematous plaques with satellite vesicles or pustules in intertriginous and occluded skin areas.
- Do not have chronic course or present with significant scarring



Inframammary intertrigo

- Topical nystatin is used for Candidal skin infections

TINEA CAPITIS

Tinea capitis	
Clinical features	• Scaly erythematous patch on scalp • Hair loss with residual black dot • Possible painful lymphadenopathy • Predominant in African Americans • Human-to-human or fomite (eg, shared combs) transmission
Management	• KOH examination of hair shaft to document spores • Treatment: **Oral griseofulvin (1st line)**, terbinafine, itraconazole, or fluconazole

KOH = potassium hydroxide.

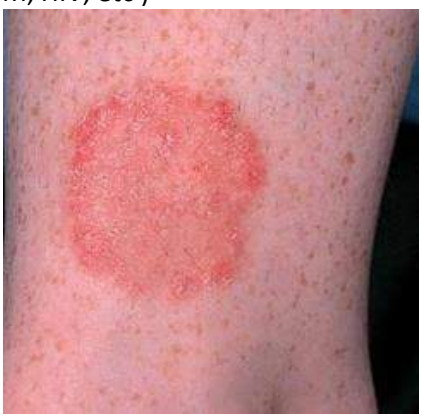
- Most commonly occur in small children. Can occur in immunocompromised adults
- **Most common type in US**: black dot tinea capitis—caused by *Trichophyton tonsurans*. Loss common causes*: Microsporum canis* and *Microsporum audouinii*
- As dermatophyte carriers can be asymptomatic, many experts recommend treating household contacts with selenium sulfide or ketoconazole shampoo

TINEA CORPORIS

Tinea corporis (ringworm)	
Risk factors	• Athletes who have skin-to-skin contact • Humid environment • Contact with infected animals (eg, rodents)
Presentation	• Scaly, erythematous, pruritic patch with centrifugal spread • Subsequent central clearing with raised annular border
Treatment	• First-line/localized: Topical antifungals (eg, clotrimazole, terbinafine) • Second-line/extensive: Oral antifungals (eg, terbinafine, griseofulvin)

2% antifungal lotions and creams—continue until lesion resolves—may take up to 3 wks

- **Cause:** Any species of dermatophyte, but *Trichophyton rubrum* is the most frequent culprit
- **Most predominant symptom**: itching
- **Dx:** clinical but skin scrapings and microscopic examination using KOH is confirmatory for atypical and refractory cases → reveal the presence of hyphae.
- **Rx:**
  - Patients with extensive disease should be investigated for underlying disorders that cause immunosuppression (eg. DM, HIV, etc)



TINEA VERSICOLOR

Tinea versicolor (pityriasis versicolor)	
Pathogenesis	*Malassezia globosa* skin flora grows in exposure to hot & humid weather
Clinical features	• Hypopigmented, hyperpigmented, or mildly erythematous lesions (face in children, trunk & upper extremities in adolescents & adults) • +/- Fine scale • +/- Pruritus
Diagnosis	KOH preparation shows hyphae & yeast cells in a "spaghetti & meatballs" pattern
Treatment	Topical ketoconazole, terbinafine, or selenium sulfide

KOH= potassium hydroxide.

- These pigment changes may take months to resolve

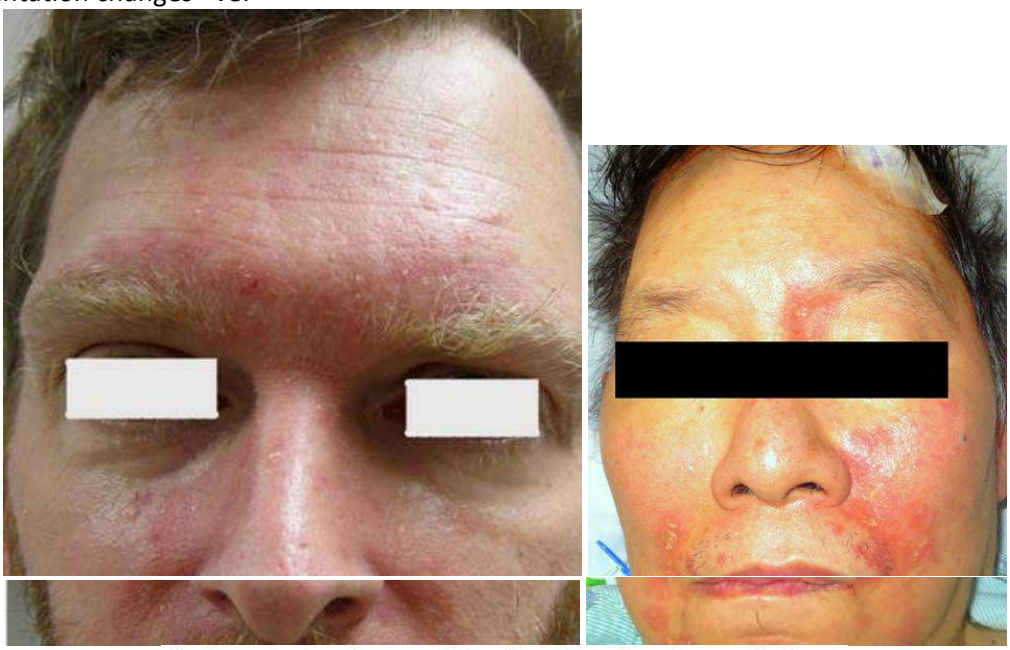
SEBORRHEIC DERMATITIS

Seborrheic dermatitis	
Clinical features	• Peaks in infancy & adulthood • Erythematous plaques &/or yellow, greasy scales • Located on scalp, face (eg, eyebrows/eyelids, posterior ears, nasolabial folds), umbilicus, diaper area
Treatment	• First-line: Emollients, nonmedicated shampoos • Second-line: Topical antifungals or low-potency glucocorticoids

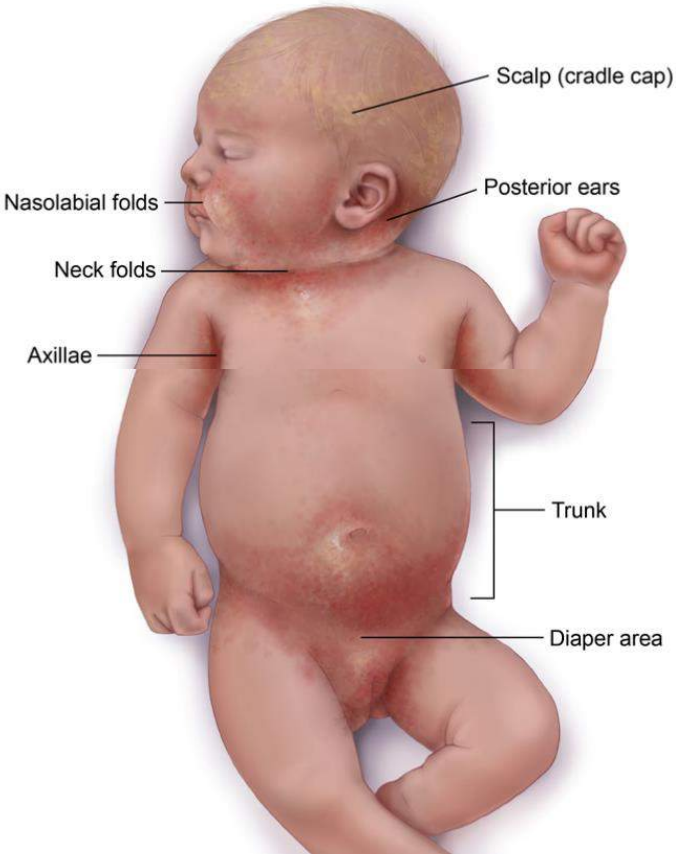
Rx is not always needed as spontaneous resolution is common

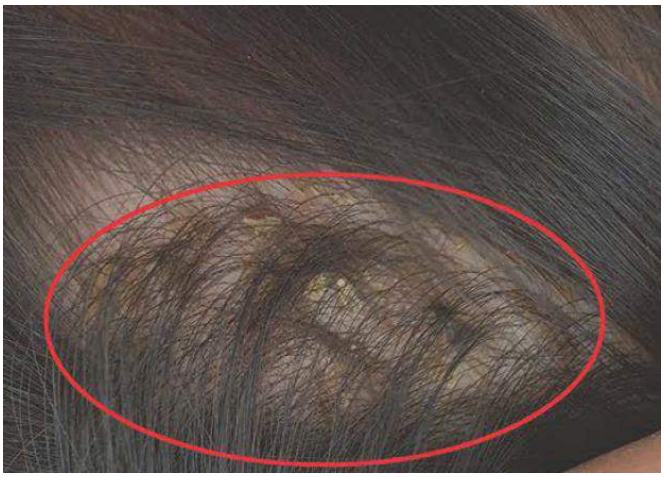
- Acute or chronic papulosquamous dermatitis
- Common inflammatory disease
- **Common locations:** Primarily affects areas with numerous sebaceous glands, although sebum production in affected patients is typically normal
  - Scalp (dandruff)
  - Face (in the skin folds around eyebrows, nasolabial folds, and external ear canal/posterior ear)
  - Chest
  - Intertriginous areas
  - Interscapular area
  - Umbilicus

- **Age group:** all ages but most common in the first year of life and again at age 30-60.
- **Associations:** also associated with central nervous system disorders (especially **Parkinson disease**) and HIV
- **Dx:** clinical, with typical findings characterized by **pruritic, erythematous plaques with fine, loose, yellow, and greasy-looking scales.**
- **Pathogenesis:** Malassezia species may play a role
- **Rx: topical antifungal agents (eg, ketoconazole, selenium sulfide)**
- Pigmentation changes –ve.



Seborrheic dermatitis distribution in an infant





Cradle scalp

PARASITIC INFECTION

SCABIES

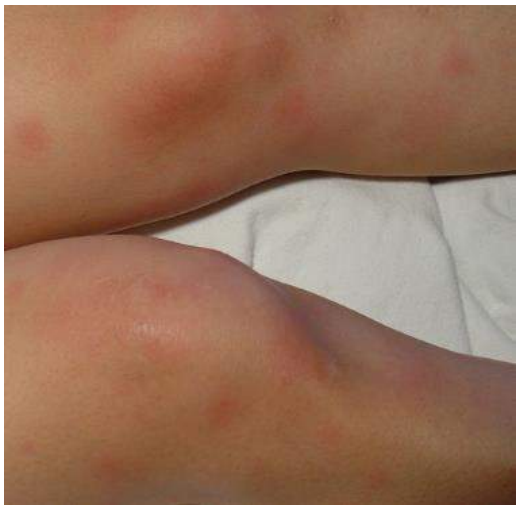
- **Cause:** infestation by the **Sarcoptes scabiei mite**— burrows into the skin
- **Spread:** direct person-to-person contact
- **Presentation:**
  - Intensely pruritic rash (often worse at night)
  - **Common locations:** flexor surfaces of the wrist, lateral surfaces of the fingers, and the finger webs.
  - **Other parts that can be involved:** eg, elbows, axillary folds, nipples and areola in women, scrotum and penis in men. Rarely seen on the back and head (except in children).
- **Pathophysiology:** Rash is due to a **delayed type IV HS** reaction to the mite (feces and eggs included).
- **PE:**
  - **S**mall, crusted, red papules scattered around the region (sometimes with **linear burrows**).
  - Small vesicles, pustules, wheals, and extensive excoriations that can obscure the classic burrows in the skin can also develop.
  - Often mimics other conditions (eg, eczema, tinea, seborrheic dermatitis).
- **Dx**: confirmed by skin scrapings from lesions revealing mites, ova, and feces under light microscopy.
- **Rx**:
  - **Topical permethrin 5% cream** (applied from the neck down and left overnight)

    or
  - **Oral ivermectin** are preferred for treating adults.
  - Antihistamines or low-potency topical steroids can be added to treat the dermatitis.
  - Bedding and clothing should be cleaned or placed in a plastic bag for at least 3 days as the mite can only live away from human skin for 2-3 days.

ERYTHEMA NODOSUM

- Inflammation of subcutaneous fat cells

- Results in red, tender, discrete pretibial nodules.
- Multiple, tender, erythematous subcutaneous nodules/plaques on lower extremities—arthralgia and malaise can develop alongside nodule
- Thought to represent delayed hypersensitivity reaction to antigens associated with various conditions
- **Causes**: medications, infections like streptococcal infection, TB, coccidioidomycosis or autoimmune disease like Sarcoidosis, IBD and Behcet disease but itself is not infectious
- relatively benign
- Can be an early sign of more serious disease – identify cause to prevent morbidity
- Do not usually ulcerate—resolve in 2-8 wks without scarring
- **Initial workup**: basic laboratory tests (CBC, liver function, renal function), antistreptolysin-O antibodies and TB skin test. In addition, Chest X-ray done to assess for findings consistent with sarcoidosis (absence of pulmonary symptoms does not rule out sarcoidosis) and TB



BLISTERING SKIN DISORDERS

BEHCET SYNDROME

Behçet disease	
Epidemiology	• Young adults • Turkish, Middle Eastern, or Asian descent
Clinical findings	• **Recurrent**, painful **oral aphthous ulcers** • **Genital** ulcers • Eye lesions (eg, uveitis) • Skin lesions (eg, erythema nodosum, acneiform lesions) • Thrombosis
Evaluation	• **Pathergy** - Exaggerated skin ulceration with minor trauma (eg, needlestick) • **Biopsy** - Nonspecific vasculitis of different-sized vessels

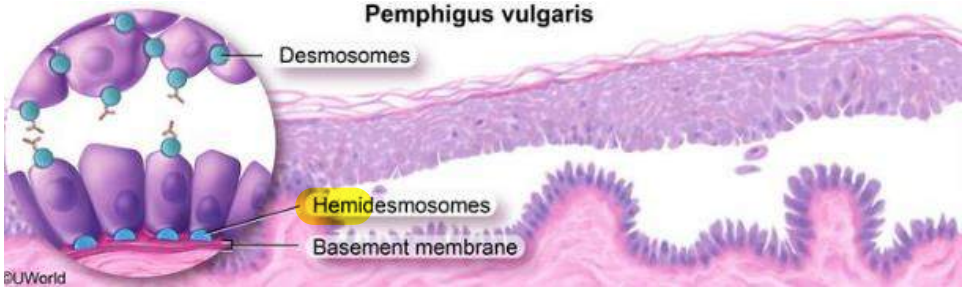
High risk of vascular disease (vasculitis) with venous and arterial thrombosis→ major cause of morbidity

Diagnosis—mainly clinical, labs done to rule out other causes

PEMPHIGUS VULGARIS

Pemphigus vulgaris	
Autoantibody target	• Desmosomes (desmogleins 1 & 3)
Clinical features	• **Flaccid bullae** & ulcers • Mucosal erosions • Separation of epidermis by light friction (Nikolsky sign) Painful
Histopathology	• **Intraepidermal** cleavage • **Acantholysis** (detached keratinocytes) • "Tombstone cells" along basal layer
Immunofluorescence	• Netlike intercellular IgG
Treatment	• Systemic glucocorticoids • Corticosteroid-sparing agents • Aggressive wound care

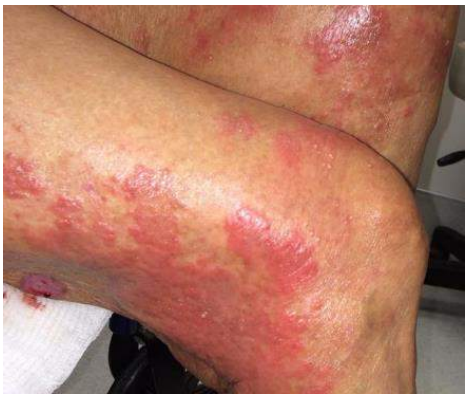
- A single cell layer remains along the basement membrane with an appearance described as a "row of tombstones."
- Immunofluorescence microscopy reveals IgG and C3 deposits in a netlike or "chicken wire" pattern.
- Serology for antibodies to desmoglein 1 and 3 can further support the diagnosis



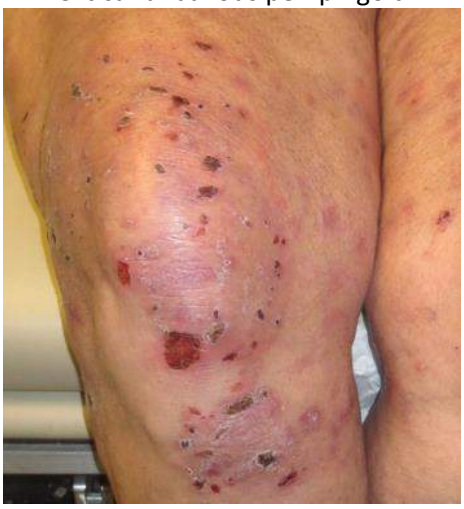
BULLOUS PEMPHIGOID

- Autoimmune blistering disease
- Severe pruritic, tense bullae in the flexural surfaces, groin, and axilla. Can range from few to hundreds covering large portion of body
- A **pre-bullous prodrome**—common and present as **urticarial or eczematous lesions**
- ~~Mucosal lesions— only in a minority of patients~~
- **Etiology:** IgG autoantibodies against hemidesmosomes and basement membrane zone→ activation of compliment and inflammatory mediators→ inflammation→ blister formation
- **Dx:**
  - **Biopsy** shows subepidermal cleavage, with
  - **Immunofluorescence studies:** linear IgG and C3 deposits along the basement membrane
- **Management:**
  - **High potency topical glucocorticoid** (e.g. clobetasol)—1st line—also effective against extensive disease

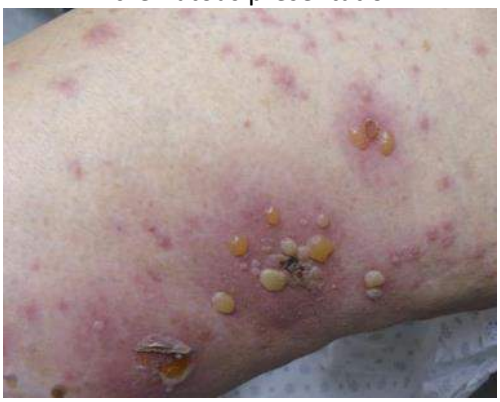
- **Systemic steroids—**not more effective than topical—more treatment related complications—can be use when topical treatment fails



Urticarial bullous pemphigoid



Eczematous presentation



Bullous pemphigoid

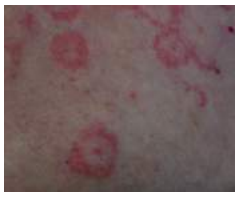
DERMATITIS HERPETIFORMIS

- Causes intensely pruritic erythematous papules, vesicles, and bullae
- Occur symmetrically in grouped ("herpetiform") clusters on the extensor surfaces of the elbows, knees, back, and buttocks.
- Autoimmune dermal reaction due to dietary gluten
- Commonly associated with celiac disease—although it may precede the gastrointestinal manifestations.
- **Skin biopsy** in DH shows subepidermal microabscesses (blisters) at the tips of the dermal papillae;
- **Immunofluorescence studies** show deposits of anti-epidermal transglutaminase IgA in the dermis.
- **Rx:**

- Initial treatment includes **dapsone**— anti-inflammatory and immunomodulatory properties and provides rapid relief of symptoms.
- Long-term management requires a **gluten-free diet**.

ERYTHEMA MULTIFORME

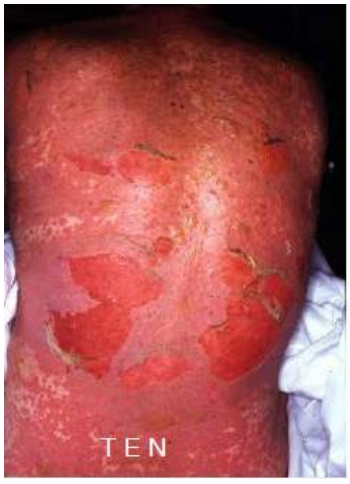
- Self-limited illness characterized by an acute erythematous rash—cell mediated inflammatory disorder
- Usually occurs after herpes simplex infection.
- May cause mucosal lesions similar to those of SJS, but the predominant skin lesions are typically **targetoid plaques** favoring the distal extremities rather than desquamating bullae—palmar involvement is common
- Systemic symptoms are not a prominent as in SJS.
- **Biopsy:** perivascular lymphocytic infiltrate and epidermal necrosis



STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome & toxic epidermal necrolysis	
Nomenclature	<10% of BSA: SJS 10%-30%: SJS/TEN overlap >30%: TEN
Clinical features	• 4-28 days after exposure to trigger (2 days after repeat exposure) • Acute influenza-like **prodrome** • Rapid-onset erythematous macules, vesicles, bullae • Necrosis & **sloughing of epidermis** • **Mucosal involvement**
Common triggers	**Drugs** • Allopurinol • Antibiotics (eg, sulfonamides) • Anticonvulsants (eg, carbamazepine, lamotrigine, phenytoin) • NSAIDs (eg, piroxicam) • Sulfasalazine
	Other • *Mycoplasma pneumoniae* • Vaccination • Graft-vs-host disease

BSA = body surface area; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **SJS** = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.



- **Systemic signs**: common and may include acute high grade fever, tachycardia, hypotension, altered level of consciousness, conjunctivitis, seizures, and coma.

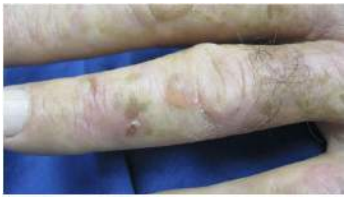
- **+ve** Nikolsky sign
- **Dx**: based on typical mucocutaneous lesions, systemic signs and exposure to a likely causative agent
- **Rx**:
  - Supportive, with aggressive fluid support
  - Wound care similar to that for burns and often done in burn unit
- **Prognosis:** Secondary infections are common, antiseptic precautions are needed and fatalities may occur despite treatment

WARFARIN-INDUCED SKIN NECROSIS

- Serious complication of oral anticoagulants
- Protein C deficiency is sometimes associated
- More common in females
- Commonly involved sites: breast, buttock, thighs, and abdomen
- **C/F:**
  - Initial complaint: pain
  - Followed by bullae and skin necrosis
  - Mostly occur within weeks after starting therapy
- **Management:**
  - Promptly administer vitamin K in early stages
  - Discontinue warfarin if lesion progresses
  - Heparin for anticoagulation until lesion heals
  - Few pts require skin grafting

PORPHYRIA CUTANEA TARDA

- Arises from the deficiency of **uroporphyrinogen decarboxylase,** an enzyme in the heme synthesis pathway
- **C/F:** painless blisters, increased skin fragility on the dorsal surfaces of the hands, facial hypertrichosis and hyperpigmentation.
- **Triggers:** ingestion of certain substances (e.g, ethanol, estrogens) discontinue once suspected, HCV infection
- **Dx:** Elevated urinary porphyrin levels
- **Management:**
  - Phlebotomy or hydroxychloroquine may provide relief, as can interferon-alpha, in patients simultaneously infected with Hepatitis C virus.



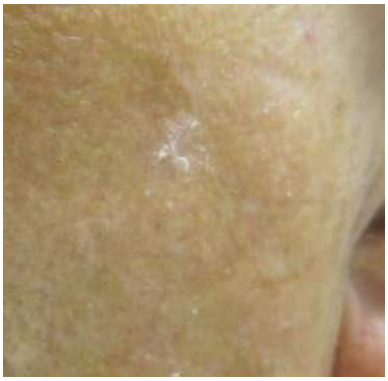
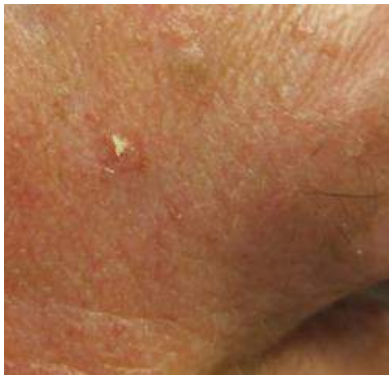
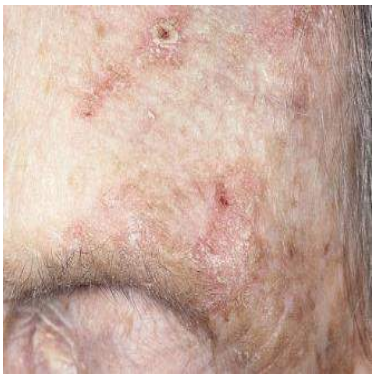
MISCELLANEOUS SKIN DISORDERS

ACANTHOSIS NIGRICANS

- Hyperkeratotic, hyperpigmented plaques with a classic velvety texture
- Divided in to benign and malignant forms
  - **Benign AN**: occurs in young individuals with insulin resistance states. ↑ insulin and/or IGF→ epidermal and dermal proliferation. Skin tags are also common. Lesions common in axilla, groin and back of neck
  - **Malignant AN**: pts usually not obese, in fact lose weight. Lesions occur in uncommon areas like mucous membranes, palms and soles

ACTINIC KERATOSIS

- Regarded as either a premalignant condition or a carcinoma in situ, but <1% will evolve into frank SCC
- **C/F:**
  - Erythematous papules with a central scale due to hyperkeratosis
  - A "**sandpaper-like**" texture on palpation— typical.
  - Lesions are small and flat at first, but may enlarge and become elevated—usually does not exceed 10 mm in diameter. Hyperkeratosis in such lesions may become prominent and turn into "cutaneous horns".
- **Predisposing factor:** develops in genetically predisposed individuals— 40-60 years of age under the influence of excessive sun exposure.
- **Commonly affected areas:** face, ears, scalp and the dorsa of the arms and hands, but any other chronically sun-exposed site (legs, back, upper chest) can be involved.
- **Light microscopy:**
  - Acanthosis (thickening of the epidermis),
  - Parakeratosis (retention of nuclei in the stratum corneum),
  - Dyskeratosis (abnormal keratinization), and
  - Hyperkeratosis (thickening of stratum corneum).
  - Keratinocytes display various degrees of atypia
  - Mitoses and an inflammatory infiltrate are present
- **Rx**: fluorouracil cream (also used for Bowen disease [SCC in situ] and other low risk SCC lesions

PITYRIASIS ROSEA

- Likely due to viral etiology—self-limiting
- The first symptom is pink or brown scaly plaque with central clearing (crinkled, cigarette-paper like appearance) and a collarette of scale (herald patch) on the trunk, neck or flexural surfaces of extremities. Measure up to 2 cm in diameter—much larger than later lesions
- It is followed by development of maculopapular rash classically in a "Christmas tree" pattern along the skin tension/cleavage lines in 1-2 wks

ICHTHYOSIS VULGARIS

- H/o normal skin at birth with gradual progression to dry scaly skin—typical feature
- Can be hereditary or acquired
- **C/F:** skin is usually dry and rough with horny plates over the extensor surfaces of the limbs

- **In children:** there may be relative sparing of face and diaper area
- Worsens in winters due to ↑ dryness
- Sometimes referred to as "lizard skin"

EXFOLIATIVE DERMATITIS

- Also known as erythroderma
- Widespread, scaly eruption of the skin.
- May be drug-induced, idiopathic, or secondary to an underlying dermatological or systemic disease.

SUNBURN

Sunburn	

Prevention	• Remain indoors between 10 AM-4 PM
	• Wear protective clothing:
	  ◦ Hats, pants, long-sleeved shirts
	  ◦ Tightly woven, thick, or dark-colored fabrics
	• Apply sunscreen 30 minutes before sun exposure
	• Avoid tanning beds

Treatment	• Mild-moderate sunburn:
	  ◦ Topical: Cool compresses, calamine lotion, aloe vera
	  ◦ Oral: NSAIDs
	• Severe sunburn: Hospitalization
	  ◦ Intravenous fluids & analgesia
	  ◦ Wound care

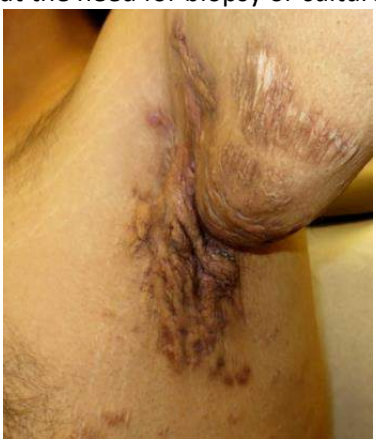
Complications	• Cancer:
	  ◦ Melanoma
	  ◦ Basal cell carcinoma
	  ◦ Squamous cell carcinoma
	• Photoaging

- Best method of prevention is sun avoidance→ not possible then sun screen with SPF 15-30 or higher should be used—apply 15-30 min before sun exposure for it to form protective layer—reapply every 2 hours even if the product is water proof or very water proof
- Clouds do not prevent UV light exposure
- Avoid sunscreen in children < 6mo→ they have thin skin and high surface area to body ratio→ ↑ exposure to sun screen chemicals→ however, if sun exposure can't be avoided, small amount can be applied and additional protection is necessary
- Sunscreens are rated by the strength of their SPF. The amount of UVB radiation filtered by SPF 15, 30, and 50 sunscreens is 93%, 97%, and 98%, respectively. Sunscreens with SPF >50 provide a negligible increase in UV protection (eg, SPF 100 sunscreen filters 99% of UVB rays)

HIDRADENITIS SUPPURATIVA/ ACNE INVERSA

- **Most commonly involved areas:** intertriginous areas (eg, axilla; inguinal, perineal areas) but can occur in any hair-bearing skin.
- **Pathogenesis:** chronic inflammatory occlusion of folliculopilosebaceous units→ prevents keratinocytes from properly shedding from the follicular epithelium→ HS
- **Risk factors:** family history, smoking, obesity, diabetes, and mechanical stress on the skin (eg, friction, pressure).
- **Initial presentation:** solitary, painful, i**nflamed** nodules—can last for several days to months.

- Nodule may regress or can progress to abscesses that open to the surface with purulent or serosanguineous drainage
- Most patients have a **chronic, relapsing course**.
- **Complications:**
  - Sinus tracts,
  - Comedones, and
  - Scarring— Severe scarring can lead to **dense, rope-like bands in the skin with strictures and lymphedema**
- **Dx:** usually made clinically without the need for biopsy or cultures.

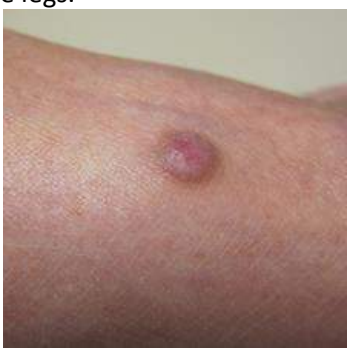


KELOIDS

- May form in the setting of established scar
- Usually not ulcerated
- Symptomatic keloid treated with intralesional glucocorticoids

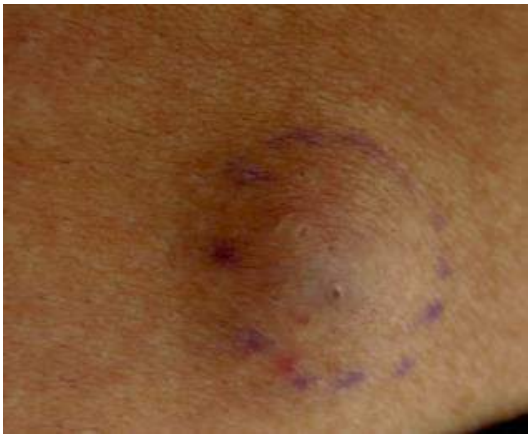
DERMATOFIBROMA

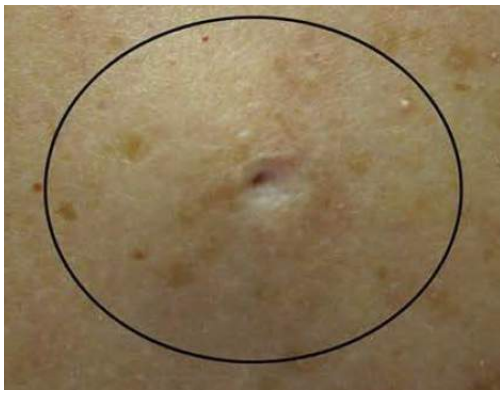
- Due to fibroblast proliferation causing isolated or multiple lesions,
- **Most common site:** lower extremities.
- **Etiology:** unknown, but some patients may develop lesions after trauma or insect bites.
- **C/F:**
  - Typically nontender and appear as discrete, firm, hyperpigmented nodules
  - Usually <1cm in diameter.
  - Have a fibrous component that may cause dimpling in the center when the area is pinched ("dimple" or "buttonhole" sign).
- **Dx:** made clinically based on the appearance of the lesion.
- **Treatment:** (cryosurgery or shave excision) is **usually not required unless** the lesion is symptomatic, bleeds, or changes in color or size. Patients may also request treatment for cosmetic reasons or because of recurrent cuts when shaving the legs.



EPIDERMAL INCLUSION CYST/EPIDERMAL CYST

- A discrete benign nodule containing normal epidermis that produces keratin.
- Occurs when epidermis becomes lodged into the dermis due to trauma or comedones, although many patients have no history of trauma or acne.
- **Location:** can occur anywhere on the body (most commonly the face, neck, scalp, or trunk).
- **Progression:** can remain stable or gradually increase in size.
  - Some patients may develop significant inflammation with rupture and involvement of surrounding tissue.
- **Dx:** made clinically with examination showing a dome-shaped, firm, and freely movable cyst or nodule with a central punctum (small, dilated, pore-like opening). Larger and more inflamed lesions can have a thick, yellowish-white, cheesy, and malodorous discharge.
- **Management:** usually resolve spontaneously but can often recur. Excision is typically reserved for patients who desire removal of the lesion for cosmetic reasons. Incision and drainage is usually needed for infected and fluctuant cysts that are painful and erythematous

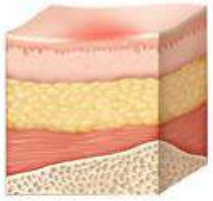
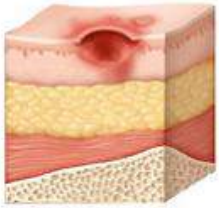
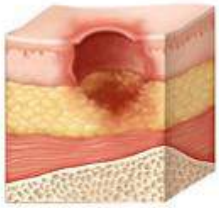
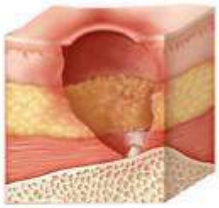




LICHEN PLANUS

- Skin: **pruritic,** planar, polygonal, purple, papules, plaques.
  Mucosa: Wickham striae (white, lacy, reticulated patches).
- most commonly occur on flexural surfaces of the extremities, trunk, and genitalia.
- Associated conditions: HCV
- **Tx:** topical steroids

PRESSURE NECROSIS/DECUBITUS ULCER

Stage	Clinical features	Illustration
I	• Intact skin • Non-blanchable with localized redness	
II	• Shallow, open ulcer • Red-pink wound with no sloughing • Possible intact or ruptured blister	
III	• Full-thickness skin loss with possible visible subcutaneous fat • No exposed bone, tendon, or muscles	
IV	• Full-thickness skin loss • Exposed bone, tendon, or muscle	
Unstageable	• Full-thickness skin loss • Ulcer base covered by slough and/or eschar that needs removal to stage	

- **Risk factors:** Elderly and critically ill patients with immobility, poor nutrition and sensory impairment are at risk of developing decubitus ulcers.
- Ulcers form as a result of uninterrupted pressure on the tissue overlying bony prominences.
- **Common locations:** elbows, coccyx, ears, hips and heels.
- **Prevention:** repositioning **every two hours** and pressure reducing devices (air/foam mattresses) are important methods of prevention
  - **Do not massage**—as it will further damage skin overlying bony prominences

PYODERMA GANGRENOSUM

- Neutrophilic ulcerative skin disease

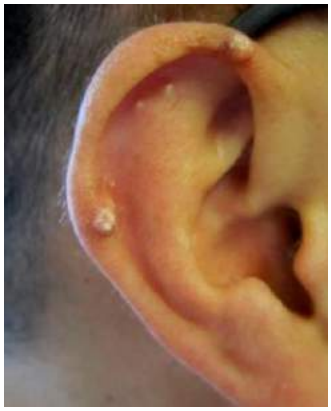
- Starts as inflammatory papule, pustule, vesicle, or nodule→ rapidly progresses to form expanding ulcer with a purulent base and ragged violaceous borders—painful
- Can be single or multiple—on trunk and lower extremities
- 30% cases triggered by trauma (pathergy)
- 50% related to systemic disease like IBD, arthropathies (eg RA) or hematologic conditions (eg AML)—May appear before or after diagnosis of systemic illness
- Dx: clinical after excluding other diagnosis like venous ulcers, panniculitis, cutaneous cancers, usually with skin biopsy
- Rx: local or systemic corticosteroids

ECTHYMA GANGRENOSUM

- Hemorrhagic nodule with surrounding erythema→ necrotic ulcer
- Often caused by P. aeruginosa and occurs in setting of profound neutropenia and in P. aeruginosa bacteremia

CALCINOSIS CUTIS

- Calcinosis cutis is characterized by deposition of calcium and phosphorus in the skin. It presents with scattered whitish papules, plaques or nodules.



BURNS

- There is usually an original insult (e.g., infection and injury) that leads to inflammation and a dysregulated host response, with a massive and uncontrolled release of pro-inflammatory substances causing extensive tissue damage. This response to an infection is referred to as **sepsis,** while noninfectious causes are known as **systemic inflammatory response syndrome (SIRS).**

Temperature >38.5° C (101.3° F) or <35° C (95° F)
Pulse >90/min
Respirations >20/min
WBC >12,000 cells/mm³, <4000 cells/mm³, or >10% bands

- SIRS is defined as having at **least two of the four above criteria**.
- It can occur in conditions such as pancreatitis, autoimmune disease, vasculitis, and burns.
- Sepsis (i.e., SIRS with a known infection) is considered severe when there is associated end-organ dysfunction, such as oliguria, hypotension (i.e., systolic <90 mm Hg), thrombocytopenia (i.e., platelet count <80,000/mm3), metabolic acidosis, or hypoxemia.

- Patients with severe burns usually manifest some evidence of SIRS and also have a hypermetabolic response in the first week after the burn. This response includes hyperglycemia (due to insulin resistance), muscle wasting, protein loss, hyperthermia, and increased energy expenditure. Another life-threatening complication of severe burns in the first week is infection leading to sepsis and septic shock, and the main causes are pneumonia and wound infections (from Staphylococcus aureus or Pseudomonas aeruginosa).
- In patients with significant total body surface area burns, the major cause of morbidity and mortality is hypovolemic shock. In the setting of adequate initial fluid resuscitation, bacterial infection (usually bronchopneumonia or burn wound infection) leading to sepsis and septic shock is the leading complication

DRUG INDUCED HYPERSENSITIVITY REACTION

- Some patients can form drug-specific IgE on exposure, although most do not (Type 1 HS)→ IgE occupy receptors on mast cells and basophils→ re-exposure→ these cells activate→ symptom onset in seconds to minutes
- Can range from mild (urticaria, pruritus, flushing) to more severe (e.g. angioedema of larynx, anaphylaxis)
- **Common drugs causing Type 1 HS:** beta lactam drugs, NM blocking agents, quinolones, platinum containing chemotherapeutic agents and foreign proteins (e.g. chimeric proteins)
- **Management:**
  - **Urticarial and pruritus without systemic Sx:** antihistamines discontinue offending drug
  - **Severe with systemic sx:** epinephrine and corticosteroids

PHOTOSENSITIVE DRUG REACTIONS

COMMON DRUGS ASSOCIATED WITH PHOTOSENSITIVE REACTION

Common drugs associated with photosensitivity reactions	
Antibiotics	Tetracyclines (eg, doxycycline)
Antipsychotics	Chlorpromazine, prochlorperazine
Diuretics	Furosemide, hydrochlorothiazide
Others	Amiodarone, promethazine, piroxicam

PHOTOTOXIC DRUG REACTION

- Drug (from above table)→ converts in to metabolites→ interact with UV radiation→ reactive oxygen species→ damage cell membrane and DNA
- Sx resemble sun burn with erythema, pain and bullae in sun exposed area—severity may be more and ↓ sun exposure needed to cause these as compared non-phototoxic sunburn
- **Advise for pts taking above meds:** minimize sun exposure and use appropriate sun screen and barrier solar protection when outdoors

PHOTOALLERGIC REACTION

- Topical (eg, sunscreens) and systemic medications can also cause photoallergic reactions, in which ultraviolet light alters the structure of the drug, which then induces a delayed hypersensitivity reaction.
- These skin manifestations are typically eczematous in appearance.
- Prior sensitization is required for a photoallergic response, but not a phototoxic reaction.

SKIN CANCER

BASAL CELL CARCINOMA

- Most common form of skin cancer in the US—approx. 75% cases of skin cancer.
- **Possible features** of BCC include:
    1. Persistent open sore that bleeds, oozes, or **crusts**
    2. Reddish patch or irritated area (**superficial BCC)**
    3. Pearly or translucent nodule with pink, red, or white color (**nodular BCC**)
    4. Elevated or rolled border with **central ulceration**
    5. Pale scar-like area with **poorly defined borders**

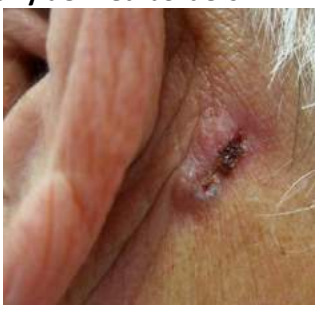


Figure 1

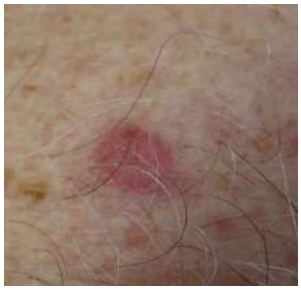


Figure 2

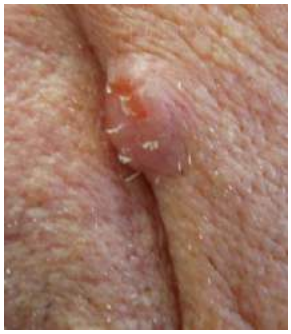


Figure 3

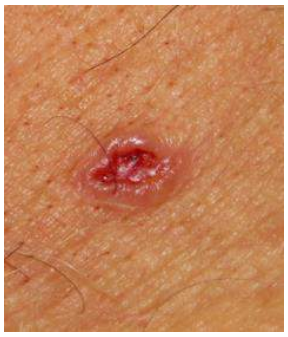


Figure 4

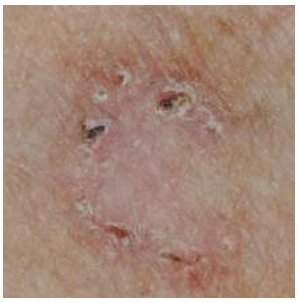
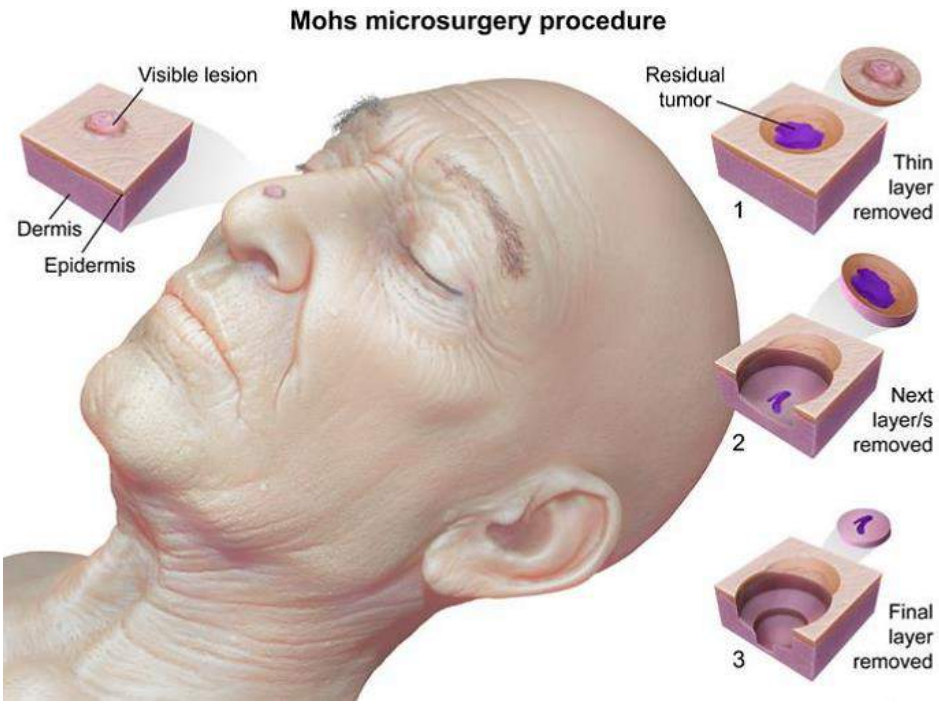


Figure 5

- **Histology:** invasive clusters of spindle cells surrounded by palisading basal cells
- **Progression:**
  - Usually remains local and only rarely spreads to distant parts of the body, but it may continue to grow and invade nearby tissues and structures, including the nerves, bones, and brain
- **Management:** Rx varies, depending on the size, depth, and location of the cancer.
  - **Low-risk lesions on the trunk or extremities** can be managed with electro-dessication and curettage (ED&C).
  - **Low-risk superficial BCC** may be managed with topical therapy using either 5-fluorouracil or imiquimod. These agents may also be used in field therapy for patients with multiple actinic keratoses.
  - **Higher-risk lesions or for BCC on the face:** ED&C is not recommended where the resulting scarring and hypopigmentation are undesirable.
    - **Nodular BCC on the trunk or extremities** may be easily managed with standard surgical excision, typically with 3-5 mm margins.
    - **Mohs micrographic surgery** is employed more often for the face. Mohs surgery is characterized by sequential removal of thin skin layers with microscopic inspection to confirm that the margins have been cleared of malignant tissue— highest cure rate for BCC and provides the least disruption to surrounding tissues→ ideal for delicate or cosmetically sensitive areas (eg, perioral region, nose, lips, ears)



- Radiation therapy rarely used for pts who are unable to undergo surgery—not 1st line
- Widely metastatic CA: systemic chemotherapy (rare condition)

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma of skin	
Risk factors	• UV, ionizing radiation • Immunosuppression • Chronic scars/wounds/burn injuries
Clinical features	• Scaly plaques/nodules • +/– Hyperkeratosis or ulceration • Neurologic signs with perineural invasion
Diagnosis	• **Biopsy**: Dysplastic/anaplastic keratinocytes

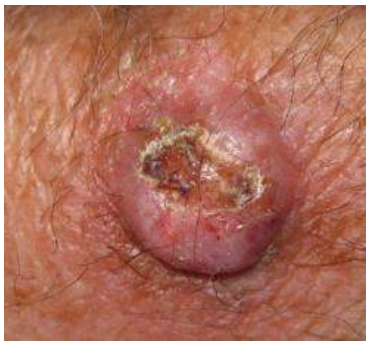
UV = ultraviolet.

Fair skin tone, tobacco, heavy alcohol intake, skin overlying osteomyelitis, venous ulcers

Typically: enlarging nodule that becomes keratinized (thick, rough surface) or non-healing painless ulcer with bleeding or crusting

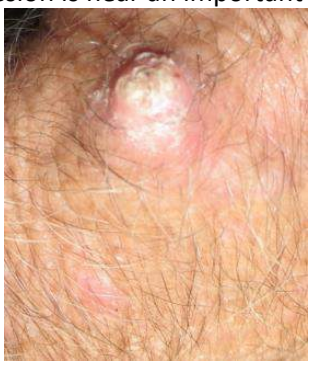
- **SCC**—can present with early perineural invasion → regional neurological sx (paresthesias and numbness)
- **Esp. common in** pts with organ transplantation and chronic immunosuppression → more aggressive and ↑ risk of local recurrence and regional mets
  - BCC is most common malignancy generally but SCC is most common in:
    - Pts on chronic immunosuppressive therapy
    - Lips (with 95% cases occurring in lower lips vermilion border due to ↑ sun exposure)—BCC is uncommon in lips—if occurs, occurs on upper lips

- **Dx:** confirmed by **skin biopsy** (punch, shave or excisional) that include deep reticular dermis to assess the depth of invasion—usually not metastasized at the time of diagnosis but if left untreated, can cause extensive local destruction and lymphatic or distant mets.
  - **SCC arising from burn or wound termed Marjolin ulcer—**has ↑ risk of mets
- **Histopathology:** invasive cords of squamous cells with keratin pearls
- **Adverse prognostic features:** large size, deeper invasion and involvement of regional LN
- **Management:**
  - **Small or low-risk lesion:** surgical excision or local destruction (e.g cryotherapy, electrodessication)
  - **High risk lesion or lesion located in cosmetically sensitive area:** refer for Mohs micrographic surgery
- **Prognosis:** very good. >90% curative rate with excision



KERATOACANTHOMA

- Variant of SCC
- Rapidly growing, "volcano-like" nodule with a central keratotic plug.
- May regress spontaneously, many are treated as well-differentiated squamous cell carcinomas.
- Early treatment is indicated if the lesion is near an important structure, such as the eye



MELANOMA

- Most common malignancy in women 25-29 and second only to thyroid and breast CA in age groups flanking 25-29
- Occurs as a solitary lesion
- **Locations:** can occur anywhere—back most common in men and legs most common in women
- **Risk factors:** fair skin types, h/o blistering sunburns, prior personal or FH (>/=2 members) of melanoma, dysplastic nevus syndrome, atypical nevi and greater than 100 (>10 in one explanation) typical nevi.
- **Presentation:** pt often complains of a mole that has changed in size or color (either darkening or lightening) or a mole that has become symptomatic (painful, itching or bleeding)

Clinical features of melanoma (ABCDEs)
• Asymmetry: When bisected, the 2 sides are not identical • Border irregularities: Uneven edges, pigment fading off • Color variegation: Variable mixtures of brown, tan, black & red • Diameter: ≥6 mm • Evolving: Lesion changing in size, shape, or color; new lesion

- A mole may represent melanoma if:

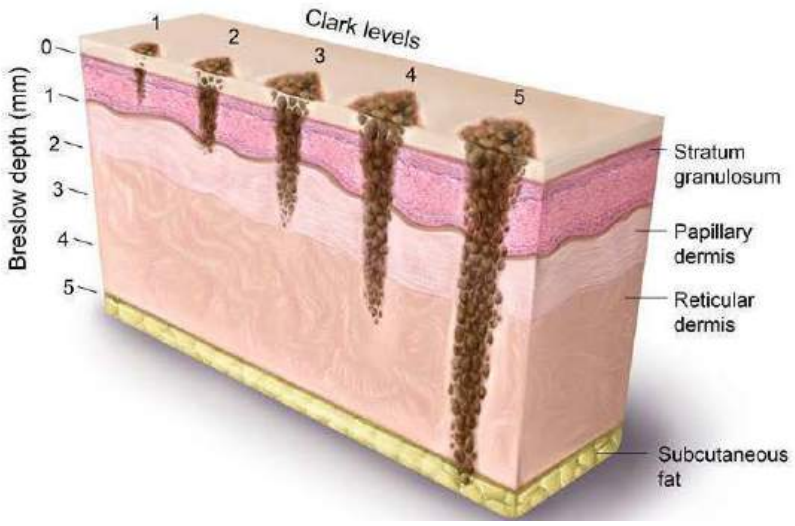
1. appears substantially different from others ("ugly duckling sign")

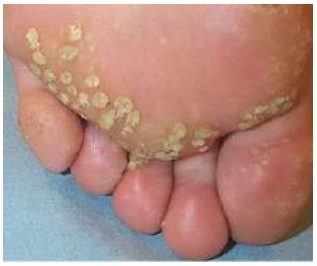
2. itches or bleeds

3. develops palpable nodularity

- **Dx:**
  - **1st step:** confirm the diagnosis histopathologically by **excisional biopsy** that removes the entire lesion with **narrow margins and depth** through the subcutaneous fat. Preferred because:
    - This allows confirmation of the diagnosis as pigmented basal cell carcinomas and some seborrheic keratoses and atypical nevi can mimic melanoma clinically.
    - Complete excision allows determination of **tumor depth (Breslow depth)**, ulceration, presence of mitosis, regression, lymphatic and vascular involvement and host response
    - Excision with wider margins is not recommended until the diagnosis is confirmed as it would be inappropriate to remove margins around a benign lesion, and because this may disrupt afferent cutaneous lymph flow and the ability to identify sentinel nodes
  - **2nd step:**
    - **Depth <1mm→** excise with 1 cm tumor free margin—99% 5 –year survival
    - **Depth >1mm→** sentinel LN study is important
- **DO NOT**:
    - Perform shave biopsy—won't determine depth of tumor which is main prognostic factor

Melanoma depth of invasion

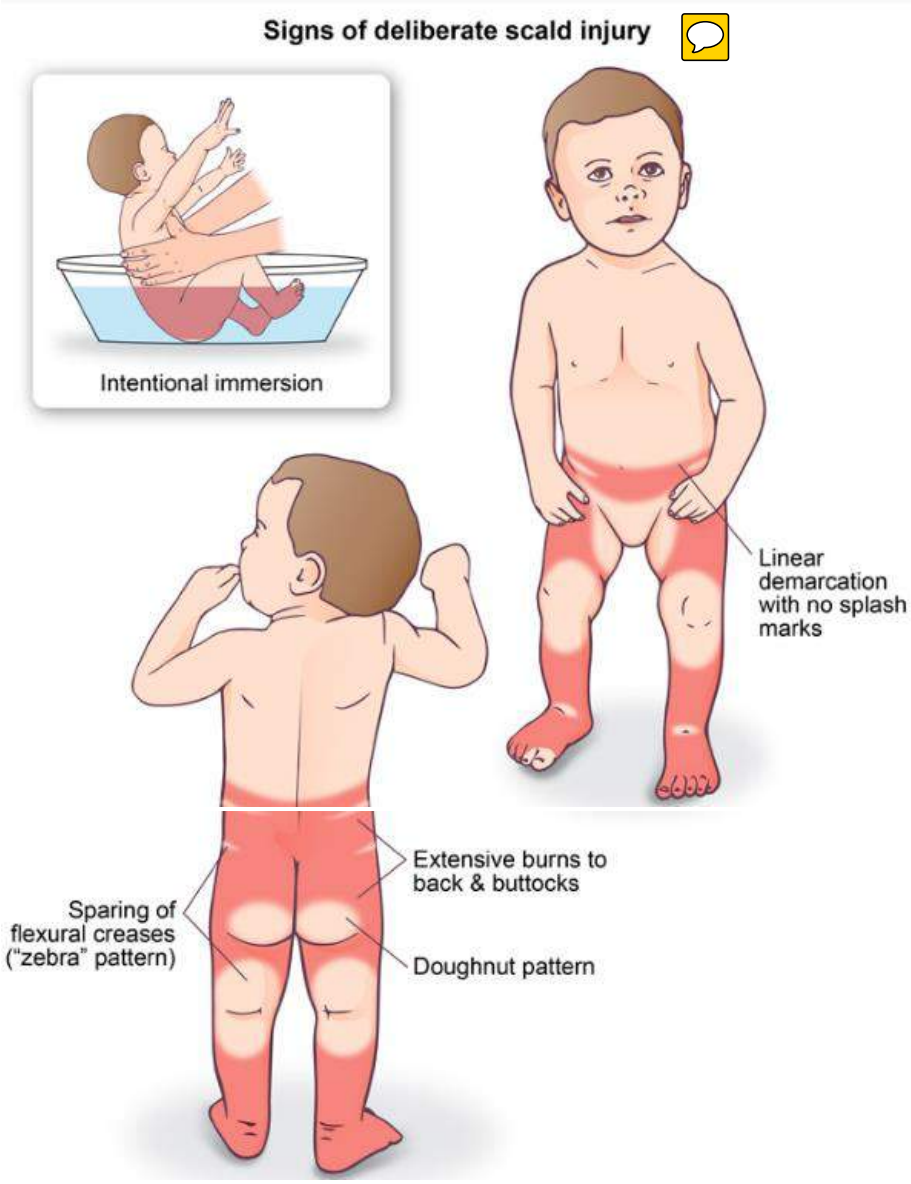




Cutaneous Warts (Verrucae) مسامير لحم **Qid:** 048!

- most common cutaneous manifestation of HPV.
- warts in various locations including the plantar, palmar, or genital areas.
- Plantar warts occur most commonly in young adults and patients with decreased cellular immunity (eg, AIDS, organ transplant patients).
- hyperkeratotic papules on the sole of the foot that can be painful with walking or standing.
- Dx is clinical.
- Tx: topical salicylic acid (1st line), cryotherapy.

SIGNS OF DELIBERATE SCALD INJURY



POINTERS

- **Ruptured Baker's cyst** causes **pseudo-thrombophlebitis syndrome**. Swelling and erythema are seen in the popliteal fossa and posterior calf. Cyst fluid may leak down the inner leg, resulting in a hematoma over the medial malleolus ("crescent sign"). As with venous thrombosis, high fever and lymphadenopathy are generally absent.
- Pearly pink penile papules are a common anatomical variant, typically presenting as small papules evenly distributed in a ring around the corona of the glans penis. They are a benign non-infectious condition, though patients often request removal to avoid the appearance of having a sexually transmitted disease.

PSORIASIS
- Epidermal hyperproliferation and hyperkaratosis.
1. **plaque psoriasis:** most common well-defined erythematous plaques with scales typically over extensor surfaces.
2. **guttate psoriasis:**1-10 mm erythematous macules with scaling, typically **following** an acute streptococcal infection
- Well demarcated plaques with silver scaling that bleed when picked up // nail pitting.
- **Dx:** clinical
- **Tx:** emollients, topical steroids, systemic biologic therapy.

Contents

MULTISYSTEM

CAUSES OF EDEMA

Causes of edema	
Primary mechanism	**Examples**
↑ Capillary hydrostatic pressure	• Heart failure • Glomerulonephritis, renal failure • Venous obstruction (eg, cirrhosis, venous insufficiency)
↓ Capillary oncotic pressure (hypoalbuminemia)	• Protein loss (eg, nephrotic syndrome, protein-losing enteropathy) • Decreased albumin synthesis (eg, cirrhosis, malnutrition)
↑Capillary permeability	• Burns, trauma & sepsis • Allergic reactions • Other systemic inflammatory processes
Lymphatic obstruction	• Malignancy & related treatment • Hypothyroidism • Congenital lymphedema

McCUNE ALBRIGHT SYNDROME

- Rare condition
- Characterized by **3p's: p**recocious puberty, **p**igmentation i.e. café au lait spots (large and irregular borders) and multiple bone defects (**p**olyostotic fibrous dysplasia)
- Responsible for 5% of the cases of female precocious puberty
- May be associated with other endocrine disorders, such as hyperthyroidism, prolactin- or GH-secreting pituitary adenomas, and adrenal hypercortisolism (Cushing syndrome)
- Sporadic and has been recently attributed to a defect in the G-protein cAMP-kinase function in the affected tissue, thereby resulting in autonomous activity of that tissue

KALLMAN SYNDROME

- X- linked recessive
- Failure of migration of fetal GnRH and olfactory neurons →
  - hypogonadotropic hypogonadism → short stature and delayed or absent puberty

- anosmia/hyposmia
- Labs: ↓ FSH and LH
- Early dx is imp as hormonal replacement can facilitate development of 2* sexual characters, build bone and muscle mass and improve fertility

PRADER WILLI SYNDROME

Prader-Willi syndrome	

Clinical features	• Hypotonia
	• Weak suck/feeding problems in infancy
	• Hyperphagia/obesity
	• Short stature
	• Hypogonadism
	• Intellectual disability
	• Dysmorphic facies
	  • Narrow forehead
	  • Almond-shaped eyes
	  • Downturned mouth

Diagnosis	• Deletions on paternal 15q11-q13
Complications	• Sleep apnea (70%) • Type 2 diabetes mellitus (25%) • Gastric distension/rupture • Death by choking (8%)

- Sporadic disorder due to **maternal uniparental disomy**
- Genetic testing is required to confirm diagnosis and begins with **karyotype and methylation studies**, followed by **fluorescence in-situ hybridization**, and then **microsatellite probes**
- **Management** revolves around obesity and its complications. Patients benefit from a structured eating environment and strict limitation of food intake (eg, locks on refrigerator, close supervision). They should be screened for sleep apnea (central and obstructive) as well as type 2 diabetes mellitus. Some patients undergo growth hormone therapy to improve linear growth and body composition, including fat-free mass and bone density.

ANGLEMAN SYNDROME

- Suffer from paternal uniparental disomy (eg, deletion of the maternal copy of chromosome 15q11-q13)
- As in PWS, these patients may have short stature and intellectual disability.
- Unique features: **frequent smiling/laughter**, hand-flapping, ataxia, and seizures

BECKWITH WIEDEMAN SYNDROME

- Congenital disorder due to disregulation of imprinted gene expression in chromosome 11 p15.

- Characteristic physical findings include macroglossia, rapid growth, hemihyperplasia, and umbilical hernia or omphalocele

MUSCULAR DYSTROPHIES

Muscular dystrophies			
Diagnosis	**Duchenne**	**Becker**	**Myotonic**
Genetics	X-linked recessive deletion of dystrophin gene on chromosome Xp21		Autosomal dominant expansion of a CTG trinucleotide repeat in DMPK gene on chromosome 19q 13.3
Clinical presentation	• Onset: age 2-3 • Progressive weakness, Gower maneuver, calf pseudohypertrophy	• Onset: age 5-15 • Milder weakness compared to Duchenne muscular dystrophy	• Onset: age 12-30 • Facial weakness, hand grip myotonia, dysphagia
Comorbidities	• Scoliosis Cardiomyopathy	• Cardiomyopathy	• Arrhythmias • Cataracts • Balding • Testicular atrophy/ infertility
Prognosis	• Wheelchair-dependent by adolescence • Death by age 20-30 from respiratory or heart failure	Death by age 40-50 from heart failure	Death from respiratory or heart failure depending on age of onset

DUCHENNE MUSCULAR DYSTROPHY

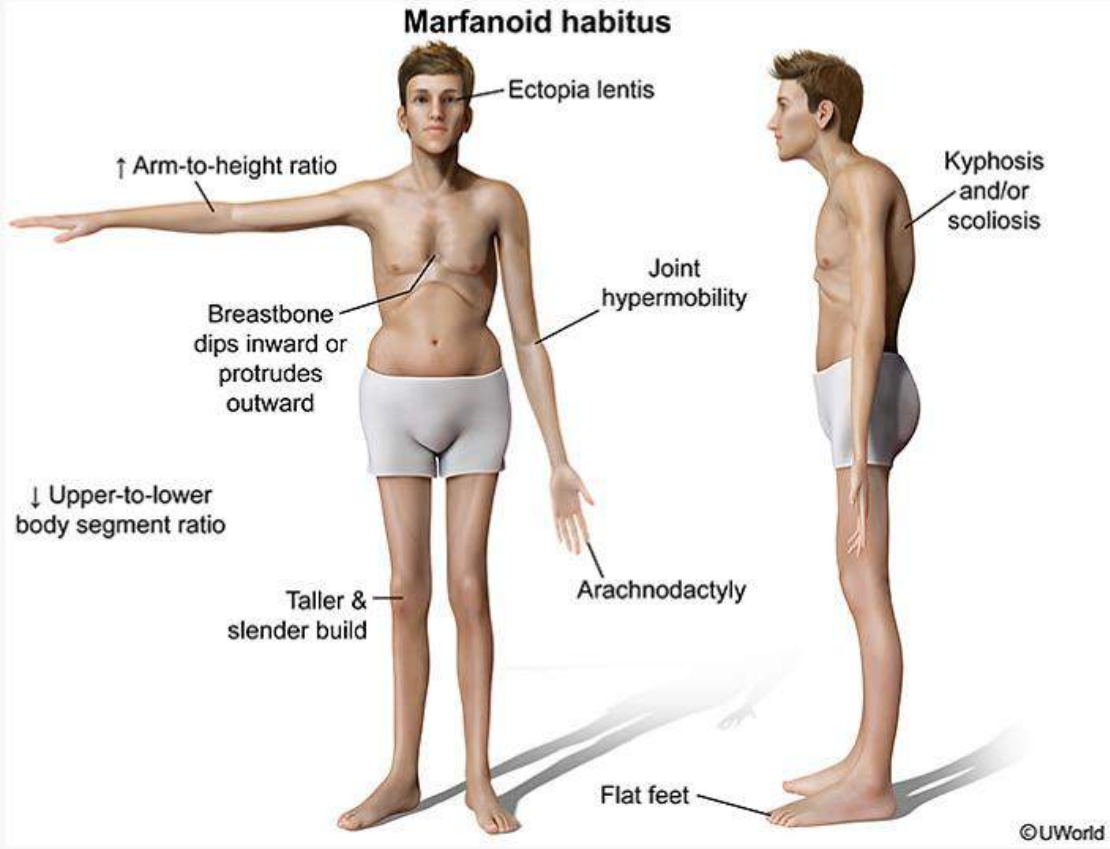
- Dx is confirmed by genetic testing (gold standard), biopsy shows muscle replacement by fat and fibrosis and **absent** dystrophin on immunochemistry staining
- CPK and aldolase are ↑ before development of muscular weakness and drop when excessive muscle mass is lost
- Myopathic pattern on electromyography (myotonic pattern in myotonic muscular dystrophy)

BECKER MUSCULAR DYSTROPHY

- ↓ dystrophin

MARFAN SYNDROME

- AD disorder of fibrillin-1 gene



- Iridodonesis (rapid contraction and dilation of iris) and myopia (from elongation of globe)
- Most life-threatening finding is aortic root dilatation. MVP is also common
- Syndrome pts require close-monitoring with echocardiography for aneurysm and aortic arch dissection
- First degree relatives should undergo genetic testing

Thumb sign

Arachnodactyly and loose joints allow the distal phalanx to protrude beyond the ulnar side of a clenched fist

CONGENITAL CONTRACTURAL ARACHNODACTLY

- Autosomal dominant condition resulting from mutations of the fibrillin-2 gene.
- **Features:** tall stature, arachnodactyly, and multiple contractures involving large joints. Ocular and cardiovascular symptoms are not present in congenital contractural arachnodactyly

HEMOLYTIC UREMIC SYNDROME (HUS)

Hemolytic-uremic syndrome	
Etiology	Enterocolitis from Shiga toxin-producing bacteria (*E coli* O157:H7, *Shigella*) most common
Presentation	• Diarrhea (often bloody) • Lethargy, irritability, pallor • Bruising or petechiae • Oliguria, edema
Laboratory Findings	• Hemolytic anemia • Thrombocytopenia • ↑ Creatinine, hematuria, proteinuria, casts (due to glomerular hemolysis) • ↑ Bilirubin (due to hemolysis)
Treatment	• Fluid & electrolyte management • Blood transfusions • Dialysis

- Consists of hemolytic anemia, thrombocytopenia, and ARF
- >90% cases are due to shiga-toxin producing E.coli 0157:H7 and Shigella
- 10% can be caused by S. pneumoniae→ which do not cause bloody diarrhea rather causes pneumonia or meningitis
- If CNS is affected, headache and irritability may be present
- As kidney function worsens, fluid overload may develop (e.g. pulm. Edema, CHF)
- Once diagnosed, management is mainly supportive
- Approx. half of pts will require dialysis due to ARF
- With supportive care, mortality rate is <5%

HENOCH SCHONLEIN PURPURA

- Immune-mediated vasculitis of childhood—most common in children <15 yrs
- Often occurs after mild illnesses such as upper respiratory tract infections.
- More common in boys
- Occurs more frequently in the fall and winter months.
- **Presentation:**
  - Pupura on legs and buttocks
  - Joint pain (arthralgias)
  - Abdominal pain
    - Although the majority of patients with HSP develop abdominal pain, the presence of severe abdominal pain should prompt further workup for gastrointestinal hemorrhage or intussusception, both of which are known complications. Intussusception, which occurs in up to 4% of cases, presents with severe episodic abdominal pain and "currant jelly" or bloody stools. The increased risk for intussusception is due to bowel wall edema and localized hemorrhage, which can act as lead-points for the intussusception. Unlike most cases of intussusception in children, which are ileo-colic, intussusceptions in HSP are more likely to be **small-bowel or ileo-**

ileal (60% of cases). Because of their location, small-bowel intussusceptions and are diagnosed by the presence of a "target" sign on ultrasound.
    - Ileo-colic intussusceptions can be treated with air or contrast enema, but ileo-ileal intussusceptions that do not reduce spontaneously often require surgical management
  - Renal disease.
  - In rare cases, patients can have scrotal pain and swelling as the initial presenting symptoms.
- Normal platelet count

➔ An increased incidence of colonic diverticula and abdominal wall/inguinal hernias is seen with autosomal dominant polycystic kidney disease

➔ **Universal screening for dyslipidemia** is recommended at age 9-11 and at age 17-21, as lipid levels are relatively stable just prior to and after puberty. Screening outside of these periods should occur in patients at high risk for cardiovascular disease (eg, history of obesity/diabetes mellitus/tobacco exposure, family history of premature coronary disease) and men age >/=35

Contents

GENERAL PRINCIPLES-IM

SCREENING TESTS

Screening tests for patients at average risk*		
Disease	**Age**	**Test & interval**
Breast cancer	Women 50-75	Mammogram every 2 years
Cervical cancer	Women 21-65	Pap smear every 3 years
Colon cancer	50-75	Fecal occult blood test yearly or colonoscopy every 10 years
HIV	15-65	HIV antibody screen 1 time
Hyperlipidemia	Men 35+	Lipid panel every 5 years
Hypertension	18+	Blood pressure measurement every 2 years
Osteoporosis	Women 65+	DEXA (interval uncertain)
*Optimum screening tests & intervals may vary for patients at increased risk or for those with abnormal or near-abnormal results.		

Should begin in high risk women at 45 yrs

"SPIKES" STEP-BY-STEP MNEMONIC FOR FAMILY MEETING

"SPIKES" step-by-step mnemonic for family meetings	
Set up situation	• Arrange for privacy • Include all appropriate participants • Provide facial tissue • Sit down and maintain eye contact • Introductions of family and team members • Eliminate or minimize interruptions
Assess family's **P**erception	• Use open-ended questions to assess the family's perception of the medical situation
Obtain family's **I**nvitation	• Ask family how much information they would like to know
Give **K**nowledge and information	• Warn the family that bad news is coming • Speak in simple and straightforward terms • Stop and check for understanding
Use **E**mpathic statements	• Use empathic statements when responding to emotions
Strategy and summary	• Summarize and create follow through plan, including end-of-life discussions if applicable

GENERAL PRINCIPLES-PEDIATRICS

NORMAL PHYSICAL FINDINGS IN NEWBORN

- Dry, flaky, peeling skin of hands and feet is common as skin adjusts to dry extrauterine environment
- "Pink stains" or "brick dust" in neonatal diapers is due to uric acid crystals
  - Uric acid excretion is esp. high at birth and ↓es until adolescence, when adult levels are observed
  - Uric acid crystals are commonly seen during 1st week as mother's milk is coming in, or in later months with morning void after infant begins to sleep through night
- Healthy infants **normally lose up to 7% of weight in 1st 5 days** of life due to excretion of excess fluid acquired in utero and during labor
- Weight loss more pronounced in exclusively breastfed infants as mother's milk production ↑es gradually to meet infant's demands→ encourage frequent breastfeeding and educate about dehydration

EVALUATION OF NEONATAL HYDRATION

Evaluation of neonatal hydration		
Signs of dehydration	• Decreased wet diapers • Absence of tears • Sunken fontanelle • Dry mucous membranes • Decreased skin turgor • Delayed capillary refill	
Management of weight loss	<7%	• Continue exclusive breastfeeding • Follow-up at age 10-14 days to check that infant has regained birth weight
	≥7%	• Assess for oromotor dysfunction • Assess for lactation failure • Daily weights • Consider formula supplementation

- **Normal urine output:** As a general rule, the number of wet diapers should equal age in days for the first week of life. For example, a 4-day-old neonate should have >/=4 wet diapers per day. After the first week, infants should have >/=6 wet diapers per day
- **Birth weight should be regained by age 10-14 days**
- Infants have immature kidneys that cannot reabsorb sodium effectively. Plain water should never be given to infants age <6 months as it can dilute the blood, resulting in dangerous hyponatremia and seizures

DEVELOPMENTAL MILESTONES

Developmental milestones during first year of life				
Age (months)	**Gross motor**	**Fine motor**	**Language**	**Social/cognitive**
2	• Lifts head/chest in prone position	• Hands unfisted 50% of the time • Tracks past midline	• Alerts to voice/sound • Coos	• Social smile • Recognizes parents
4	• Sits with trunk support • Begins rolling	• Hands mostly open • Reaches midline	• Laughs • Turns to voice	• Enjoys looking around
6	• Sits momentarily propped on hands (unsupported by 7 months)	• Transfers objects hand to hand • Raking grasp	• Responds to name • Babbles	• Stranger anxiety
9	• Pulls to stand • Cruises	• 3-finger pincer grasp • Holds bottle or cup	• Says "dada," "mama"	• Waves "bye" • Plays pat-a-cake
12	• Stands well • Walks first steps independently • Throws ball	• 2-finger pincer grasp	• Says first words	• Separation anxiety • Comes when called

Developmental milestones during toddlerhood				
Age	**Gross motor**	**Fine motor**	**Language**	**Social/Cognitive**
12 months	• Stands well • Walks first steps independently • Throws ball	• 2-finger pincer grasp	• Says first words (other than "mama" & "dada")	• Separation anxiety • Follows 1-step command with gesture
18 months	• Runs • Kicks ball	• Builds tower of 2-4 cubes • Removes clothing	• 10-25 word vocabulary • Identifies ≥1 body part	• Understands "mine" • Begins pretend play
2 years	• Walks up/down stairs with both feet on each step • Jumps	• Builds 6-cube tower • Copies a line • Turn pages	• 50+ word vocabulary • 2-word phrases	• Follows 2-step command • Parallel play • Begins toilet-training
3 years	• Walks up/down stairs with alternating feet • Rides tricycle	• Copies a circle • Uses utensils	• 3-word sentences • Speech 75% intelligible	• Knows age/gender • Imaginative play
4 years	• Balances & hops on 1 foot	• Copies a square	• Identifies colors • Speech 100% intelligible	• Cooperative play
5 years	• Skips • Walks backward	• Copies a triangle • Ties shoelaces • Independent dressing/bathing • Prints letters	• Counts to 10 • 5-word sentences	• Has friends • Completes toilet-training

Age	Fine Motor	Gross Motor	Language	Social
12 months	- Two-finger pincer grasp - Turns several pages of a book at a time	- Walks without assistance - Waves bye - Climbs up on furniture	- Says 2-3 words - Says "mama" and "dada" (can identify each parent)	- Imitates actions - Plays reciprocal games (peek-a-boo) - Indicates wants
2 years	- Builds tower of 6 cubes - Turns individual pages of a book	- Walks up and down stairs - Jumps - Throws a ball overhead	- 200 word vocabulary - Uses **two**-word phrases - **Two**-quarters (50%) of speech intelligible	- Follows **two-step** commands - Removes clothes
3 years	- Copies a circle - Uses utensils to feed self - Stacks 9 blocks	- Climbs stairs with alternating feet - Rides a **tricycle** - Kicks a ball	- Uses **three**-word sentences - States first name - **Three**-quarters (75%) of speech intelligible	- Washes/dries hands - "Helps" with simple household tasks - Group play
4 years	- Copies a cross - Draws a person - Begins to use scissors - Holds crayon with tripod grasp	- Hops on one foot without losing balance - Jumps over objects	- Counts to 10 - Tells stories - Uses plurals and prepositions	- Cooperative play - Has imaginary friends - Imitates adult roles

- By 4 months, primitive reflexes e.g. Moro, grasp have already disappeared or beginning to disappear as infant initiates purposeful movement of extremities. Tongue protruding reflex also disappears by 4 mo, allowing co-ordination to ingest food at 4-6 mo.
- Premature initiation of toilet-training can prolong the duration of training—incontinence esp. nighttime is common up to age 5. Children >/=5yrs should undergo urinalysis to screen for UTI, DM and DI

- Normal growth involves periods of rapid increase in weight and length ("growth spurts"), especially during the first 6 months of life. By **age 12 months, a child's weight should triple and height should increase by 50%.**
- **Delayed verbal milestones** should be assessed with audiologic evaluation

INTRAOSSEOUS CATHETER

- Emergency situation→ when IV access cannot be obtained→ intraosseous (IO) access should be obtained urgently
- IO access benefits over central venous catheter:
  - Require less skill and practice
  - Safer and faster
  - Cannula is large enough to deliver fluids and medicines quickly and obtain blood samples
- Most common site: **proximal tibia**. Benefits of this site:
  - Wide and flat surface
  - At distance from sternum in case cardiopulmonary resuscitation is performed simultaneously
- Any large bone can be used though
- IO catheter can be placed manually or using a driver
- Contraindications to IO placement:
  - Infection (e.g. cellulitis) over the access site
  - Fracture or previous IO attempt in chosen extremity
  - Bone fragility (e.g. osteogenesis imperfecta)

➔ Although nasogastric fluids are preferred for mild to moderate dehydration associated with gastrointestinal disease, they are not recommended in shock, when the splanchnic circulation is constricted.

GENERAL PRINCIPLES- SURGERY

GLASSGOW COMA SCALE

- All trauma pts should be first assessed by GCS which estimates severity of pts neurological injury for triage
- Also gives prognostic information when used in conjunction with the pt's age and presence of concomitant adverse clinical findings, such as hypoxia, cardiovascular compromise, ↑ ICP and radiographic evidence of midline shift of brain
- Used to predict the prognosis of coma and other medical conditions, such as bacterial meningitis, traumatic brain injury, and subarachnoid hemorrhage.
- The GCS is not used to diagnose coma in a patient.
- Findings used to diagnose coma include impaired brainstem activity (e.g., disruption of the pupillary light, extraocular, and corneal reflexes), motor dysfunction (e.g., decorticate or decerebrate posturing), and impaired level of consciousness

Eye Opening	
Spontaneous	4
To verbal command	3
To pain	2
None	1
Verbal Response	
Oriented	5
Disoriented / Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Motor Response	
Obeys	6
Localizes	5
Withdraws	4
Flexion posturing (Decorticate)	3
Extension posturing (Decerebrate)	2
None	1

CERVICAL SPINE TRAUMA

Management of cervical spine trauma	
Prehospital	• Spinal immobilization (eg, backboard, rigid cervical collar, lateral head supports) • Careful helmet removal (eg, motorcycle helmet) • Airway oxygenation
Emergency department	• Orotracheal intubation preferred unless significant facial trauma present • Rapid-sequence intubation added for unconscious patients who are breathing but need ventilatory support • In-line cervical stabilization suggested unless it interferes with intubation • CT of entire cervical spine • Monitoring for neurogenic shock from spinal cord injury

- After stabilization of cervical spine, next step is to assess the airway.
- Unstable lesions above 3rd cervical vertebra→ can cause immediate paralysis, and lower cervical lesions→ can damage the phrenic nerve.
- Cervical spine injuries can be associated with oral maxillofacial trauma, hemorrhage in the retropharyngeal space, and significant airway and neck edema; all could prevent adequate landmark visualization during intubation.
- Hypopneic and hypoxic pt requires emergency airway access.
- **Orotracheal intubation with rapid-sequence intubation** is the preferred way to establish an airway unless there is significant facial trauma.
  - Four people are required for this procedure:

    - One **manually stabilizes** the patient: requires firmly holding either side of the patient's head, with the neck midline and on a firm surface, without applying traction. This prevents neck flexion or rotation during intubation
    - One administers induction anesthesia,
    - One applies cricoid pressure to prevent passive regurgitation until endotracheal tube placement is confirmed, and
    - One places the endotracheal tube.
- A difficult intubation kit should be available in case the attempt is unsuccessful.
- **Laryngeal mask placement** is a temporary measure to stabilize the patient until another airway can be established if orotracheal intubation fails.
- **Nasotracheal intubation—**blind procedure— contraindicated in apneic/hypopneic patients. It is also contraindicated if the patient has a **basilar skull fracture** as such fractures are associated with a risk of cribriform plate disruption, which could lead to inadvertent intracranial passage of the tube.
- Due to the risk of carbon dioxide retention, **needle cricothyroidotomy** is not ideal in patients with head injury who might require hyperventilation to prevent or treat intracranial hypertension. However, it is preferred to surgical cricothyroidotomy in children age <12 as it is easier to perform anatomically.
- **Tracheostomy—** no longer a first option for establishing an airway due to its complications. Surgical cricothyroidotomy is preferred over surgical tracheostomy but should be converted to formal tracheostomy in 5-7 days if prolonged airway control is needed. Prolonged use of cricothyroidotomy has a high incidence of tracheal stenosis.

Clinical manifestations of basilar skull fractures
• Hematoma of the mastoid process or periauricular hematomas (Battle's sign) • Bilateral peri-orbital hematomas (raccoon eyes) • Hemotympanum • Cerebrospinal fluid otorrhea • Cranial nerve palsies (resulting in anosmia, vertigo, tinnitus, or hearing loss)

RUPTURED ABDOMINAL AORTIC ANEURYSM

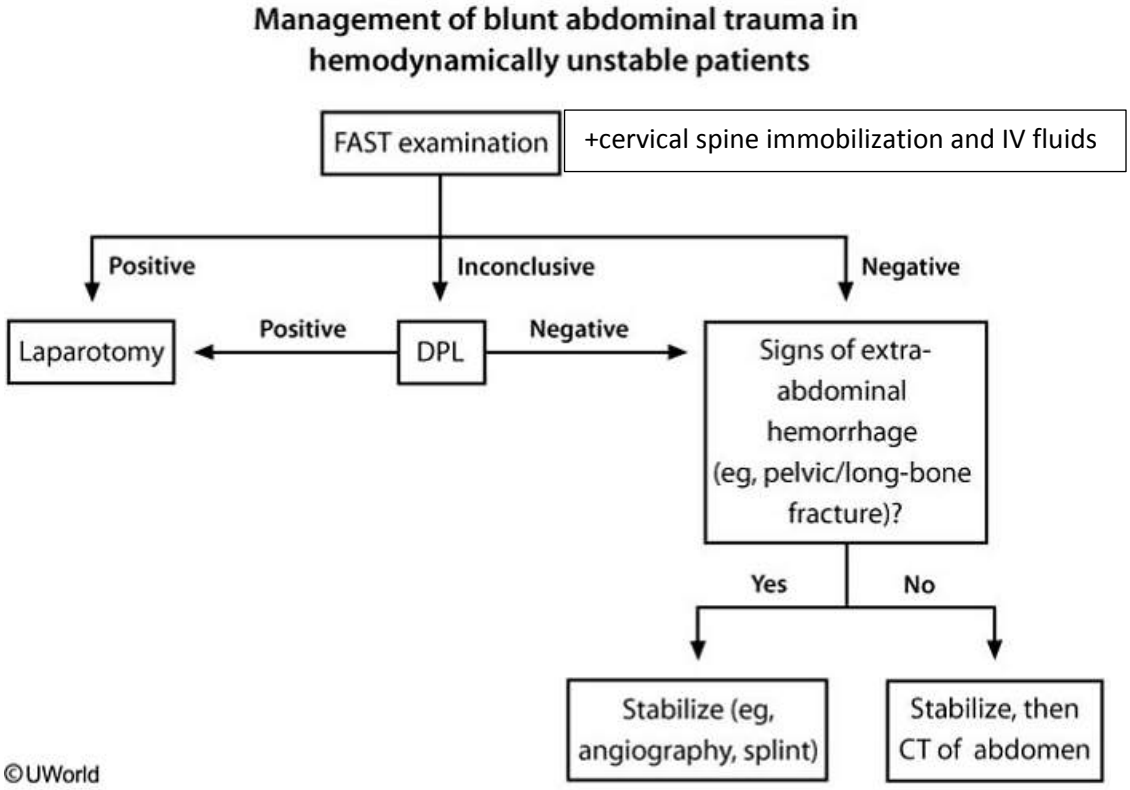
- Abdominal pain, hypotension, pulsatile abdominal mass→ evaluate in operating room with bedside USG
- CT scan is performed only in hemodynamically stable pts
- Pts with ruptured aortic aneurysm→ urgent surgery

PENETRATING ABDOMINAL TRAUMA

- Hemodynamically stable in whom injury to hollow viscus or other organ cannot be determined clinically→ laparoscopy can be performed
- Hemodynamically unstable→ urgent exploratory laparotomy
- Any penetrating injury in the thorax below the level of the nipples has potential to also involve the abdomen through the diaphragm and is assumed to involve both compartments until proven otherwise→ perform laparotomy in unstable pt

BLUNT ABDOMINAL TRAUMA

- If USG/ FAST is not available→ peritoneal lavage to detect intraperitoneal bleeding in hemodynamically unstable pt with blunt trauma
- Rupture of bladder dome is the only bladder part that can cause peritonitis—rest of bladder structures would not cause peritonitis
- Most common site for extraperitoneal bladder rupture is bladder neck



TRAUMATIC AMPUTATION

- All pts with traumatic implantation should be treated as candidates of reimplantation in the field
- Method to preserve amputated limb/digit:
  - Wrap in sterile gauze, moistened with saline→
  - Place in plastic bag→
  - Place on ice but do not let it freeze→
  - Transport to nearby emergency department
- This method prolongs the viability of amputated part by 24 hours
- Best candidates: younger patients suffering sharp amputation with no crush injury or avulsion
- **DON'TS:**
  - Immerse in water→ makes digital vessel repair more difficult
  - Place in alcohol or aseptic solution→ chemical injury
  - Place directly on ice→ cause frostbite and loss of viability

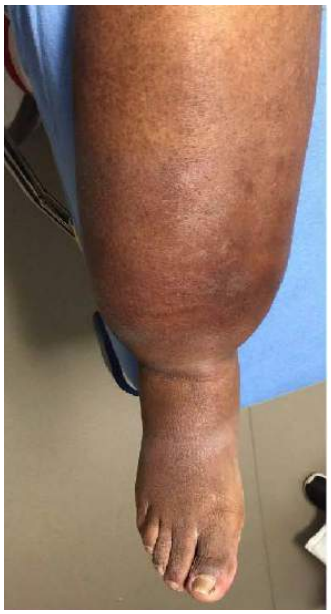
HYPOVOLEMIC SHOCK

Parameter	I	II	III	IV
Blood loss	<15% (750 ml)	15-30% (750-1500 ml)	30-40% (1500-2000ml)	> 40% (>2000ml)
Heart rate	> 72	100-120	> 120	> 140
Blood pressure	Normal	Slightly decreased	Markedly decreased	Markedly decreased
Capillary refill	Normal	May be delayed	Delayed	Markedly delayed
Urine output (cc/hr)	> 30	20-30	5-15	< 5
CNS symptoms	Normal	Anxious	Confused	Lethargic

- Pulse rate is the 1st manifestation of hypovolemic shock due to activation of sympathetic system which also causes peripheral vasoconstriction
- In Grade II, mean arterial BP is normal but pulse pressure is narrowed and BP starts ↓ing. Skin is cool and moist

LYMPHEDEMA

Lymphedema	
Etiology	• Disruption of the lymphatic system ○ Obstruction (eg, malignancy) ○ Lymph node dissection ○ Chronic inflammation (eg, recurrent cellulitis) ○ Congenital (eg, Turner syndrome) ○ Parasitic infection (eg, filariasis)
Clinical presentation	• Swelling, pain, heaviness • Early: Soft skin, pitting edema • Late: Firm & thickened skin, nonpitting edema
Treatment	• Weight loss • Limb elevation & compression • Physiotherapy



Contents

OPHTHALMOLOGY-IM

HORDEOLUM OR STYE

Internal: infx of meibomian gland.

External: infx of hair follicule.

- Common staphylococcal abscess of eyelid
- Painful, localized, small swelling along margin of eyelid
- **Management:**
  - Mostly responds to warm compresses
  - If resolution does not begin in 48 hours→ incision and drainage performed
  - May need antibiotic ointment such as bacitracin or erythromycin

CHALAZION

- Initially ~~**painful**~~ **swelling** that progresses to a **nodular rubbery lesion**.
- Chronic granulomatous condition—develops when a meibomian gland becomes obstructed.
- **Persistent or recurrent chalazion** may be due to meibomian gland carcinoma (sebaceous carcinoma). Additionally, basal cell carcinoma (most common tumor of lid margin) frequently presents as a solitary nodule on the lid margin, and may initially be clinically difficult to distinguish from a chalazions.
- **Management:** histopathologic examination to rule out malignancy
  - Direct steroid injection and incision and curettage are used in symptomatic patients who did not respond to other modes of treatment after histopathologic analysis has ruled out malignancy

DACRYOCYSTITIS

- Infection of lacrimal sac
- Usually in infants and adults >40
- **Acute:** sudden onset redness and pain in medial canthal region
- Sometimes, purulent discharge is noted from punctum
- Few present with fever, prostration and ↑ leukocyte count
- **Causative organisms:** S. aureus and β-hemolytic streptococci
- **Rx:** systemic antibiotics

CONJUNCTIVITIS

Differentiation of conjunctivitis			
	Viral	**Bacterial**	**Allergic**
Eye involvement	Unilateral; often progresses to bilateral	Unilateral; may progress to bilateral	Bilateral
Eye "stuck shut" in morning	Yes	Yes	Yes
Discharge	Watery; scant stringy mucus	Purulent; white, yellow, or green in color; thick in consistency	Watery; scant stringy mucus
Discharge reappears after wiping	No	Yes	No
Other complaints	Burning, sandy, or gritty feeling in eye; viral prodrome	Unremitting ocular discharge	Itching; history of allergy
Conjunctival appearance	Diffuse injection; follicular or "bumpy"	Diffuse injection; non-follicular	Diffuse injection; follicular or "bumpy"; conjunctival edema (chemosis)
Red flags that suggest against 1 of the etiologies: copious purulent discharge, decreased visual acuity, photophobia, ciliary flush, foreign body sensation, corneal opacity or infiltrate, fixed or distorted pupil, trouble keeping eye open, and severe headache with nausea			

Edema of eyelids

Conjunctivitis treatment	
Bacterial conjunctivitis	• Erythromycin ointment • Polymyxin-trimethoprim drops • Azithromycin drops • Preferred agent in contact lens wearers: fluoroquinolone drops
Viral conjunctivitis	• Warm or cold compresses • +/- Antihistamine/decongestant drops
Allergic conjunctivitis	• Over-the-counter antihistamine/decongestant drops for intermittent symptoms • Mast cell stabilizer/antihistamine drops for frequent episodes

VIRAL CONJUNCTIVITIS

- Most cases due to adenovirus—usually in late summers and early fall—outbreaks common in children and caregivers
- Last several days and usually self-limited and usually preceded by **typical nasopharyngeal symptoms**
- Rarely bacterial superinfection occurs→ more severe pain and purulent discharge→ requires topical antibiotics
- Uncomplicated is treated only symptomatically
- Role of mast cell stabilizers is unclear
- Prednisolone drops CI

ALLERGIC CONJUNCTIVITIS

- Acute hypersensitivity reaction
- **Causes:** exposure to environmental allergens like animal dander, dust, dust and mold spores. Reagin (i.e. IgE) mediated
- Usually FH or personal h/o atopic disorders such as asthma or seasonal allergies
- **Management:** Usually subsides in **24 hours** even without treatment. For persistent or recurrent Sx, can be treated with a variety of topical agents including: antihistamines, vasoconstrictors, mast cell stabilizers e.g. **olopatadine** and **azelastine** and artificial tears, available OTC or prescription med.
- oral antihistamines less effective for acute episodes but can be helpful if taken seasonally, prior to allergen exposure

ATOPIC KERATOCONJUNCTIVITIS

- Severe form of ocular allergy
- **Most common symptoms**: itching, tearing, thick mucus discharge, photophobia, and blurred vision.
- It can be differentiated from AC by **more severe symptoms with a prolonged course**, potential visual impairment due to corneal involvement, and thickening of the eyelids and surrounding skin.

SUBCONJUNCTIVAL HEMORRHAGE

- Red eye without any symptoms
- Completely benign condition
- **Risk factors:** results from rubbing eye vigorously, violent coughing spells, HTN episodes or coagulopathy
- **Workup:** usually results from minor bruising→ no workup needed
- **Management:** observation—best treatment—usually resolves in 24-48 hours—occasionally pts have ↑ BP which requires lowering

KERATITIS

CONTACT LENS ASSOCIATED KERATITIS

- Painful, red eye, opacification and ulceration of cornea
- Most cases are due to Gram –ve organisms such as Pseudomonas and Serratia, but can be due to Gram +ve organisms as well as fungi and amoebas
- Medical emergency
- Can lead to corneal perforation, scarring and permanent vision loss if not addressed promptly
- **Management:**
  - Remove and discard lens
  - Topical broad spectrum antibiotics

HSV KERATITIS

- Most frequent cause of corneal blindness in US
- Usually occurs in adults
- **C/F:** pain, photophobia, blurred vision, tearing and redness. H/o prior episodes may be present
- **Precipitating factors for recurrences:** excessive sun exposure, outdoor occupation, fever, immunodeficiency
- **Examination:** corneal vesicles and dendritic ulcers (most common presentation)—characteristic.
- **Dx:** primarily clinical, although epithelial scrapings will show multi-nucleated giant cells
- **Rx:** oral or topical antiviral therapy—effective

HERPES ZOSTER OPHTHALMICUS

- Caused by VZV
- Virus remains latent in trigeminal ganglion→ immunosuppression→ virus travels via ophthalmic branch to forehead and eye
- **Sx:** fever, malaise and burning, itching sensation in the periorbital region
- **Examination:** vesicular rash in distribution of cutaneous branch of first div. of trigeminal nerve. Conjunctivitis and dendriform corneal ulcers characterize eye involvement
- **Rx** started within 72 hrs after eruption with high dose acyclovir → ↓development of complications

CORNEAL ABRASION

- Presents with severe pain and photophobia.
- Usually a history of trauma to the eye
- Slit lamp examination with fluorescein will reveal the corneal abrasion.

HIGH VELOCITY INJURY TO EYE

- Foreign body sensation, photophobia and excessive lacrimation
- Most commonly associated with drilling, hammering, grinding etc
- In contrast to low velocity, high velocity injury has greater probability of globe penetration and intraocular foreign body formation
- Even if initial presentation is subtle, clinician should be cognizant of such probability
- **Gross examination**: abrasion or foreign body may not be visible
- **Fluorescein application** following **Wood's lamp or preferably slit lamp examination**—most reasonable next step after gross exam
- If a foreign body not demonstrated and a strong suspicion remains→ **CT or USG** can be considered.
- MRI is contraindicated for the diagnosis of a foreign body→since it can dislodge the foreign body because of the strong magnetic field.
- Topical antibiotic applied after removal of FB

SYMPATHETIC OPHTHALMIA

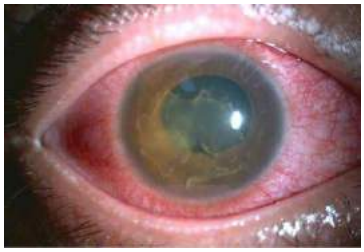
- Also known as **"spared eye injury** "
- Characterized by immune-mediated inflammation of one eye (the sympathetic eye) after a penetrating injury to the other eye.
- The typical manifestation is **anterior uveitis**, but panuveitis, papillary edema, and blindness may develop
- **Pathophysiological mechanism**: uncovering of 'hidden' antigens. Some antigens contained within the eye are protected from immunologic recognition by natural barriers. Breaking these barriers results in the uncovering of 'hidden' antigens. An immune response against these antigens can involve autoantibodies as well as a cell-mediated reaction

UVEITIS

- Uveitis presents with moderate pain and blurred vision.
- Cornea may be hazy
- The anterior chamber shows flare and cells on slit lamp examination.
- The pupil is constricted with a poor light response

ANTERIOR UVEITIS (IRITIS)

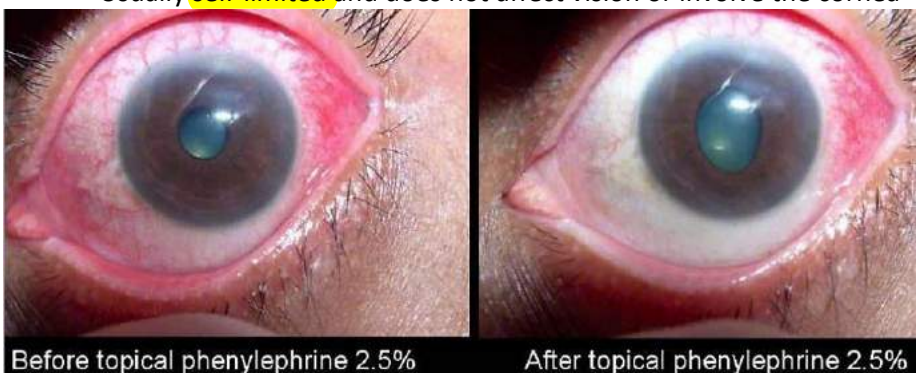
- Inflammation of anterior uveal tract—esp. iris
- **Presentation:**
  - May have associated conjunctival inflammation adjacent to cornea (perilimbal injection)—but cornea itself is usually spared. Corneal stromal edema may be present
  - Discharge—uncommon, if present, not profuse
  - Usually significant pain, miosis and photophobia; visual loss may be present
- **Examination**—keratic precipitates "mutton fat", iris nodules
- Associated with HLA-B27 related conditions



EPISCLERITIS

- Common cause of red eye
- Distinguished by its **localized or patchy distribution**
- Generally mild associated pain and discharge
- May be associated with rheumatoid arthritis and other autoimmune disorders, but many cases are idiopathic

- Usually self-limited and does not affect vision or involve the cornea



RETINITIS IN AIDS PATIENTS

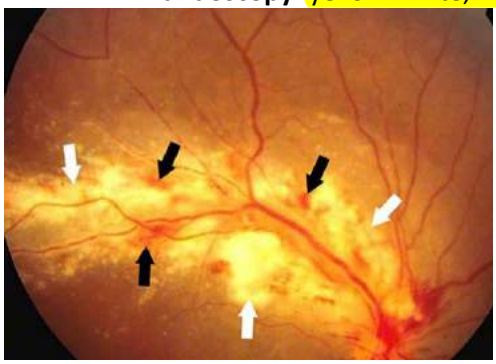
- Occurs in approx. Half of AIDS pts
- Usually a complication of opportunistic infection—most are believed to be reactivation of previous infection

HIV RETINOPATHY

- Cotton wool retinal lesions that are **rarely** hemorrhagic
- Usually resolves over weeks to months
- Usually no floaters or blurred vision

CMV RETINITIS

- Most common serious complication of HIV pts
- CMV causes asymptomatic initial infection but causes lifelong latent infection
- Pts with significantly compromised cell-mediated immunity (e.g. advanced HIV with CD4 <100/mm3)→ reactivation of CMV→ may cause viremia or end-organ disease
- **CMV retinitis:** characterized by **full-thickness retinal inflammation** that moves centripetally along the vasculature → edema and scarring
- **C/F:** blurred vision, floaters and photopsia (sensation of flashing lights)—painless, not usually associated with keratitis or conjunctivitis
- Lesions near fovea and optic nerve→ can cause **blindness**
- Scarring→ ↑es risk of **retinal detachment**
- **Dx:**
  - **Fundoscopy:** yellow-white, fluffy, hemorrhagic lesions along the vasculature.



  - **Blood tests** for CMV (polymerase chain reaction)—not sufficient for diagnosis as viremia may develop independently of end-organ disease.
- **Rx:**

- Usually treated with **oral antivirals** (eg, valganciclovir); if lesions are near the fovea or optic nerve, intravitreal injections are added. All patients should be initiated on antiretroviral therapy (usually 2 weeks after beginning CMV treatment) to prevent recurrence and progression

HSV AND VZV RETINITIS

- Both VZV and HSV cause severe devastating intraocular inflammation (severe, acute retinal necrosis)
- In an immunocompromised individual, HSV retinitis may be characterized by rapidly progressing bilateral necrotizing retinitis (referred to as the "**acute retinal necrosis syndrome**")
- **Initial symptoms:** keratitis, uveitis and conjunctivitis with **eye pain**, followed by rapidly progressive visual loss.
- **Funduscopy** reveals widespread, pale, peripheral lesions and central necrosis of the retina
- HSV infection of the eye is the most common cause of corneal blindness in the United States.

TOXOPLASMIC CHORIORETINITIS

- Causes eye pain and ↓ vision
- Retinal lesions occur in non-vascular distribution

SYPHILITIC CHORIORETINITIS

- Usually presents with uveitis and diminished visual acuity
- Almost always occurs with syphilitic meningitis.

ENDOPHTHALMITIS

- Invasive infection of globe (bacterial or fungal)
- Due to disruption of external surface of eye (e.g. trauma)
- May show conjunctival irritation as well
- Usually have purulent haziness of ocular contents and may have layering-out of pus in anterior chamber (hypopyon)

POSTOPERATIVE ENDOPHTHALMITIS

hypopyon = pus in ant chamber

Hyphema = blood in ant chamber

- Most common form of endophthalmitis
- It usually **occurs within six weeks of surgery**
- It is an infection within the eye, particularly the vitreous.
- Patients usually present with pain and decreased visual acuity.
- **Examination:** swollen eyelids and conjunctiva, hypopyon, corneal edema and infection.
- The vitreous can be sent for Gram stain and culture.
- **Rx:** Based on the severity, intravitreal antibiotic injection or vitrectomy is done.

CANDIDAL ENDOPHTHALMITIS

- Can occur esp. with disseminated candidiasis
- Patients with candida fungemia who appear sick should be evaluated by an ophthalmologist for possible endophthalmitis

DIABETIC RETINOPATHY

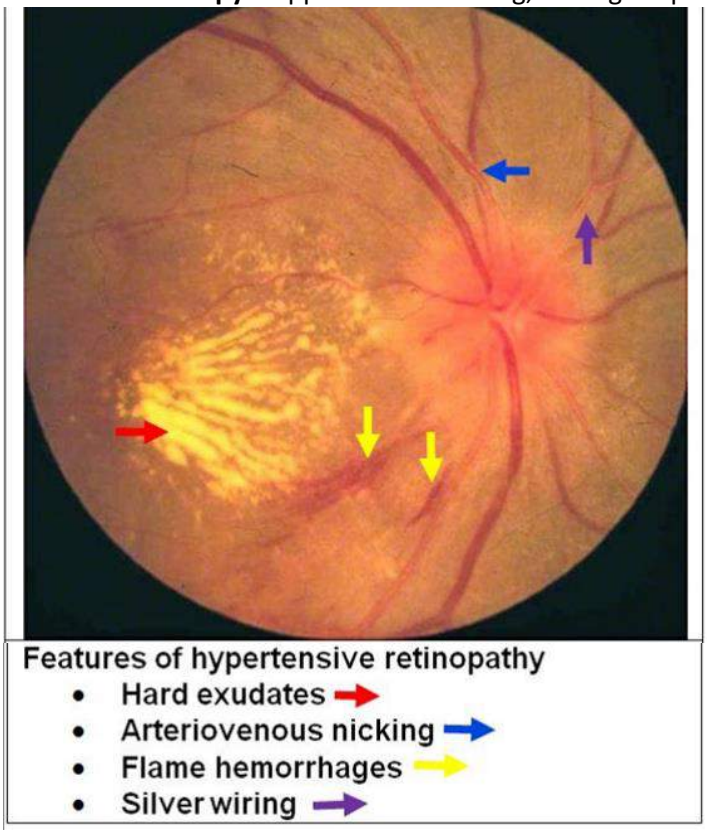
- Can occur in both, insulin-dependent and non-insulin dependent DM
- Has 3 types:

1. Background or simple retinopathy or non-proliferative- consists of dilation of veins, microaneurysms, dot and blot hemorrhages, hard exudates, and retinal/macular edema→ blurred vision
2. Pre-proliferative retinopathy- with cotton wool spots
3. Proliferative or malignant retinopathy- consists of newly formed vessels.

- Pts are usually asymptomatic initially, despite early signs of retinopathy (e.g. microaneurysms)
- Visual impairment occurs with development of macular edema
- **Management:** Argon laser photocoagulation is suggested treatment for prevention of complications

HYPERTENSIVE RETINOPATHY

- Acute vision changes like hemorrhages, exudates and/or papilledema→ require malignant BP (DBP >120-130). Acute vision loss not typical
- There is initially focal spasm of arterioles, followed by progressive sclerosis and narrowing
- **Funduscopy:** copper or silver wiring, findings depend on the severity of retinopathy



NON-KETOTIC HYPEROSMOLAR SYNDROME (NKHS)

- Can occur in type 2 diabetics in association with recent stressor like URTI
- Stress→ ↑ cortisol and catecholamine → hyperglycemia (serum glucose >600 mg/dL) without ketosis→ glycosuria → diuresis→ dehydration and serum hyperosmolarity (often >320 mOsm/L)
- Altered consciousness ranging from confusion to coma – main symptom in NKHS
- Blurred vision due to myopic ↑ in lens thickness and intraocular hypotension 2* to **hyperosmolarity**

RETINAL DETACHMENT

- Separation of layers of retina

- Usually occurs in 40-70 yo pts
- **C/F:** photopsia, floaters, "curtain coming down over my eyes"
- Inciting event usually occurs months before retinal detachment
- **Risk factors:** myopia or trauma (e.g. cataract surgery) can cause retinal breaks→ fluid seeps in and separates retinal layers
- **Ophthalmoscopy:** grey, elevated retina
- **Management:** Laser therapy and cryotherapy are done to create permanent adhesions between the neurosensory retina, retinal pigment epithelium, and choroid.

AMAUROSIS FUGAX

- Transient monocular visual loss, sometimes described as "curtain falling down"
- **Cause:** most commonly from retinal emboli from ipsilateral carotid artery, mostly due to atherosclerosis→ once clot breaks or displaces→ blood flow restored→ vision returns
- **Funduscopy:** depends on cause. Examination may be normal or show zones of whitened retina (from edema) following distribution of retinal arterioles. Rarely, plaques or emboli seen
- **Workup:** non-invasive evaluation of carotids to provide information regarding stenosis
- **Rx:** atherosclerosis treatment ↓ risk of stroke

CENTRAL RETINAL ARTERY OCCLUSION (CRAO)

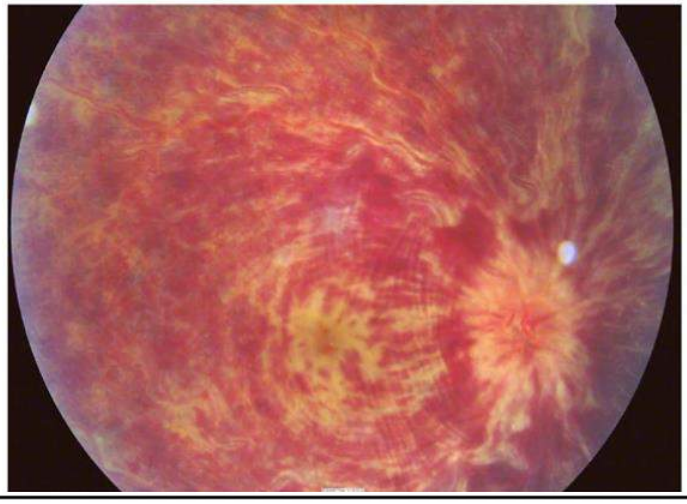
- It occurs when a severe, abrupt diminution of blood flow through the central retinal artery causes ischemia of the inner retina
- Ophthalmic artery is the first intracranial branch of internal carotid artery. Supplies blood to eyes via:
  1. Central retinal artery→ supplies inner retina
  2. Ciliary branches→supplies choroid and anterior portion of globe
- Emboli can travel to more distal branches causing loss of only a section of visual field
- Commonly associated with amaurosis fugax
- Visual acquity typically 20/800 (6/240) or worse
- **Fundoscopy:** diffuse ischemic retinal whitening, pale optic disc, cherry red fovea (typical but not specific) and boxcar segmentation of blood in retinal veins
- **Ophthalmic emergency**—delay in Rx can lead to permanent vision loss
- **Rx:**
  - Immediate intervention: ocular massage—dislodges embolus to more distal branch and improves vision—most rapid
  - Medical management and anterior chamber paracentesis to lower IOP—may be used
  - Carbogen therapy (5% CO2 and 95% O2) or hyperbaric oxygen—beneficial if given early
  - Thrombolytic therapy may be helpful if given in 4-6 hours—given intraarterially—efficacy not systematically studied

CENTRAL RETINAL VEIN OCCLUSION (CRVO)

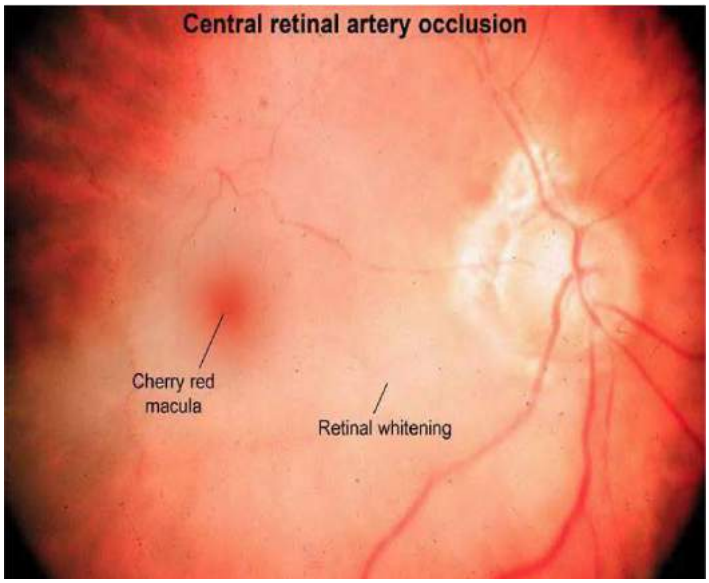
- Must be kept on differentials in pts with acute or subacute u/l visual loss but usually not as acute as CRAO
- Characterized by sudden, unilateral visual impairment that **is usually noted upon waking in the morning**
- Caused by thrombosis
- **Risk factors:** patients with coagulopathy, hyperviscosity, chronic glaucoma, and atherosclerotic risk factors (eg, age, diabetes, hypertension).
- **Ophthalmoscopy:** disc swelling, venous dilation and tortuosity, retinal hemorrhages and cotton wool spots

- **Dx:** confirmed with fluorescein angiography
- **Management:**
  - No significant macular edema or neovascularization→ conservatively with close observation.
  - Significant macular edema→ intravitreal injection of vascular endothelial growth factor inhibitors.
  - No treatment is particularly effective, but some may have partial recovery of vision within the first 3 months.

Funduscopic findings in central retinal vein occlusion



- Venous dilation & tortuosity due to venous occlusion
- Scattered & diffuse hemorrhages due to backup of blood & increased resistance, leading to ischemic damage
- "Blood & thunder" appearance due to diffuse hemorrhages
- Cotton wool spots
- Disk swelling



Suspect optic neuritis in a patient with central scotoma, afferent pupillary defect, changes in color perception and decreased visual acuity. Remember the association between optic neuritis and multiple sclerosis **(The USMLE loves this topic!).**

OPTIC NEURITIS

- Usually in pts 20-45—females more commonly affected
- Rapid impairment of vision in one eye (rarely both) and pain on eye movement
- Marked changes in color perception
- Afferent pupillary defect and field loss occur, usually with central scotoma.
- Swollen disc on exam
- More common in patients with multiple sclerosis; such patients will usually give a history of similar occurrences in the past

VITREOUS HEMORRHAGE

- Typically presents as a sudden loss of vision and onset of floaters.
- **Most common cause:** diabetic retinopathy—most commonly occurs in proliferative diabetic retinopathy
- **Ophthalmoscopic evaluation:** fundus is hard to visualize, and even if it is visualized, details may be obscured, floating debris and dark red glow may be seen
- **Management:**
  - Immediate ophthalmologic consultation is required
  - For patients with underlying medical conditions, conservative treatment (ie , upright position during sleep, which enhances settling of the hemorrhage) is recommended

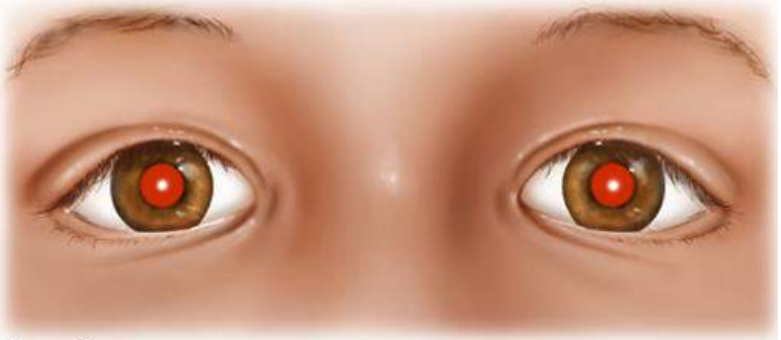
CHOROIDAL RUPTURE

- Occurs due to blunt ocular trauma.
- Examination reveals central scotoma, retinal edema, hemorrhagic detachment of the macula, subretinal hemorrhage and crescent-shaped streak concentric to the optic nerve.
- The usual complaint is blurred vision following blunt trauma.

CATARACT

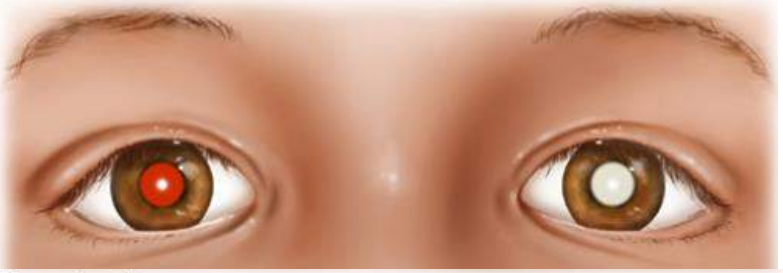
- Vision-impairing opacification of the lens.
- Oxidative damage of the lens occurs with aging
- **Risk factors:** advancing age, diabetes, smoking, chronic sunlight exposure, and glucocorticoid use.
- Usually bilateral, but patients may become symptomatic in one eye before the other.
- **C/F:** Painless blurred vision, glare, and often halos around lights. Loss of night time vision is very characteristic
- **Ocular examination in early cataract formation** may show a normal red reflex and retinal visualization, but as the cataract progresses, the red reflex is lost and retinal detail may not be visible
- Typically follow a slowly progressive course
- Treatment is indicated when loss of vision impairs activities of daily living.
- Definitive treatment is lens extraction with artificial lens implantation
- The risk of perioperative complications in cataract surgery is low, and anticoagulants do not need to be held.

Red reflex & corneal light reflection



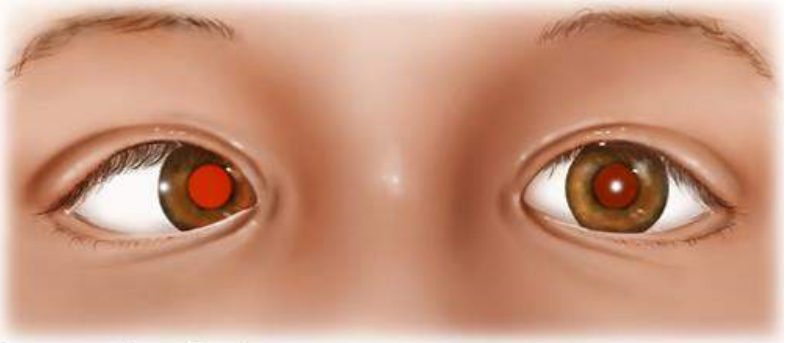
Normal eyes

Red reflexes & corneal light reflexes are equal



Absent reflex

White reflex on abnormal eye can result from opacities of the lens (eg, cataract), or tumor (eg, retinoblastoma)



Asymmetric reflections

In strabismus, the red reflex is more intense in the deviated eye. The corneal light reflexes are also asymmetric.

GLAUCOMA

ACUTE GLAUCOMA

- Emergency condition
- Narcotics are used for pain control
- Meds to ↓ intraocular pressure:
  1. IV Mannitol—1st line—osmotic diuretic—works immediately
  2. Acetazolamide—rapidly ↓es further aqueous humor production → ↓ intraocular pressure
  3. Pilocarpine—applied topically→ opens canal of Schlemm→ drainage of aqueous humor

4. Timolol—applied topically→ ↓ production of aqueous humor

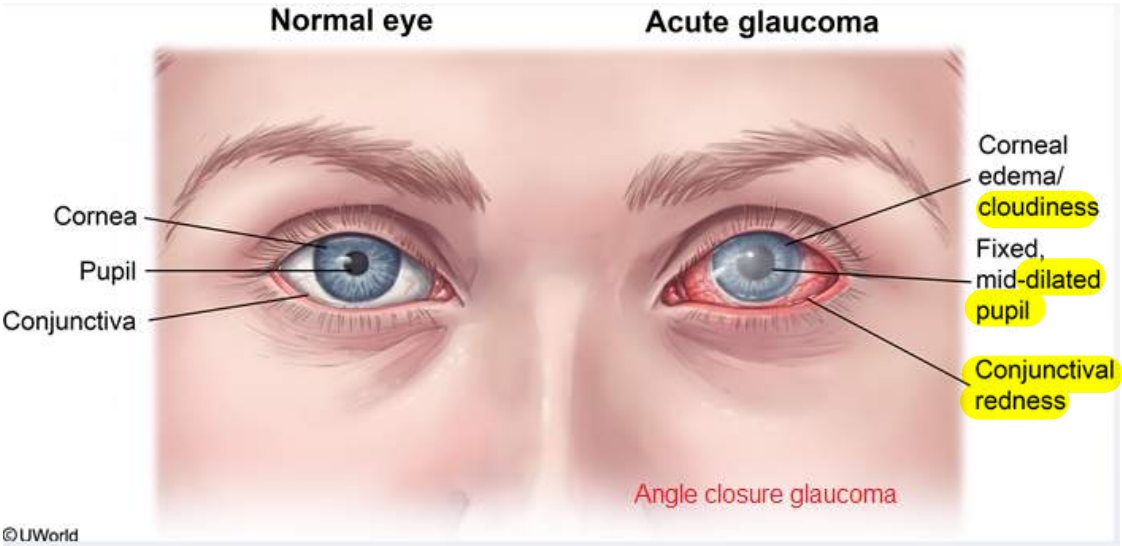
- **Contraindicated drugs:** mydriatic agents like atropine (causes pupillary dilation→ precipitates or aggravate glaucoma)

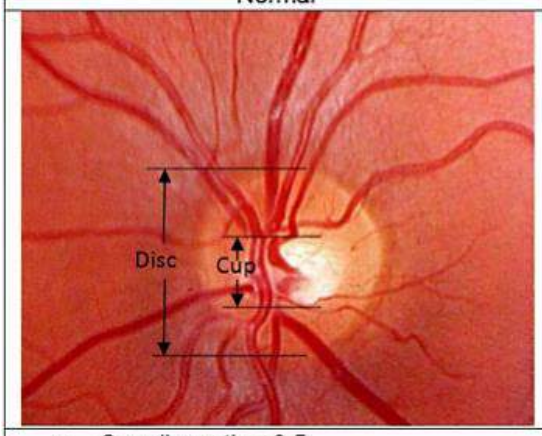
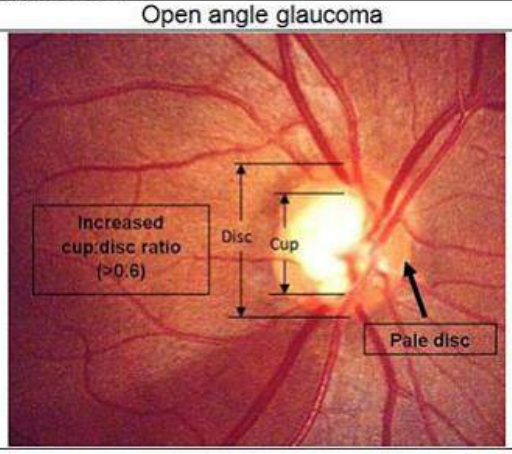
ACUTE ANGLE CLOSURE GLAUCOMA

- Occurs with closure of pre-existing narrow anterior chamber angle— acute
- Predominantly occurs in pts 55-70 yrs
- Usually occurs following pupillary dilation, e.g. in dark, stress or due to drugs
- **C/F:** severe pain, blurry vision, N/V
- **PE:** red eye with steamy/hazy cornea and moderately dilated pupil that is non-reactive to light. Shallow anterior chamber with inflammatory changes
- **Management:**
  - Ophthalmology consultation
  - **Gonioscopy:** gold standard— ophthalmologist uses a specialized prismatic lens with a slit lamp to visualize the iridocorneal angle
  - **Tonometry**→ reveals ↑ IOP—device is placed against the anesthetized cornea, quantitated pressure is applied, and the resulting indentation is measured—performed if additional info is needed or ophthalmologic consult is not available
- **Rx:** IV acetazolamide (with subsequent oral administration)→ may lower IOP
- **Permanent cure:** offered with laser peripheral iridotomy or surgical intervention (iridotomy or iridectomy)

OPEN ANGLE GLAUCOMA

- **Prevalence:** African-Americans, FH of glaucoma and diabetes
- Insidious onset
- Asymptomatic initially
- Gradual loss of peripheral vision over years, eventually resulting in tunnel vision
- Persistently ↑ed IOP
- Pathologic cupping of optic disc
- **Prevention:** Annual examination in high-risk populations→ beneficial
- Beta-blockers such as Timolol eye drops are effective in the initial management of the patient. Laser trabeculoplasty is used as an adjunctive measure. If there is a continuous increase in intraocular pressure, surgical trabeculectomy is done



Optic disc in glaucoma	
Normal	Open angle glaucoma
	
• Cup:disc ratio <0.5 • Clear disc rim	• Enlarged cup with cup:disc ratio >0.6 • Increase in cup size over time • Thinning of disc rim • Pale disc (optic nerve atrophy)

MACULAR DEGENERATION

- Usually in pts >50 yrs. Smoking is also a risk factor
- Leading cause of blindness in industrialized countries
- **Pathogenesis:** degeneration and atrophy of outer retina, retinal pigment epithelium, Bruch's membrane and choriocapillaries
- **C/F:**
  - May be asymptomatic, some may complain of u/l or b/l visual problems
  - Driving and reading affected 1st as they require fine visual acuity provided by macula
  - Distortion of straight lines such that they appear wavy—usually initial finding—Grid test performed to screen for MD
  - Progressive **b/l loss of central vision.** Peripheral and navigational vision are preserved—but may become impaired by development of cataracts

ATROPHIC "DRY" MACULAR DEGENERATION

- Slowly progressive b/l vision loss
- Drusen and patchy depigmentation in macular region

EXUDATIVE/ NEOVASCULAR "WET" MACULAR DEGENERATION

- May be acute or insidious—U/L aggressive vision loss
- **Ophthalmoscopy:** growth of abnormal vessels in retinal space
- Sudden visual loss if complicated by retinal detachment

OPHTHALMOLOGY-PEDIATRICS

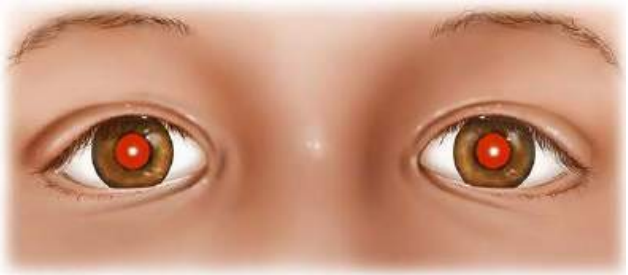
VISION ASSESSMENT OR SCREENING

- Vision assessment should be performed at every well child exam during first few years to prevent permanent vision loss
- **During infancy:** by observation fixation and tracking

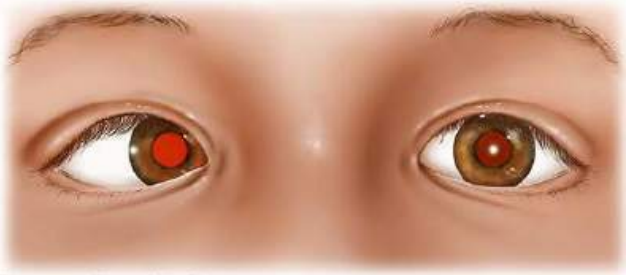
- **Older infants and children:** cover-uncover test for strabismus
- **Age 3 onwards:** monocular visual acuity using Snellen's chart or tumbling E chart.
  - Visual acuity worse that 20/40 at 3-5 years or worse than 20/30 at >6 years→ ophthalmologic evaluation for refractive errors
- Abnormal red reflexes, misalignment, pupillary asymmetry of >1mm, corneal asymmetry, ptosis or other lesions obstructing the visual axis, and nystagmus are additional indications for referral.

STRABISMUS

Strabismus (ocular misalignment)	
Abnormal findings	• Constant strabismus at any age • Eye deviation after 4 months of age • Asymmetric corneal light reflexes • Asymmetric intensity of red reflexes • Deviation on cover test • Torticollis or head tilt
Treatment options	• Penalization therapy: Cycloplegic drops to blur normal eye • Occlusion therapy: Patch normal eye • Prescription eyeglasses • Surgery
Complications	• Amblyopia • Diplopia



Normal eyes
Red reflexes & corneal light reflexes are equal

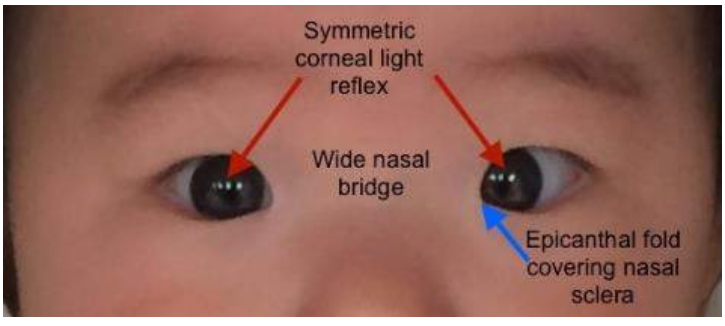


Asymmetric reflections
In strabismus, the red reflex is more intense in the deviated eye. The corneal light reflexes are also asymmetric.

- Can be intermittent or constant
- Ocular malalignment due to nasal deviation (**esotropia**) or rarely temporal deviation (**exotropia**)
- (watch video of cover test on youtube)
- Intermittent strabismus can be expected in infants age <4 months due to immaturity of the extraocular muscles (**ocular instability of infancy)** →reassurance and observation
- **Esotropia beyond early infancy** must be treated to **prevent amblyopia** (vision loss from disuse of deviated eye). The first 5 years of life are extremely critical to the development of visual acuity as it is the time for visual cortex maturation. During this stage, any anomaly (eg, strabismus, refractive error, cataract) can compromise vision.

PSEUDOSTRABISMUS

- Provide reassurance



TRACHOMA

- Major cause of blindness worldwide
- Caused by Chlamydia trachomatis A-C
- **Active phase:** follicular conjunctivitis and pannus (neovascularization) formation in cornea. Concurrent infection occurs in nasopharynx→ nasal discharge
- **Dx:** Giemsa stained examination of conjunctival scrapings
- **Rx:** topical tetracycline or oral azithromycin—start immediately
- **Repeated infections→** corneal scarring

OPTIC GLIOMA IN NEUROFIBRAMATOSIS TYPE 1

- Occurs in 15% pts with NF, type 1 (axillary freckling and café-au-lait spots)
- Occurs mostly in children <6yrs
- H/o slowly progressive u/l visual loss and dyschromatopsia
- Exophthalmos sometimes present
- Optic disk may be normal, swollen, pale or atrophic

→ Retinal hamartoma typical of tuberous sclerosis

RETINOBLASTOMA

• Extremely high yield question!!!

- Every case of leukocoria is considered retinoblastoma until proven otherwise→ refer to ophthalmologist
- Most common intraocular tumor of childhood
- Inactivation of tumor suppressor Rb gene→ familial or sporadic
- Highly malignant→ delay in treatment→ mets to liver and brain→ death
- **Other manifestations:** strabismus, ↓ vision, ocular inflammation, eye pain, glaucoma, and orbital cellulitis
- **Dx:** highly suspected on US or CT findings of mass with calcifications

Presbyopia is a common age-related **decrease in lens elasticity** that leads to difficulty with near vision. A history of a middle-aged individual who has to hold books at an arms length to read is classic.

Hollenhorst plaque is a relatively common retinal finding in the geriatric population. Patients often are visually **asymptomatic** and present with **retinal emboli** from plaque ulceration in the internal carotid artery.
BNS = Doppler US

Contents

ORAL CAVITY

SALIVARY GLANDS

SIALADENOSIS

- Benign, non-tender, non-inflammatory enlargement of salivary glands
- **Causes:** Commonly in pts with advanced **liver disease** (e.g. alcoholic and non-alcoholic cirrhosis), also in pts with altered dietary patterns or **malnutrition** (e.g. diabetes, bulimia)
- Associated with abnormal autonomic innervation of the glands, with accumulation of secretory granules in acinar cells.
- **D/D:** sialadenitis (focal tenderness, erythema, fever), salivary gland stones (glandular swelling and pain with meals), and malignancy
- No management is needed other than to address any underlying nutritional disorders.

PLEOMORPHIC ADENOMA

- Benign neoplasm affecting salivary glands
- Present as firm nodule

ORAL LEUKOPLAKIA

- Reactive precancerous lesion that represent **hyperplasia of squamous epithelium**
- **Risk factors:** same as those for squamous cell CA, with **smokeless tobacco (tobacco chewing)** or **alcohol use** accounting for most cases
- **C/F:** white granular patch or plaque over buccal mucosa, cannot be scraped off.
- **Natural history** depends on degree of dysplasia, with 1-20% lesions progressing to squamous cell CA in 10 years
- **Most resolve** within a few weeks with cessation of tobacco use
- The development of areas with induration and/or ulceration should prompt biopsy to rule out malignant transformation of the lesion

ORAL CANDIDIASIS

- **Risk factors:** DM, immunodeficiency, use of antibiotics or inhaled glucocorticoids
- **C/F:** white plaques on oral mucosa, tongue, or oropharynx with underlying erythema→ can be scraped off with tongue depressor

TEMPOROMANDIBULAR JOINT (TMJ) DYSFUNCTION

- Most pts have a h/o nocturnal teeth grinding
- Pts usually interpret pain as coming from ear—worsened by chewing
- Many have audible clicks or crepitus with jaw movement—not seen in all pts

- Radiologic imaging is of limited use
- **Management:**
  - Initial management: conservative such as nighttime bite guard
  - Surgical intervention is sometimes necessary

GLOSSOPHARYNGEAL NEURALGIA

- Intermittent, severe, stabbing pain in areas innervated by CN IX and X, which includes ear

RAMSAY HUNT SYNDROME

- Form of herpes zoster infection
- Causes Bell's palsy
- Vesicles seen on outer ear

EAR

HEARING LOSS

Interpretation of Weber & Rinne tests		
	Rinne result	**Weber result**
Normal	Air conducted > bone conducted bilaterally	Midline
Conductive hearing loss	BC > AC in **affected** ear, AC > BC in **unaffected** ear	Lateralizes to **affected** ear
Sensorineural hearing loss	AC > BC in **both** ears	Lateralizes to **unaffected** ear, **away** from affected ear
Mixed hearing loss	BC > AC in **affected** ear, AC > BC in **unaffected** ear	Lateralizes to **unaffected** ear, **away** from affected ear

CONDUCTIVE HEARING LOSS

- **Causes:** cerumen impaction, middle ear fluid or infection, ↓ movement of small bones of ear or bony tumor of middle ear

OTOSCLEROSIS

- Common cause of conductive hearing loss in adults, typically in 20s and 30s
- Slight female predominance
- **Pathophysiology:** abnormal remodeling of otic capsule, thought to be a possible autoimmune process in genetically susceptible individuals. The stapes footplate becomes fixed to the oval window, resulting in loss of its piston action. Sometimes referred to as otospongiosis as CT scan may show a lucent (as opposed to sclerotic) focus in the temporal bone near the oval window.
- Low frequency hearing loss
- **Rx:** hearing amplification or surgical stapedectomy

SEROUS OTITIS MEDIA

- Most common middle ear pathology in pts with AIDS
- Due to auditory tube dysfunction arising from HIV LAD or obstructive lymphomas
- **Characterized by**: middle ear effusion without acute infection
- **C/F**: conductive hearing loss (most common feature)
- **Examination**: dull, hypomobile tympanic membrane on pneumatic otoscopy

SENSORINEURAL HEARING LOSS

PRESBYCUSIS

- Disease of aging and usually first noticed in 6th decade of life.
- Although dis. of aging but many factors have been shown to influence rate of hearing loss, including medicines, genetics, h/o infections, and exposure to loud noise
- Begins with symmetrical, high frequency hearing impairment
- Pts often complain of difficulty hearing in crowded or noisy environment, trouble hearing high-pitched noises or voices

MALIGNANT OTITIS EXTERNA

- Typically seen in elderly diabetic pts (poorly controlled) or otherwise immunosuppressed pts
- **Most common cause:** Pseudomonas aeruginosa
- **C/F:** ear pain (typically worse at night), purulent ear drainage with sense of fullness not responsive to topical meds and conductive hearing loss, fever and elevated ESR
- **Otoscopy: Granulation tissue** and edematous external auditory canal is characteristic
- **Progression**→ osteomyelitis of skull base→ CN damage e.g. facial nerve. Or osteomyelitis of TMJ→ pain with chewing
- **Dx:** CT or MRI to confirm diagnosis
- **Rx: systemic antibiotics** effective against P. aeruginosa. **IV ciprofloxacin**—DOC for elderly pts. in patients with fluoroquinolone-resistant P aeruginosa, alternate therapies include anti-pseudomonal penicillins or cephalosporins such as piperacillin and ceftazidime.
    - Failure to respond to antibiotics→ surgical debridement of necrotic tissue (not surgical excision) and biopsy to exclude malignancy

Classification & features of hearing loss		
Type	**Sensorineural**	**Conductive**
Cause	Disorder involving inner ear, cochlea, or auditory nerve	Any cause that limits sound from gaining access to the inner ear
Examples	• Presbycusis • Meniere disease • Barotrauma • Acoustic neuroma • Cerebrovascular ischemia	• Otitis externa or media • Cholesteatoma • Trauma • Cerumen • Tympanic membrane perforation

Antibiotics effective against *Pseudomonas aeruginosa*	
Class	**Drugs**
Anti-pseudomonal penicillins	• Ticarcillin • Piperacillin
Cephalosporins	• Ceftazidime (3rd generation) • Cefepime (4th generation)
Aminoglycosides	• Amikacin • Gentamicin • Tobramycin
Fluoroquinolones	• Ciprofloxacin • Levofloxacin
Monobactams	• Aztreonam
Carbapenems	• Imipenem • Meropenem

Otitis externa	
Risk factors	• Trauma/foreign material (eg, cotton swab, hearing aid) • Exposure to outdoor water sources (eg, swimming) • Skin disruption (eg, psoriasis, eczema, contact dermatitis)
Clinical manifestations	• Pruritus, pain & discharge, hearing loss • Tenderness with tragal pressure/auricle manipulation • Ear canal with erythema, edema & cerumen/purulent debris
Management	• Remove debris from canal (eg, wire loop) • Ototopical corticosteroid (inflammation) plus antibiotic (infection) • Culture of exudate in recalcitrant cases

DIZZINESS

- Need to be classified as:
  1. Vertigo—spinning of room
  2. Presyncope
  3. Disequilibrium

VERTIGO

- Classified as:
  - Central—lasts longer than peripheral
  - Peripheral

MENIERE'S DISEASE

- Abnormal accumulation of endolymph within inner ear
- Ear fullness
- Tinnitus
- Sensorineural hearing loss→ preference of using cell phone on other ear

NOSE

ALLERGIC RHINITIS

Allergic rhinitis	
Symptoms	• Rhinorrhea, nasal congestion, sneezing, nasal itching • Cough secondary to postnasal drip • Fatigue, irritability • Ocular itching & tearing
Physical examination	• "Allergic shiners" (infraorbital edema & darkening) • Dennie-Morgan lines (prominent lines on lower eyelids) • "Allergic salute" (transverse nasal crease) • Pale, bluish, enlarged turbinates • Pharyngeal cobblestoning • "Allergic facies" (high-arched palate, open-mouth breathing)
Treatment	• Intranasal corticosteroid • Allergen avoidance

Conjunctival edema, or thick green nasal discharge may be present

- **Intranasal glucocorticoids—**most effective, effect usually felt in several hours but maximal benefits require use for several days to weeks
- Nonsedating oral antihistamines (eg, loratadine, cetirizine), antihistamine (eg, azelastine) or cromolyn nasal sprays, and leukotriene modifiers (eg, montelukast) are less effective but can be considered based on the patient's symptoms and drug tolerances

ASPIRIN EXACERBATED RESPIRATORY DISEASE (AERD)

- Consists of:
  - Asthma
  - Chronic rhinosinusitis with nasal polyposis → recurrent nasal discharge and congestion and bland tasting food due to anosmia
  - Bronchospasm or nasal congestion following ingestion of aspirin or NSAIDS
- **Dx:** clinical when all above 3 are present. Examination should reveal:
  - Presence of b/l grey, glistening mucoid masses in nasal cavity
- **Management:** surgery provides temporary relief as polyps reappear. Ultimate treatment should be geared towards medical management of underlying etiology

→ Pregnant women have an increased incidence of pyogenic granulomas on the anterior nasal septum. These highly vascular lesions are frequent sources of nose bleeds during pregnancy

THROAT

PERITONSILLAR ABSCESS

- Complication of tonsillitis (fever, chills and sore throat)
- **C/F:** muffled voice or "**hot potato voice",** difficulty swallowing, deviation of uvula, prominent U/L LAD (U/L LAD and deviation of uvula distinguishes it from epiglottitis)
- Can be fatal 2* to airway obstruction or spread of infection to parapharyngeal space which may involve carotid sheath→ erosion of carotid artery and jugular thrombophlebitis
- **Management:**
  - **Initial:** needle aspiration of tonsillar abscess and initiation of IV antibiotics
  - **Surgical drainage** if purulent material cannot be removed with aspiration alone

ENT-SURGERY

NASOPHARYNGEAL CARCINOMA

- Undifferentiated CA of squamous cell origin
- Higher frequency in Mediterranean and Far Eastern population
- Usually asymptomatic until disease is advanced; usually metastasized by the time of diagnosis
- **Sx:** recurrent otitis media (due to obstruction of Eustachian tube by tumor), recurrent epistaxis, and/or nasal obstruction
- **Strong association:** positive serologies for EBV. The association is so strong that EBV titer levels may be used to track the progress of therapy for this malignancy
- **Other associations:** smoking and with chronic nitrosamine consumption (as in diets rich in salted fish)

DEEP NECK SPACE INFECTION

- They have become rare because of antibiotics
- Can spread rapidly and can be fatal

RETROPHARYNGEAL SPACE INFECTION/ABSCESS:

- **C/F:** neck pain, fever, and limited neck mobility secondary to pain, difficulty swallowing (dysphagia), pain with swallowing (odynophagia). Trismus (inability to open the mouth normally) and limited cervical extension— very common
- **Source of infection:** usually local penetrating trauma, which may occur after instrumentation or following an injury from a chicken bone
- **Complete evaluation of extent of infection:** CT of the neck and/or lateral radiographs of the neck— may demonstrate lordosis of the cervical spine with gas and swelling in the retropharyngeal space.
- **Treatment:** IV broad-spectrum antibiotics and urgent drainage of the abscess—to avoid spread into the mediastinum
- **Complications:**
  - Highest risk of spread to mediastinum, particularly anterior and posterior portions of superior mediastinum + entire length of posterior mediastinum
  - Abscess can form in "danger space", which is the space between alar and prevertebral fascia and drain by gravity in to posterior mediastinum, resulting in acute necrotizing mediastinitis
  - Early diagnosis and debridement of mediastinum—essential in treatment of this severe complication

LUDWIG ANGINA

- An infection in the submandibular space, also known as Ludwig's angina, typically begins in the floor of the mouth and extends through the submandibular and sublingual space into the tissues surrounding the airway It does not commonly extend into the mediastinum
- Sublingual space is a division of the submandibular space. As a result, an infection in the sublingual space is classified as a submandibular infection as well, which typically involves the tongue, palate, pharynx, epiglottis, and tissues surrounding the upper airway.

TORUS PALATINUS

- Chronic benign bony growth (i.e. exostosis) located on midline suture of hard palate
- Can be due to genetic or environmental factors
- More common in younger pts, women and Asians
- Usually <2cm but can ↑ in size throughout a person's life
- Non-tender and chronic
- Thin epithelium overlying bony growth, ulcerates with normal trauma of oral cavity and heal slowly due to poor vascular supply
- **Management:** surgery for those in whom mass becomes symptomatic, interferes with speech or eating, causes problems with fitting of dentures later in life

ENT-PEDIATRICS

EAR

Hearing imapirment in children
- Undetected hearing impairment can lead to poor language development and social skills.
- Children suffer from poor self-esteem, isolate themselves and apparent "**inattentiveness".**
ما بعبرك زي واحد حاط سماعة

- Can be easily confused with pervasive and behavioral disorders of childhood (ADHD)
- Children with hearing impairment may be incorrectly diagnosed with ADHD However, poor language development and social isolation are not features of ADHD.

- **Repeated ear infections** can result in conductive hearing loss, so screen them.

- Hearing tests should be routinely conducted in all children presenting with social or language deficits
Qid: **4050**

OTALGIA

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of otalgia	
Diagnosis	**Clinical features**
Acute otitis media	Middle ear effusion **plus** acute eardrum inflammation (eg, bulging eardrum, fever)
Otitis media with effusion	Middle ear effusion without acute inflammation
Bullous myringitis	Serous liquid-filled blisters on the tympanic membrane
Cerumen impaction	Liquid or hard wax in auditory canal obstructing eardrum visualization
Hemotympanum	Purple or red eardrum +/- bulging
Otitis externa	Pain with tragal traction, erythematous & swollen external auditory canal +/- otorrhea

Uncommon complication of acute otitis media

ACUTE OTITIS MEDIA

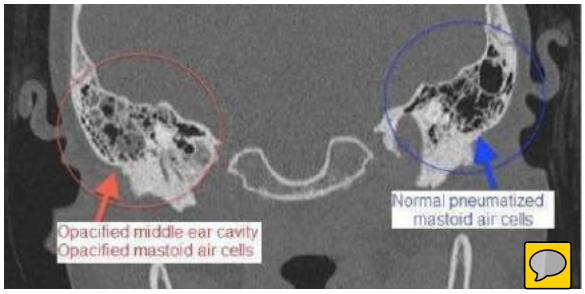
Acute otitis media	
Microbiology	• *Streptococcus pneumoniae* • Nontypeable *Haemophilus influenzae* • *Moraxella catarrhalis*
Clinical features	• Middle ear effusion **plus** • Bulging tympanic membrane
Treatment	• Initial: Amoxicillin • 2nd line: Amoxicillin-clavulanic acid
Complications	• Conductive hearing loss • Mastoiditis • Meningitis

Indicated by hypomobility of membrane on pneumatic insuffulation

Sign of inflammation

Chronic suppurative OM, labrynthitis, cholesteatoma, tympanosclerosis, **eardrum perforation**

- Most common in children **6-36 months (**daycare exposure) and those **around 5 years** (school initiation) as their Eustachian tube is short and easily clogged
- **Risk factors:**
  - Formula rather than breastmilk
  - Exposure to cigarette smoke



    - Allergic rhinitis or viral **URTI**
    - Craniofacial anomalies
    - Chronic middle ear effusion
- **Rx:**
    - 1st line rx: 10-day course of high-dose amoxicillin
    - If pt returns within a month of initial rx→ amoxicillin-clavulanate should be given in anticipation of beta-lactamase-resistant strains
    - Empiric antibiotics usually adequate
    - Tympanocentesis and culture during myringotomy with tympanostomy tube placement should be considered in children with multiple episodes of AOM (eg, >/=3 episodes within 6 months or >/= 4 episodes within 12 months) despite appropriate antibiotic treatment
    - Observation is reasonable if child is >/=2 years, has normal immune system and Sx are mild and u/l
- Children who recover from AOM often have persistent effusion for weeks but do not require ongoing antibiotic treatment

CHRONIC SUPPURATIVE OTITIS MEDIA

- Common pediatric problem.
- Typical symptoms include hearing loss, tympanic membrane perforation, and otorrhea for >6 weeks.
- It can be distinguished from AOM by lack of fever and ear pain + prolonged duration of symptoms

CHOLESTEATOMA

- Can be congenital or acquired

CONGENITAL

- Usually in children around 5 yo

ACQUIRED

- Usually 2* to **chronic middle ear disease**→ formation of retraction pocket in tympanic membrane→ which can fill with granulation tissue and skin debris
- Suspect in pt with continued ear drainage for several weeks despite appropriate antibiotic
- **Complications:** hearing loss, cranial nerve palsies, vertigo and potentially life-threatening infections like brain abscesses or meningitis
- **Refer to otorhinolaryngologist** for dedicated otologic exam, possibly accompanied by CT and/or surgical visualization to confirm diagnosis

---

NOSE

RHINOSINUSITIS

- Most cases are viral and can be treated by observation with follow-up
- But if sx worsen or persist, treatment for bacterial should be started

Diagnostic features of acute bacterial rhinosinusitis
• *Persistent* symptoms ≥ 10 days without improvement OR • *Severe* symptoms, fever ≥ 39 C (102 F), purulent nasal discharge, or face pain ≥ 3 days OR • *Worsening* symptoms ≥ 5 days after initially improving viral upper respiratory infection

- If pts develops complications like periorbital edema, vision abnormalities, altered mental status→ perform CT to identify suppurative complications
- No role of x-ray for diagnosing sinusitis
- **Rx:** oral amoxicillin-clavulanic acid—DOC—covers S. pneumoniae and non-typeable H. influenza. Intranasal steroids may be added for pts with h/o allergic rhinitis. No role of antihistamine
- **Microbiology** unnecessary in uncomplicated ABRS who improve as expected with antibiotic. If symptoms persist or worsen after 3 days of antibiotics, cultures should be obtained by sinus aspiration to better target antimicrobial therapy

JUVENILE ANGIOFIBROMA

- Any adolescent who presents with a nasal obstruction, visible nasal mass, and frequent nosebleeds (epistaxis) is considered to have a juvenile angiofibroma (JNA), unless proven otherwise.
- Typically found in the back of the nose or upper throat (nasopharynx) of adolescent boys.
- Benign growth, but capable of eroding and locally invading
- **Potentially very dangerous because:**
  - Composed of many blood vessels which may bleed readily
  - Common areas of occurrence are difficult to access surgically
- For these reasons, such tumors should only be touched by a specialist
- **Management:**
  - No treatment is necessary in some cases
  - Rx is required if it is enlarging, obstructing the airway, or causing chronic nosebleeds.
  - Surgical treatment includes removal of the tumor— often difficult because the tumor is unencapsulated and may be deeply invasive.
  - Recurrence of the tumor after surgical resection is common.

Loop diuretics can cause reversible or permanent **hearing loss** and/or tinnitus. These ototoxic effects typically occur in patients taking high doses of loop diuretics, those with coexistent renal failure, or in patients who are also being treated with other known ototoxic medications, such as **aminoglycosides**.

Contents

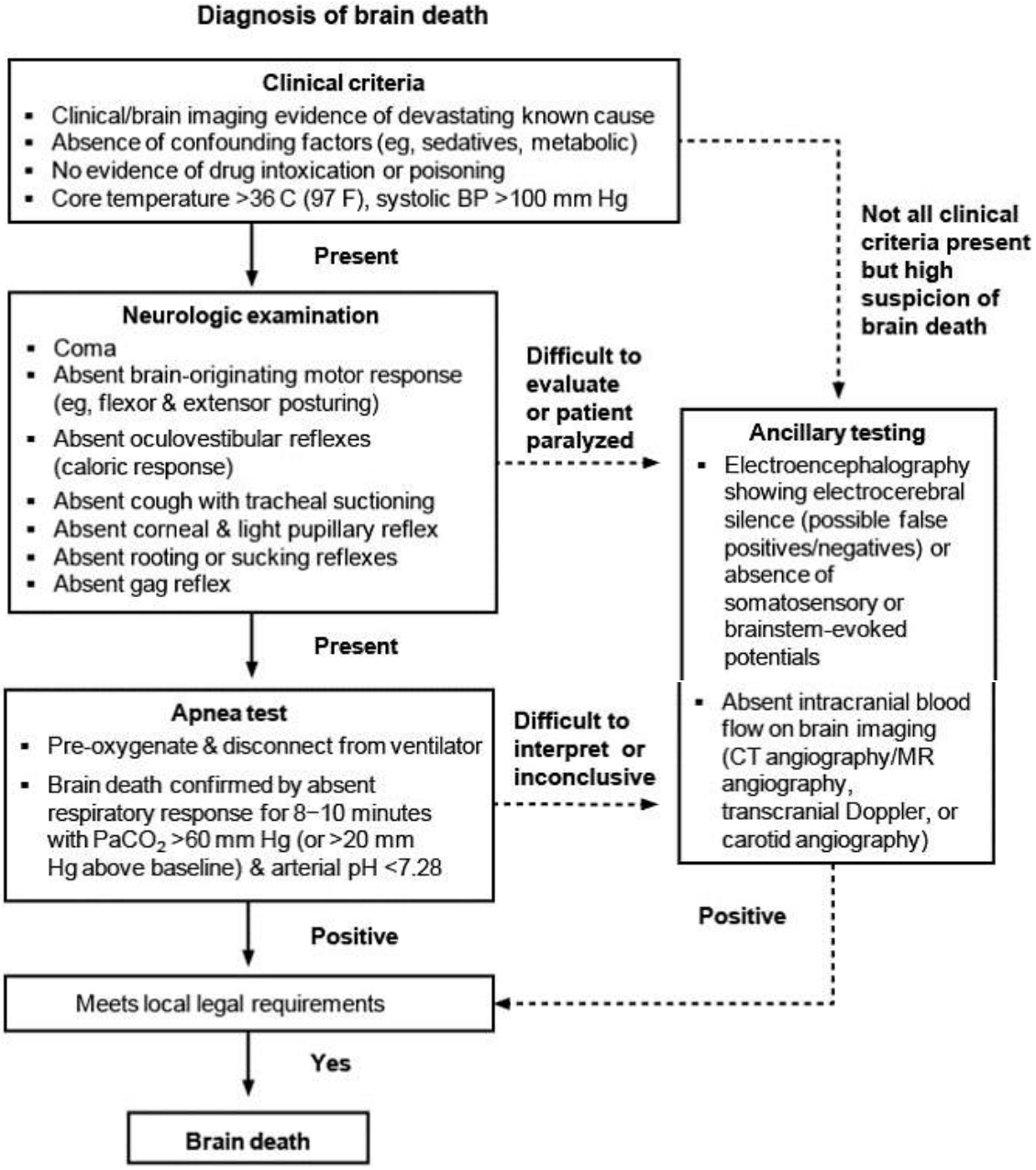
HOSPICE MODEL

Hospice model
• Focus on quality of life, not cure or life prolongation • Symptom control (pain, nausea, dyspnea, agitation, anxiety, depression) • Interdisciplinary team (medical, nursing, psychosocial, spiritual, bereavement care) • Services provided at home, assisted living facility, or dedicated facility • Requires survival **prognosis of ≤6 months**

FIREARM INJURY

Firearm injury	
Risk factors	• Male adolescent • Behavior or psychiatric problems • Impulsive, violent, or criminal behavior • Low socioeconomic status
Prevention	• **Remove all firearms from the home** • Store firearms unloaded • Lock firearms & ammunition in separate containers

BRAIN DEATH


Diagnosis of brain death
Clinical criteria
Clinical/brain imaging evidence of devastating known cause
Absence of confounding factors (eg, sedatives, metabolic)
No evidence of drug intoxication or poisoning
Core temperature >36 C (97 F), systolic BP >100 mm Hg
Present
Not all clinical criteria present but high suspicion of brain death
Neurologic examination
Coma
Absent brain-originating motor response (eg, flexor & extensor posturing)
Absent oculovestibular reflexes (caloric response)
Absent cough with tracheal suctioning
Absent corneal & light pupillary reflex
Absent rooting or sucking reflexes
Absent gag reflex
Difficult to evaluate or patient paralyzed
Ancillary testing
Electroencephalography showing electrocerebral silence (possible false positives/negatives) or absence of somatosensory or brainstem-evoked potentials
Absent intracranial blood flow on brain imaging (CT angiography/MR angiography, transcranial Doppler, or carotid angiography)
Present
Apnea test
Pre-oxygenate & disconnect from ventilator
Brain death confirmed by absent respiratory response for 8−10 minutes with PaCO2 >60 mm Hg (or >20 mm Hg above baseline) & arterial pH <7.28
Difficult to interpret or inconclusive
Positive
Positive
Meets local legal requirements
Yes
Brain death

CIRCUMSTANCES IN WHICH MINORS DO NOT NEED CONSENT

Circumstances in which minors do not require consent	
Medical circumstances	• Emergency care • Sexually transmitted infections • Substance abuse (most states) • Prenatal care (most states)
Emancipated minor	• Homeless • Parent • Married • Military • Financially independent • High school graduate

Mental health services

- Minor with emergency situation→ no consent needed
- Stable minor but life-threatening condition and parents not agreeing to treatment → hospital ethics committee, social services, and hospital risk management can also assist→ in some cases parents may agree but if they continue to refuse treatment→ obtain court orders to give treatment

PERFORMING PROCEDURES ON DECEASED PATIENT

- Permission from patient before death or from family is must before performing procedures on deceased pt for training
- If previously obtained consent from pt is not documented or appropriate family member is not available to give consent→ do not perform procedure

CLINICAL FEATURES OF POSSIBLE CHILD ABUSE

Clinical features of possible child abuse	
Risk factors	**Caregiver background** • Young or single parents • Lower education levels • Drug or alcohol abuse • Psychiatric conditions (depression, impulsive behavior) • Nonbiological caregivers **Home environment** • Unstable family situation (eg, divorce) • Financial difficulties or loss of job • Social isolation **Victims** • Pre-existing medical, psychological, or developmental disorder
Clinical presentation	• Unexplained injuries (eg, bruises, fractures, burns) • Injuries in different stages of healing • Forced ingestion or intentional poisoning of child • Starvation of child • Sudden behavioral changes in child • Change in scholastic performance

Contents

POISONING

SMOKE INHALATION INJURY

- Estimated to cause 60%-80% of deaths during **fire incidents**.
- Smoke injury causes:
  - Glottic edema from heat
  - Airway irritation due to particulate matter found in smoke.
  - Smoke also contains multiple toxins that are absorbed systemically.
- Hydrogen cyanide (HCN) and carbon monoxide (CO) are the 2 major products of combustion in closed spaces.

CARBON MONOXIDE POISONING

Features of carbon monoxide (CO) poisoning	
Symptoms	Mild-moderate intoxication: • **Headache** (most common), confusion • Malaise, dizziness, nausea Severe intoxication: • Seizure, syncope, coma • Myocardial ischemia, arrhythmias
Causes	• **Smoke inhalation** (most common) • Defective heating systems • Use of fuel-burning appliances or motor vehicles in poorly ventilated areas
Diagnosis	• **Carboxyhemoglobin level** • Check ECG in all patients • Measure cardiac enzymes in the elderly & in those with cardiac risk factors or signs of ischemia
Treatment	• **100% oxygen** (non-rebreathing face mask)

Competes with CO for binding to Hb and also ↓ CO half-life from 5 hours at room air to 1-2 hours at 100% O2—monitor for >/=4 hrs after 100% O2→ hospitalize if condition does not improve

- Colorless, odorless gas emitted by automobiles, furnaces and charcoal grills
- **Pathogenesis:** prevents utilization of oxygen by tissues
- **Acute poisoning C/F:** vomiting, abdominal discomfort. Some have pinkish-red skin hue. Bright cherry lips can be a sign but non-specific
- **Dx:** clinical and confirmed by carboxyHb (e.g. >3% in non-smoker and >10% in smokers)
- **Rx:** hyperbaric oxygen is sometimes used if pt does not respond to face-mask administered O2

CYANIDE TOXICITY

- **MOA of cyanide:** potent inhibitor of cytochrome oxidase a3 in the mitochondrial electron transport chain. It binds to ferric iron (Fe3+), inhibiting its reduction to ferrous iron (Fe2+) and blocking production of ATP from oxidative phosphorylation→ cells switch to anaerobic metabolism→ lactic acid formation→

metabolic acidosis→ ↓ in serum bicarbonate in an attempt to buffer excess acid. Metabolic acidosis also triggers central and peripheral chemoreceptors, increasing alveolar ventilation → tachypnea→↓ in arterial PCO2 (PaCO2).

- Combustion of nitrogen-containing synthetic polymers (eg, foam, cotton, paint, silk, rubber, plastic), mining or pesticides→ inhalational, dermal or intestinal hydrogen cyanide (HCN) poisoning
- Sx very similar to CO poisoning—hence, history very imp
- Bitter almond breath is characteristic
- HCN—potent and fast-acting poison
- Blood levels cannot be measured rapidly to confirm diagnosis prior to treatment→ hence empiric treatment is given in smoke cases
- **Exposure to moderate to high concentrations** causes symptoms to develop within seconds to minutes.
- **Early acute toxicity:** neurologic and cardiorespiratory stimulation→ headache, vertigo, dizziness, hyperventilation, tachycardia, nausea, and vomiting.
- **Neurologic, respiratory, and cardiovascular depression** eventually occurs→ causes coma, seizures, bradycardia, hypotension, and cardiorespiratory arrest.
- HCN can also cause anoxic brain injury leading to permanent neurologic deficits.
- Markedly elevated lactate (typically >10 mEq/L)
- **Management:**

Treatment overview for suspected cyanide poisoning	

Decontamination	**Dermal exposure**
	• Removal of clothing
	• Skin decontamination
	Ingestion
	• Activated charcoal
	All exposures
	• Antidote
	  ◦ Hydroxocobalamin preferred
	  ◦ Sodium thiosulphate as alternate therapy
	• Antidote not available
	  ◦ Nitrites to induce methemoglobinemia

Respiratory support	• No mouth-to-mouth resuscitation • Supplemental oxygen • Airway protection (intubation)
Cardiovascular support	• Intravenous fluids for hypotension

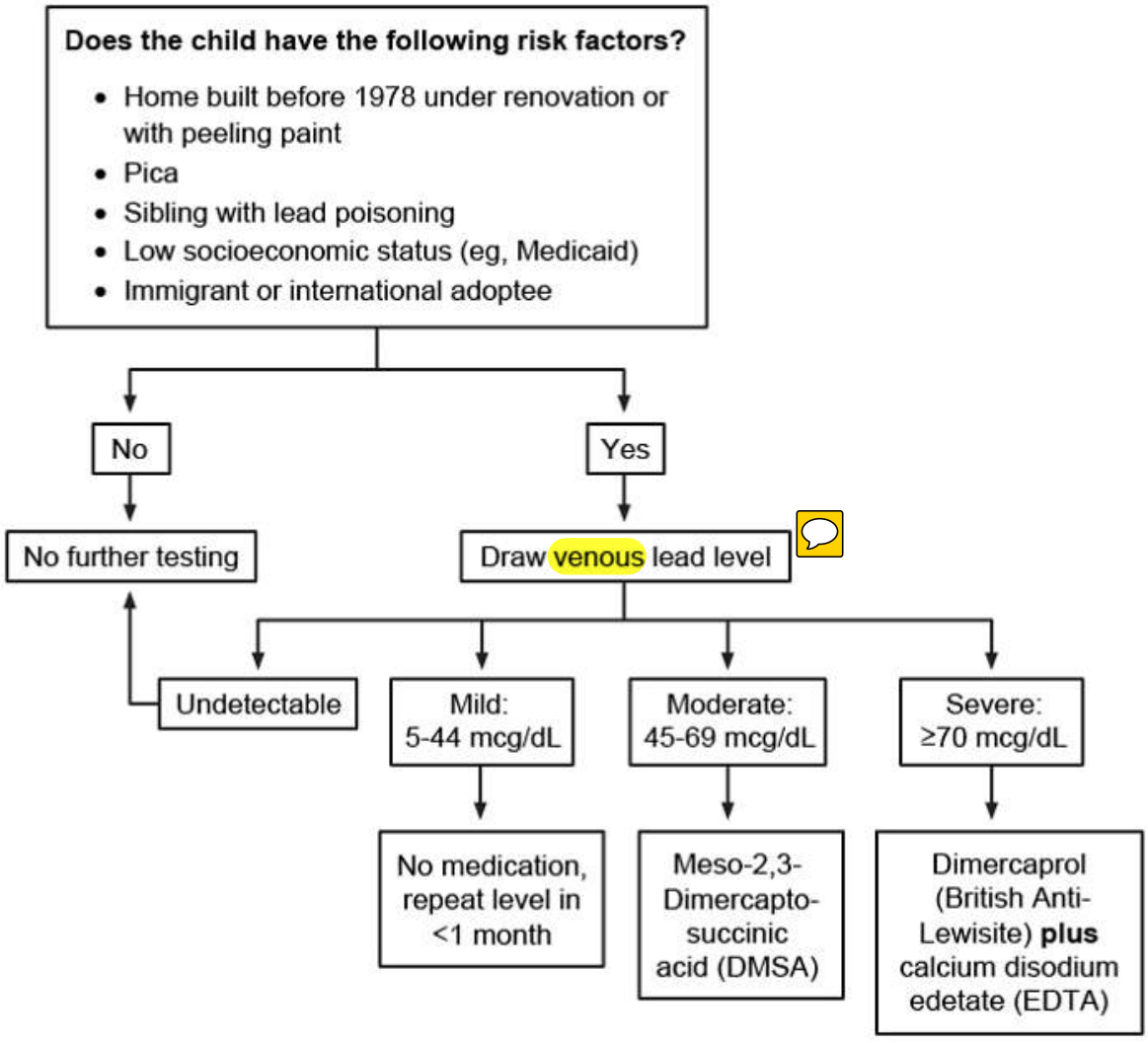
METHEMOGLOBINEMIA

- Methemoglobin forms when Fe2+ is oxidized to Fe3+. Oxygen does not bind to Fe3+ and ↑es affinity of Fe2+ for oxygen→ left shift in oxygen dissociation curve→ functional anemia due to ↓ oxygen supply to tissues
- Many similarities to CO poisoning
- Can be due to oxidizing agents (e.g. dapsone, nitrates, topical/local anesthetics) or environmental exposure
- Presents with cyanosis and bluish discoloration of skin and mucous membranes

- **Rx:** methylene blue

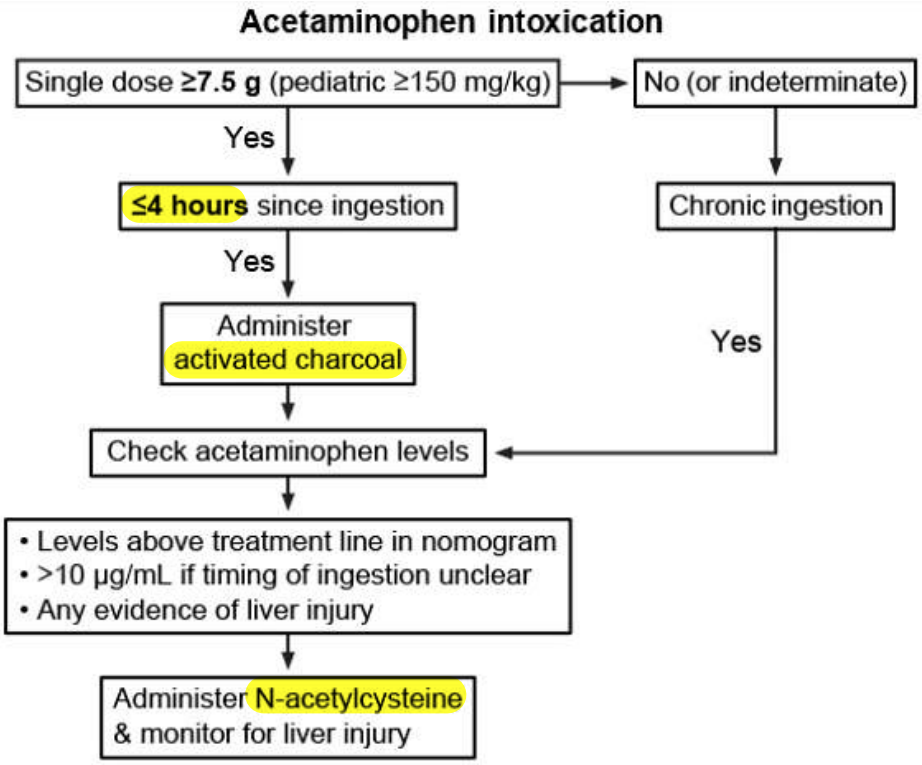
LEAD POISONING

Approach to childhood lead poisoning



- **Other risk factors**: lead piping, living near a battery recycling plant, having a parent who works with batteries or pottery, or having a playmate or sibling with a history of lead poisoning, or play with toys passed from older generations.
- **Targeted screening of high-risk population**→ imp. As may be initially asymptomatic but may have cognitive and behavioral problems that become apparent on start of schooling
- **Capillary (fingerstick) blood specimens**— widely used in screening for lead poisoning, but **false-positive** results are common. Confirmatory **venous lead measurement** is required if a screening capillary lead level is >/=5 µg/dL→ confirmed→ removal from environment is best step
- **Moderate or severe or abdominal Sx (**e.g. constipation, abdominal pain, nausea)→ abdominal x-ray cn be done. May show abdominal lead flecks—not routinely indicated

ACETAMINOPHEN INTOXICATION



- Usually asymptomatic within 24 hours or may have only nonspecific symptoms such as N/V and anorexia
- After 24 hours, pts may develop severe liver injury
- No hematemesis
- The Rumack-Matthew nomogram provides the likelihood of hepatotoxic effects of acetaminophen overdose after a single ingestion based on plasma acetaminophen level and hours since ingestion. This tool is also used in guiding the administration of N-acetylcysteine in patients with dangerous acetaminophen levels. The first data point begins at 4 hours. However, patients with an overdose often report incorrect times and doses; although an acetaminophen level may not be predictive of hepatotoxicity at this stage, it is prudent to obtain one. If the level is not within the toxic range by the nomogram, it should be repeated in 2 hours based on the patient's history of ingestion.

SALICYLATE INTOXICATION

- Tinnitus, N/V, fever
- Altered mental status and acid base abnormalities (combined metabolic acidosis and resp. alkalosis)
- **Rx:** alkalinization of urine with sodium bicarb

** salicylates have multiple effects on the body:
- hyperventilation and **early respiratory alkalosis**
aspirin directly stimulates the respiratory centers in the brainstem
- later metabolic acidosis, resulting metabolic **metablic acidosis-respiratory alkalosis**
- ABGs show **near-normal pH** with mixed respiratory alkalosis and metabolic acidosis.

IRON POISONING

Iron Poisoning	

Clinical features	• Within 30 minutes to 4 days:
	  • Abdominal pain
	  • Vomiting (eg, hematemesis)
	  • Diarrhea (eg, melena)
	  • Hypotensive shock
	  • Metabolic acidosis
	• Within 2 days: hepatic necrosis
	• Within 2-8 weeks: pyloric stenosis

Diagnostic findings	• Anion gap metabolic acidosis • Radiopaque pills On x-ray
Treatment	• Whole bowel irrigation • Deferoxamine • Supportive care for circulation, airway and breathing

Coagulopathy, seizure and death can occur

Dx confirmed by serum iron levels. X-ray further proves diagnosis

- **Mechanism of iron poisoning:** free radical production and lipid peroxidation→ impair various cell processes → systemic manifestations. Also a potent vasodilator→ hypotensive shock and anion gap metabolic acidosis (↓ bicarb) due poor perfusion and accumulation of lactic acid
- Respiratory alkalosis develops as a result of compensation of metabolic acidosis
- **Management:** depends on severity of poisoning
  - IV volume resuscitation
  - IV deferoxamine, antidote for moderate to severe iron poisoning→ binds ferric iron and causes its urinary excretion
- Other methods of decontamination like activated charcoal, ipecac, gastric lavage are not routinely recommended

CAUSTIC INGESTION

Caustic ingestion	
Clinical features	Chemical burn or liquefaction necrosis resulting in: • Laryngeal damage: Hoarseness, stridor • Esophageal damage: Dysphagia, odynophagia • Gastric damage: Epigastric pain, bleeding
Management	• Secure airway, breathing, circulation • Decontamination: Remove contaminated clothing & visible chemicals; irrigate exposed skin • Chest x-ray if respiratory symptoms • Endoscopy within 24 hours
Complications	• Upper airway compromise • Perforation • Strictures/stenosis (2-3 weeks) • Ulcers • Cancer

IV hydration

Hospitalize under close supervision for any developing airway compromise

- **Sodium or potassium hydroxide (lye)—**strong caustic alkaline solution
- **Management:**
  1. **Serial chest and abdominal x-ray:** look for perforation
  2. **Suspected perforation:** upper GI x-ray with water soluble contrast
  3. **Upper GI endoscopy** within 12-24 hours in the absence of perforation and severe respiratory distress in hemodynamically stable pt—extent of damage may not be apparent if performed early and delay ↑es risk of perforation—nasogastric tube can be placed during this under direct visualization and not blindly
     - No or mild esophageal injury: may be managed with simple supportive care
     - Significant injury: may require tube feeding and possible surgery (esophagectomy)
     - Pt with persistent dysphagia or significant esophageal burns on endoscopy→ perform **barium swallow 2-3 wks** after ingestion to assess for esophageal strictures or pyloric stenosis
- **DON'Ts:**
  - Any measure that can cause vomiting, as vomiting can ↑ extent of mucosal damage, like giving:
    - Milk
    - Water
    - Ipecac—induces vomiting
    - Activated charcoal—also inhibits visualization of esophagus during endoscopy
    - Vinegar—also combines with alkaline substance→ exothermic reaction → burn mucosa further
    - Nasogastric lavage

CHEMICAL CONTACT WITH EYE

- In the case of any chemical contact with the eye, the first priority is to **immediately begin flushing** the affected eye with **copious amounts of running water**. This can best be achieved by holding the eyelid open under a running faucet for **at least 15 minutes before evaluation**.

- Calling the emergency room, 911, or the neighborhood doctor would all be appropriate actions after initiating flushing of the eye.
- Exposure to acid→ good chance of full recovery
- Exposure to alkali→ permanent corneal damage more likely.
- Regardless, flushing the eye with water is the appropriate initial course of action for both cases.

➔ In case of cut, scratch or foreign body in eye→ seek medical care first

ORGANOPHOSPHATE POISONING

- Inhibits acetylcholine esterase→ ↑ Ach→ cholinergic symptoms
- **Presentation:**
  - Bradycardia
  - Miosis
  - Bronchorrhea→ rhonchi
  - Muscle fasciculations
  - Salivation
  - Lacrimation
  - Diarrhea
  - Urination
- **Management:**
  - Give atropine immediately→ competes with Ach at muscarinic receptors→ reverse muscarinic symptoms
  - Equally important is removal of clothing which may be contaminated by pesticide and washing skin to prevent organophosphate absorption through skin

DIPHENHYDRAMINE POISONING

- Antihistamine with anticholinergic properties
- Overdose can cause:
  - **Antihistaminic effects:** confusion and drowsiness
  - **Anticholinergic effects:**
    - Dry mouth/dry skin ("dry as a bone")
    - Blurry vision/mydriasis ("blind as a bat")
    - Hyperthermia from impaired heat dissipation ("hot as a hare")
    - Urinary retention ("full as a flask")
    - Decreased bowel sounds
    - Cutaneous vasodilation (“red as a beet”)
    - Hallucinations or delirium (“mad as a hatter”)
- **Management:** physostigmine, cholinesterase inhibitor

THEOPHYLLINE INTOXICATION

- Low therapeutic index
- **Intoxication can cause**: seizures, hyperthermia, cardiac arrhythmias, tachycardia, and hypotension.

TRICYCLIC ANTIDEPRESSANTS (TCA) OVERDOSE

Clinical features & management of tricyclic antidepressant overdose		
Clinical presentation	Central nervous system	• Mental status changes (eg, drowsiness, delirium, coma) • Seizures, respiratory depression
	Cardiovascular	• Sinus tachycardia, hypotension • Prolonged PR/QRS/QT intervals • Arrhythmias (eg, ventricular tachycardia, fibrillation)
	Anticholinergic	• Dry mouth, blurred vision, dilated pupils • Urinary retention, flushing, hyperthermia
Management	Supportive care & therapy	• Supplemental oxygen, intubation • Intravenous fluids • Activated charcoal for patients within 2 hours of ingestion (unless ileus present) • Intravenous sodium bicarbonate for QRS widening or ventricular arrhythmia

If QRS >100msec

- The EKG, with specific attention to the QRS complex, is the best indicator of the extent of overdose because QRS duration has been shown in studies to have value in predicting the likelihood of seizures and ventricular arrhythmia
- **Major cause of mortality:** TCA induced hypotension
- **1st step in management:** ABC
  - **Airway:** ensure patent airway
  - **Breathing:** ensure adequate breathing
  - **Circulation:** cardiac monitors, oximetry and IV lines should be established
- **Role of sodium bicarbonate:** Alleviate the inhibitory action of TCA on fast sodium channels of the His-Purkinje and myocardium, improving hypotension and decreasing the risk of fatal ventricular arrhythmias (by shortening the QRS interval). Sodium bicarb. ↑es serum pH (goal 7.50-7.55) and ↑ serum sodium level:
  - **↑ pH→** ↓es drug avidity for sodium channel
  - **↑ Na+→** ↑ electrochemical gradient across cardiac cells and affects the ability of TCAs to bind fast sodium channel
- **Seizures cox' of TCA:** caused by inhibition of GABA—hence treated with GABA agonist like benzodiazepines instead of Na+-channel blocking agents like phenytoin (as it can cause hypotension and arrhythmia)

LITHIUM TOXICITY

- Hemodialysis is the treatment choice for severe lithium toxicity because it is the most dialyzable toxin.

OPIOID

INTOXICATION

- **Sx:**
  - Depressed mental status
  - Depressed respiratory rate and effort→ **best indicator of intoxication** and a frequent cause of mortality
  - Small constricted pupils (miosis)—can be normal or enlarged as can be counteracted by coingestants + meperidine and propoxyphene do not cause miosis even if taken alone—hence not reliable
  - Bradycardia
  - Hypotension due to histamine release
  - ↓ bowel sounds
  - Hypothermia—due to environmental exposure and impaired thermoregulation
- **Management:**
  - Administer **naloxone** with goal of ↑ing resp. rate to 12/min or greater and improving oxygen saturation
  - Methadone and buprenorphine—long acting opioid agonists not used in acute intoxication—rather used for withdrawal

WITHDRAWAL

- Typically develop withdrawal symptoms within 6-12 hours after last dose of short-acting opioids and peak at 24-48 hours
- **Sx:**
  - Nausea/vomiting
  - Cramps
  - Diarrhea
  - Dysphoria
  - Restlessness
  - Rhinorrhea
  - Lacrimation
  - Myalgias
  - Arthralgia
- **PE:**
  - Mydriasis
  - Piloerection
  - Hyperactive bowel sounds
- Not life-threatening but very uncomfortable
- **Management: oral or IM methadone** to relieve withdrawal symptoms.
- Methadone replacement therapy for chronic management of addiction in the outpatient setting should not be confused with therapy in the inpatient setting as the protocols used in these venues are different. Under federal law, the Drug Enforcement Agency permits treatment or prevention of opioid withdrawal with methadone without regulatory restriction provided the treatment is inpatient and the primary disease is medical (i.e., not opioid withdrawal).
- Benzodiazepines, along with clonidine, antiemetics (promethazine, diphenhydramine), loperamide, or octreotide (for diarrhea and abdominal cramps), are frequently used as adjunctive medications for symptomatic treatment. However, they are not the primary treatment.

COCAINE

INTOXICATION

- Characterized by sympathetic stimulation
  - ↑ HR
  - ↑ BP
  - Dilated pupils (mydriasis)
  - Euphoria
  - Sense of self-confidence
  - ↑ arousal
  - Improved performance on tasks of alertness and vigilance

WITHDRAWAL

- ↑ appetite

PCP

INTOXICATION

- Impaired judgement
- Aggressive behavior
- Ataxia
- Multidirectional nystagmus
- Tachycardia
- Mild HTN

MARIJUANA

INTOXICATION

- Cannabinoid
- **Other names**: pot/weed
- **Signs**:
  - ↑ appetite
  - Tachycardia
  - Tachypnea
  - HTN
  - Dry mouth
  - Conjunctival injection
  - Slow reaction time
  - Impaired attention, concentration and short term memory
  - Impairment of cognition, judgment, and coordination can last much longer than the acute euphoric effect, affecting the ability to operate automobiles and increasing the risk of motor vehicle accidents.

ALCOHOL RELATED TOXICITIES

Toxicity	Clinical features	Laboratory results
Alcohol ketoacidosis	Slurred speech, unsteady gait, altered mentation	High osmolar gap, increased anion gap metabolic acidosis due to ketosis
Methanol ingestion	Visual blurring, central scotomata, afferent pupillary defect, altered mentation	High osmolar gap, increased anion gap metabolic acidosis
Ethylene glycol ingestion	Flank pain, hematuria, oliguria, cranial nerve palsies, tetany	High osmolar gap, increased anion gap metabolic acidosis, **calcium oxalate crystals** in urine
Isopropyl alcohol ingestion	CNS depression, disconjugate gaze, absent ciliary reflex	High osmolar gap, but **no** increased anion gap and **no** metabolic acidosis

METHANOL POISONING

- Sometimes used as a substitute of alcohol—found in antifreeze solutions
- **Initial symptoms:** similar to alcohol ingestion, i.e. disinhibition
- **Within 24 hours**: can lead to headache, N/V, epigastric pain, blurred vision
- **Most severe consequences**: vision loss and coma
- **PE**: optic disc hyperemia
- **Lab results**: anion gap metabolic acidosis. ↑osmolar gap is also seen sometimes. Vomiting and alcoholism can also cause hypokalemia

ETHYLENE GLYCOL POISONING

- Also sometimes used as substitute of alcohol—found in antifreeze solutions
- Initial sx similar to alcohol ingestion
- Clinical consequences occur as alcohol dehydrogenase metabolizes ethylene glycol into glycolic acid and oxalic acid→
  - Glycolic acid→ injures renal tubules
  - Oxalic acid→ binds calcium→ hypocalcemia and calcium oxalate crystal deposition in kidneys
- **Management:**
  - Fomepizole (alcohol dehydrogenase inhibitor) or ethanol→ prevent breakdown of ethylene glycol into toxic metabolites—integral part of treatment
  - Sodium bicarb→ for acidosis
  - Hemodialysis→ if severe acidosis and/or end organ damage

➔ **Profound anion gap metabolic acidosis is found in a few condition like these two, diabetic ketoacidosis** (↑ ketones) **and lactic acidosis** (lactic acid level is very high in lactic acidosis)

SEROTONIN SYNDROME

- **Cause:** Overdose or interaction of serotonergic drugs such as MAO inhibitors and SSRIs

- **C/F:**
    - Autonomic hyperactivity (e.g., tachycardia, hyperthermia, increased bowel sounds, hypertension)
    - Mental status changes
    - Dilated pupils
    - Neuromuscular findings (e.g., clonus, hyperreflexia).

NEUROLEPTIC MALIGNANT SYNDROME

- Dopaminergic antagonists, **"typical" antipsychotics** such as haloperidol are most likely causative agents but atypical antipsychotics can also cause NMS
- Sx typically begin within 2 wks of initiation of causative agent
- Mortality rate: 10-20%
- **Sx:** confusion, fever, muscle rigidity, autonomic instability, diaphoresis, ↑ CK
- **Rx:**
    - Dantrolene: muscle relaxant→ most effective, followed by
    - Bromocriptine: dopamine agonist and
    - Amantadine: antiviral with dopaminergic properties
    - Cessation of causative agent and supportive care

HYPOTHERMIA CAUSED BY FLUPHENAZINE

- Fluphenazine— typical antipsychotic—more potent than haloperidol
- Injected every 2-3 wks to schizophrenics with poor compliance
- Can cause hypothermia by inhibiting the body's shivering mechanism and/or inhibiting autonomic thermoregulation.
- For this reason, patients taking antipsychotic medications should be advised to avoid prolonged exposure to extreme temperatures. Under such conditions, they can develop extreme hypothermia.

BURN INJURY

- Moderate full thickness burn→ give IV fluids and pain management + topical antibiotics (no use of parenteral) and wound dressing→ monitor for signs of healing and development of eschar (i.e. dead tissue)→ sometimes sloughs off and sometimes need surgical debridement
- Eschar in limbs can sometimes cause vascular and lymphatic compromise→ edema and ↓ pulses distal to burn→ perform Doppler USG to document pulses and tissue compartment pressure
- Pressure of 25-40 mmHg—threshold for escharotomy (incision of only eschar layers)→ evaluate for perfusion→ if no signs of improvement → fasciotomy (incision through all fascial layers—also used for compartment syndrome)

HEAT STROKE

- **Types:** exertional and non-exertional
- **Pathogenesis:** In heat stroke, the **thermoregulatory center fails to dissipate heat** at the rate necessary to maintain a euthermic state. Although inadequate fluid and salt replacement may contribute to heat stroke, it does not cause it.
- **Non-exertional:**
    - Occurs in pts with chronic medical conditions, often because they cannot remove themselves from inciting stimulus and/or have impaired thermoregulation due to medications and underlying illness
- **Exertional:**

- Occurs in otherwise healthy individuals undergoing conditioning in extreme heat and humidity. The **body loses its ability to dissipate heat** when the humidity is over 75% and the temperature is elevated.

- **S/S:**
  - Temperature > 40° C (105°F)→ can cause rhabdomyolysis and organ system damage→ large blood but no RBCs on urine dipstick
  - Altered mental status
  - Hypotension
  - Tachycardia
  - Tachypnea
  - Patients may have moist or dry skin and often are not volume-depleted, depending on underlying medical conditions, original hydration status, and rapidity of onset.

HEAT EXHAUSTION

- Inadequate sodium and water replacement during physical activity can lead to heat exhaustion because of the body's inability to maintain adequate cardiac output.
- Core body temperature is usually < 40°C (104°F).
- Significant CNS dysfunction (eg, seizure, delirium) is not present.

HYPOTHERMIA

Clinical features of hypothermia

Classification	**Mild:** 32-35 C (90-95 F) • Tachycardia, tachypnea • Ataxia, dysarthria, **increased shivering** **Moderate:** 28-32 C (82-90 F) • Bradycardia, lethargy, hypoventilation, **decreased shivering**, atrial arrhythmias **Severe:** <28 C (82 F) • Coma, cardiovascular collapse, ventricular arrhythmias
Treatment	**General** • Warmed (42 C [107 F]) crystalloid for hypotension • Endotracheal intubation in comatose patients **Rewarming techniques** • **Mild hypothermia**: Passive external warming (remove wet clothing, cover with blankets) • **Moderate hypothermia**: Active external warming (warm blankets, heating pads, warm baths) • **Severe hypothermia**: Active internal rewarming (warmed pleural or peritoneal irrigation, warmed humidified oxygen)

Confusion

Marked CNS depression, hypotension

Marked hypotension, areflexia and significant acidosis

Laboratory abnormalities in hypothermic patients	
Abnormality	**Mechanism**
Metabolic acidosis	Decreased tissue perfusion
Respiratory acidosis	Hypoventilation
Azotemia	Decreased renal perfusion
Hyperkalemia	Cellular lysis
Hyperglycemia*	Loss of insulin effect <30 C (86 F)
Elevated lipase	Cold-induced pancreatitis
Elevated hematocrit	Hemoconcentration
Coagulopathy	Impaired coagulation pathways
Leukopenia, thrombocytopenia	Splenic sequestration

* Hypoglycemia may be seen in a few patients for reasons that are unclear.

- Treatment should target a warming rate of approximately 1-2 C/hr. Core temperature may initially fall slightly due to increased return of blood from cold extremities. Once patients are euthermic and hemodynamically stable, they may be transitioned to oral fluids and nutrition
- IV fluids and rewarming ineffective in restoring normal BP→ inotropic support with dopamine

POINTERS

- Calcium gluconate is cardioprotective in hyperkalemia
- Vitamin A toxicity: acute→ N/V, blurry vision and chronic→ pseudotumor cerebri
- Vitamin D toxicity: Sx are due to hypercalcemia→ N/V, confusion, polyuria and polydipsia
- Vitamin K toxicity—very rare—in infants can cause hemolytic anemia and hyperbilirubinemia
- Beta-blocker intoxication→ hypotension and bradycardia→ give glucagon

ARSENIC POISONING

Arsenic poisoning	
Mechanism	• Binds to sulfhydryl groups • Disrupts **cellular respiration** & gluconeogenesis
Sources	• Pesticides/insecticides • Contaminated water (often from wells) • Pressure-treated wood
Manifestations	• Acute: Garlic breath, vomiting, watery diarrhea, QTc prolongation • Chronic: Hypo/hyperpigmentation, hyperkeratosis, stocking-glove neuropathy
Treatment	• **Dimercaprol** (British anti-Lewisite) • DMSA (meso-2,3-dimercaptosuccinic acid, succimer)

Arsenic toxicity should be suspected in a patient with possible environmental exposure (eg, pressure-treated wood, pesticides) who has painful sensorimotor polyneuropathy, skin lesions hypo- and hyperpigmented, hyperkeratotic), pancytopenia, and mild transaminase elevation.) .Diagnosis is confirmed with elevated urine arsenic levels

Contents

Language disorder

ASSESSMENT OF DECISION MAKING CAPACITY

Assessment of decision-making capacity	
Criterion	**Patient task**
Communicates a choice	Patient able to clearly indicate preferred treatment option
Understands information provided	Patient understands condition & treatment options
Appreciates consequences	Patient acknowledges having condition & likely consequences of treatment options, including no treatment
Rationale given for decision	Patient able to weigh risks & benefits & offer reasons for decision

DEFENSE MECHANISMS

Key defense mechanisms

Immature (includes primitive & neurotic)

- Acting out: Expressing unacceptable feelings through actions
- Denial: Behaving as if an aspect of reality does not exist
- Displacement: Transferring feelings to a more acceptable object
- Intellectualization: Using intellect to avoid uncomfortable feelings
- Passive aggression: Avoiding conflict by expressing hostility covertly
- Projection: Attributing one's own feelings to others
- Rationalization: Justifying behavior to avoid difficult truths
- Reaction formation: Responding in a manner opposite to one's actual feelings
- Regression: Reverting to earlier developmental stage
- Splitting: Seeing others as all bad or all good

Mature

- Sublimation: Channeling impulses into socially acceptable behaviors
- Suppression: Putting unwanted feelings aside to cope with reality

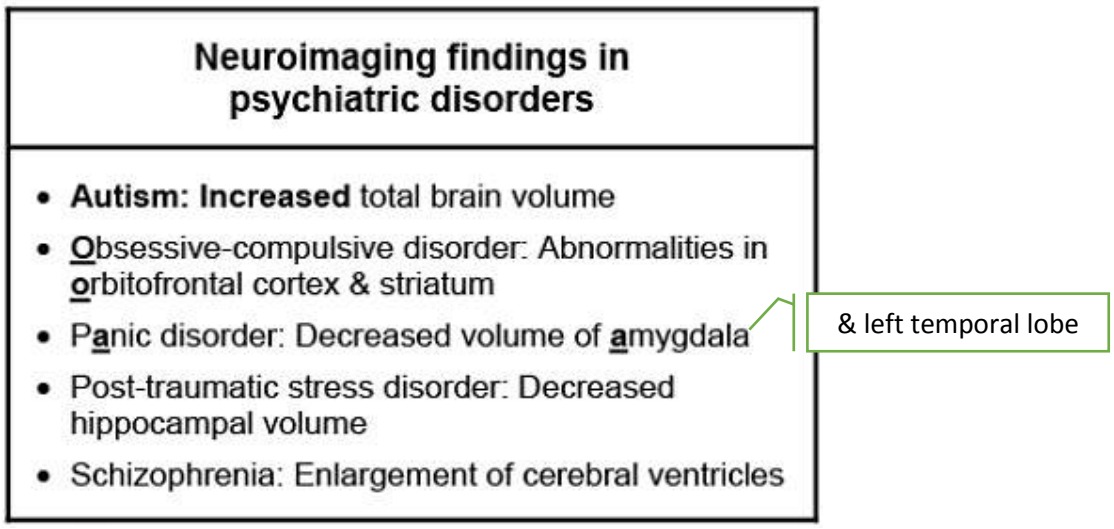
Ego defenses *(continued)*

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Fixation	Partially remaining at a more childish level of development (vs regression).	A surgeon throws a tantrum in the operating room because the last case ran very late.
Idealization	Expressing extremely positive thoughts of self and others while ignoring negative thoughts.	A patient boasts about his physician and his accomplishments while ignoring any flaws.
Identification	Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.	A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.
Intellectualization	Using facts and logic to emotionally distance oneself from a stressful situation.	In a therapy session, patient diagnosed with cancer focuses only on rates of survival.
Isolation (of affect)	Separating feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Passive aggression	Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.	Disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager.
Projection	Attributing an unacceptable internal impulse to an external source (vs displacement).	A man who wants to cheat on his wife accuses his wife of being unfaithful.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	After getting fired, claiming that the job was not important anyway.
Reaction formation	Replacing a warded-off idea or feeling by an (unconsciously derived) emphasis on its opposite (vs sublimation).	A patient with libidinous thoughts enters a monastery.
Regression	**Involuntarily** turning back the maturational clock and going back to earlier modes of dealing with the world (vs fixation).	Seen in children under stress such as illness, punishment, or birth of a new sibling (eg, bedwetting in a previously toilet-trained child when hospitalized).
Repression	Involuntarily withholding an idea or feeling from conscious awareness (vs suppression).	A 20-year-old does not remember going to counseling during his parents' divorce 10 years earlier.
Splitting	Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Commonly seen in borderline personality disorder.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.
MATURE DEFENSES		
Sublimation	Replacing an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system (vs reaction formation).	Teenager's aggression toward his father is redirected to perform well in sports.
Altruism	Alleviating negative feelings via unsolicited generosity.	Mafia boss makes large donation to charity.
Suppression	**Intentionally** withholding an idea or feeling from conscious awareness (vs repression); temporary.	Choosing to not worry about the big game until it is time to play.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.
	Mature adults wear a SASH.	

ALTRUISM

- Mature defense mechanism in which a person manages unpleasant emotions through service to others. This service provides gratification, unlike in reaction formation, in which a true sense of internal pleasure is lacking

NEUROIMAGING IN PSYCHIATRIC DISORDERS



In clinical practice, structural neuroimaging (CT or MRI) is often performed as part of the diagnostic workup for patients with new-onset psychosis to rule out non-psychiatric disorders. Routine neuroimaging is not indicated in a patient with a known psychotic disorder. Functional neuroimaging techniques (e.g., PET, functional MRI, and magnetic resonance spectroscopy) are important research tools in psychiatry, and are used to study neural activity in brain pathways involved in psychiatric disorders. However, they are not routinely used in clinical practice

SELECTIVE MUTISM

- A condition in which children have a fear of situations that call for them to speak (e.g., school, formal social gathering).
- Social phobia (also called social anxiety disorder) is often a co-morbid condition in children suffering from selective mutism, with anxiety and avoidance commonly occurring.
- The **DSM-5 criteria for selective mutism** are as follows:
    - Consistent failure to speak in some specific situations (eg, home, school) but not others in which a person is expected to speak
    - Duration of at least 1 month
    - Interference with educational or other expected achievement or with social communication
    - Not attributable to lack of knowledge or comfort with the spoken language
    - Other communication or autism spectrum disorders or psychosis do not account for the presentation

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Attention-deficit hyperactivity disorder	

Clinical features	• Inattentive &/or hyperactive/impulsive symptoms for ≥6 months
	  ○ **Inattentive symptoms**: Difficulty focusing, distractible, does not listen or follow instructions, disorganized, forgetful, loses/misplaces objects
	  ○ **Hyperactive/impulsive symptoms**: Fidgety, unable to sit still, "driven by a motor," hyper-talkative, interrupts, blurts out answers
	• Several symptoms present **before age 12**
	• Symptoms occur in at least 2 settings (home, school) & cause functional impairment
	• Subtypes: Predominantly inattentive, predominantly hyperactive/impulsive, combined type

Treatment	• Stimulants (methylphenidate, amphetamines) • Non-stimulants (atomoxetine, alpha-2 adrenergic agonists) • Behavioral therapy

- **Adverse effects of methylphenidate:**
  - Nervousness, loss of appetite, nausea, abdominal pain, insomnia, and tachycardia. Prolonged therapy has been shown to cause mild growth retardation or weight loss. Methylphenidate should not be used in children younger than 6 years old because safety and efficacy in this age group have not been evaluated.

Attention-deficit hyperactivity disorder	
DSM-5 criteria	• ≥6 inattentive &/or ≥6 hyperactive/impulsive symptoms for ≥6 months • Several symptoms present before age 12 • Symptoms occur in at least 2 settings (home, school, peer relations) • Functional impairment (social, academic) • Subtypes: Predominantly inattentive, predominantly hyperactive/impulsive, combined type
Inattention symptoms	• No attention to detail; makes careless mistakes • Difficulty focusing (eg, games, tasks, reading, lectures) • Does not appear to listen when spoken to • Cannot follow instructions, gets sidetracked, unable to finish tasks • Difficulty organizing tasks (disorganized work, poor time management) • Avoids tasks requiring sustained concentration • Loses/misplaces objects required to perform tasks (eg, books, phone, keys) • Easily distracted by extraneous stimuli • Forgetful (chores, appointments)
Hyperactivity-impulsivity symptoms	• Fidgets • Difficulty staying seated • Runs or climbs inappropriately • Cannot perform activities quietly • Physically active all the time (as if driven by a motor) • Talks constantly • Blurts out answers, completes others' sentences • Difficulty awaiting turn (eg, in line) • Interrupts/intrudes when others are busy or speaking

- Pts with ADHD are at higher risk of developing conduct disorder in adolescence

CONDUCT DISORDER

DSM-5 diagnostic criteria for conduct disorder	
Aggression toward people & animals	• Initiating physical fights • Bullying, threatening, or intimidating others • Using a weapon to cause serious harm to others • Being physically cruel to people • Being physically cruel to animals • Stealing while confronting a victim • Forcing someone into sexual activity
Destruction of property	• Setting fires • Intentionally destroying the property of others
Serious violation of rules	• Running away overnight at least twice or once without returning for a lengthy period • Being truant from school often starting before age 13 • Frequently staying out at night despite parental prohibitions starting before age 13
Deceitfulness or theft	• Frequently lying to obtain goods or favors • Breaking into a car or building • Stealing items of nontrivial value without confronting a victim

- Diagnosed when at least 3 behaviors have been present within past 12 months with at least one present in past 6 months
- At risk of developing antisocial personality as adults
- Diagnosis of antisocial is not given to pts <18years

Treatment
• Cognitive-behavioral therapy, family therapy
• Parent management training

KLEPTOMANIA

Kleptomania	
Clinical features	• Rare impulse control disorder with typical onset in adolescence • Repetitive failure to resist impulses to steal • Stolen objects have little value • Increasing tension prior to theft; pleasure or relief when committing theft • Stolen objects given away, discarded, or returned; guilt & remorse are common
Differential diagnosis	• Shoplifting: Theft for personal gain; much more common • Antisocial personality disorder: General pattern of antisocial behavior • Bipolar disorder, manic episode: Impulsivity, impaired judgment • Psychotic disorders: Stealing in response to delusions, hallucinations

- Can be treated with psychotherapy as well as medications. Psychotherapy involves **a cognitive behavioral therapy orientation**, focusing on techniques to resist and manage urges and anxiety. Medications that have been used include selective serotonin reuptake inhibitors, opioid antagonists, lithium, and anticonvulsants

PYROMANIA

Pyromania
DSM-5 diagnosis • Deliberate fire setting on more than 1 occasion • Tension, arousal prior to act • Fascination with fire & its consequences • Pleasure or relief when setting/witnessing fires • No external gain, revenge, or political motivation; not done to attract attention • Not better explained by conduct disorder, manic episode, psychosis, antisocial personality disorder, or impaired judgment (neurocognitive disorder, substance intoxication)

- Pyromania is characterized by intentional and repeated fire setting with no obvious motive. Individuals with conduct disorder can also have a history of fire setting, but other features (eg, lying, theft, cruelty to others) are also present.

- Individuals with this condition tend to be fascinated by fire and anything related to it (eg, fire stations, firefighters). They deliberately start fires to reduce tension and feel pleasure or relief afterward.

TOURETTE DISORDER

Tourette syndrome	
Clinical features	• Both **multiple motor & ≥1 vocal tics** (not necessarily concurrent, >1 year) ◦ Motor: Facial grimacing, blinking, head/neck jerking, shoulder shrugging, tongue protrusion, sniffing ◦ Vocal: Grunting, snorting, throat clearing, barking, yelling, coprolalia (obscenities) • Onset age <18
Treatment	• Behavioral therapy (habit reversal training) • Antidopaminergic agents ◦ Tetrabenazine (dopamine depleter) ◦ Antipsychotics (receptor blockers) Risperidone • Alpha-2 adrenergic receptor agonists → guanfacine and Clonidine

- The tics occur many times a day (frequently in bouts) nearly every day or at regular intervals. The tics may wax and wane, but they must persist for one year after initial onset, which must occur before age 18.
- Exacerbated in stress and fatigue and relieved during sleep
- **Comorbid conditions:** مهم
  - ADHD—60% pts
  - OCD—27% pts— develops within 3-6 years after the tics first appeared. It may peak in late adolescence or in early adulthood at a time when the tics are waning.
  - Less common comorbid conditions include anxiety, depression, and impulse control disorders.
- **Management:** pharmacotherapy given if it interferes in social, academic and occupational functioning.
  - Based on older trials, the first-generation antipsychotics haloperidol and pimozide are the only FDA-approved medications for Tourette disorder.
  - However, due to side effects of first-generation anti psychotics and prolongation of the QTc interval associated with pimozide, second-generation antipsychotics are generally preferred. Among the second-generation antipsychotics, risperidone is the best studied.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder	

DSM-5 criteria
Clinical features
	• Multiple, persistent deficits in social communication & interactions currently or by history involving:
	  ○ Social-emotional reciprocity
	  ○ Nonverbal communicative behaviors
	  ○ Developing, maintaining & understanding relationships
	• Restricted, repetitive patterns of behavior currently or by history:
	  ○ Repetitive motor movements
	  ○ Insistence on sameness or inflexible adherence to routines
	  ○ Fixated interests of abnormal intensity or focus
	  ○ Adverse responses to sensory input
	• Onset in early developmental period
	• May occur with or without language & intellectual impairment
	Not better explained exclusively by intellectual disability or another condition

Assessment & management principles	• Early diagnosis & early intervention • Comprehensive, multimodal treatment (speech, behavioral therapy, educational services) • Adjunctive pharmacotherapy for psychiatric comorbidities

- Risperidone has been shown to improve aggression in ASD pts but after other therapies.
- The DSM-5 diagnosis of autism spectrum disorder encompasses high-functioning autism (Asperger syndrome), childhood disintegrative disorder, and any pervasive developmental disorder not otherwise specified. Diagnosis is based on history and behavioral observations (Table). The physician should empathically listen to the parents' concerns and complete a comprehensive evaluation before making a definitive diagnosis. This evaluation includes structured assessments of social, language, and intellectual development in addition to hearing, vision, and genetic (eg, Fragile X syndrome) testing.

SEXUAL BEHAVIOUR IN PRE-ADOLESCENTS

Sexual behavior in preadolescents	
Normal	**Abnormal**
Toddler 1-3 years • Exploring own or others' genitals • Masturbatory movements • Undressing self or others	• Repeated object insertion into vagina or anus • Sex play involving genital-genital, oral-genital, or anal-genital contact • Use of force, threats, or bribes in sex play • Age-inappropriate sexual knowledge
School-age 6-12 years • Increased interest in sex words & play • Asking questions about sex & reproduction • Masturbatory movements (may become more sophisticated)	

PSYCHOTIC DISORDERS

Differential diagnosis of DSM-5 psychotic disorders	
Brief psychotic disorder	**>1 day & <1 month**, sudden onset, full return to function
Schizophreniform disorder	**>1 month & <6 months**, same symptoms as schizophrenia, functional decline not required
Schizophrenia	**At least 6 months** (includes at least 1 month of active symptoms, can include prodromal & residual periods), requires functional decline
Schizoaffective disorder	Concurrent mood episode, active-phase symptoms of schizophrenia + at least 2-week lifetime history of delusions or hallucinations in the absence of prominent mood symptoms
Delusional disorder	**One or more delusions >1 month, no other psychotic symptoms**, normal functioning apart from direct impact of delusions

Prior to diagnosis, it would be appropriate to rule out substance-induced psychosis and psychosis secondary to a general medical condition

SYMPTOMS OF SCHILZOPHRENIA

- *Two or more* of the following must be present for at least *1 month:*
  1. Delusions
  2. Hallucinations
  3. Disorganized speech
  4. Grossly disorganized or catatonic behavior
  5. Negative symptoms

Note: At least one must be 1, 2, or 3.

The 5 A's of schizophrenia (negative symptoms):
1. Anhedonia
2. Affect (flat)
3. Alogia (poverty of speech)
4. Avolition (apathy)
5. Attention (poor)

SCHIZOAFFECTIVE DISORDER

Schizoaffective disorder	
DSM-5 criteria	• Major depressive or manic episode concurrent with symptoms of schizophrenia • Lifetime history of **delusions or hallucinations for ≥2 weeks in the absence of major depressive or manic episode** • Mood symptoms are present for majority of illness • Not due to substances or another medical condition
Differential diagnosis	• **Major depressive or bipolar disorder with psychotic features:** Psychotic symptoms occur exclusively during mood episodes • **Schizophrenia:** Mood symptoms present for relatively brief periods

DELUSIONAL DISORDER

Delusional disorder	
Clinical features	• ≥1 delusions for ≥1 month • Other psychotic symptoms absent or not prominent • Ability to function apart from delusion; behavior not obviously bizarre or odd • Subtypes: Erotomanic, grandiose, jealous, persecutory & somatic
Differential diagnosis	• Schizophrenia: Other psychotic symptoms present (eg, hallucinations, disorganization, negative symptoms); greater functional impairment • Personality disorders: Pervasive pattern of suspiciousness (paranoid), grandiosity (narcissistic), or odd beliefs (schizotypal), but no clear delusions
Treatment	• Antipsychotics • Cognitive-behavioral therapy

Delusional disorder involves one or more delusions and the absence of other psychotic symptoms in an otherwise high-functioning individual.

SHARED PSYCHOTIC DISORDER (folie a' deux)

- Rare form of delusional disorder
- Same delusion is present in individuals who share **close relationship**
- Usually, dominant individual in pair becomes delusional and transfers delusion on to the second
- **Management:** most appropriate course is to **separate the pair** → breaks the chain of reinforcing each other's belief
  - Usually the dominant one requires psychiatric treatment (sometimes inpatient)—whereas other requires treatment only in some cases—first assess the other one by separating the two
  - **Indications for hospitalization:** inability to function or obtain outpatient treatment or being a threat to self or others.
  - If both require inpatient treatment, preferably admit to different units
  - If psychotic disorder is confirmed → antipsychotic and CBT is recommended

Educational objective: Qid: 3794

Acutely psychotic patients should be assessed for suicidal/homicidal ideation, command hallucinations to hurt self or others, and ability to care for self. Indications for involuntary psychiatric hospitalization include being a danger to self or others and/or grave disability.

Schizophrenia	
Clinical features	• Positive symptoms (delusions, hallucinations, disorganized speech/behavior) • Negative symptoms (flat affect, poverty of speech, lack of motivation, social withdrawal, anhedonia) • Duration ≥6 months (includes prodromal, active & residual phases) • Significant functional decline
Management	• Psychiatric consultation (emergent for danger to self or others OR first episode) • Antipsychotic medication • Psychosocial interventions to augment antipsychotics (cognitive-behavioral therapy, social skills training, family therapy)

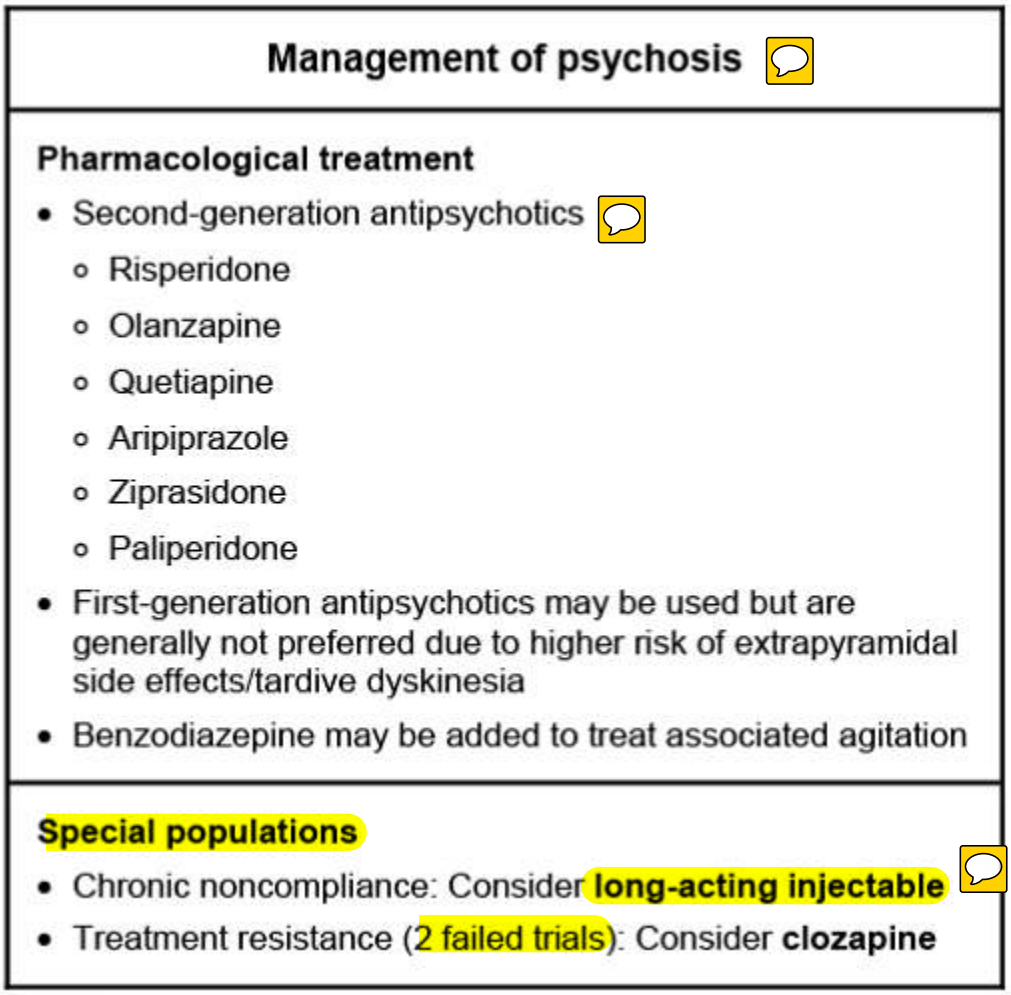
SECONDARY CAUSES OF PSYCHOSIS IN CHILDREN AND ADOLESCENTS

Secondary causes of acute-onset psychosis in children & adolescents	
Medical disorders	**Central nervous system injury/dysfunction** • Trauma • Space-occupying lesions • Infection • Stroke • Epilepsy • Cerebral hypoxia **Metabolic/electrolyte disturbances** • Urea cycle disorders • Acute intermittent porphyria • Wilson disease • Renal/liver failure • Hypoglycemia • Sodium/calcium/magnesium disturbances **Systemic disorders** • Systemic lupus erythematosus • Thyroiditis
Illicit substance use	• Hallucinogens (eg, PCP, LSD, ketamine) • Marijuana • Sympathomimetics (eg, cocaine, amphetamines) • Alcohol withdrawal • Bath salts
Medication side effects	**Intoxication** • Anticholinergics (eg, diphenhydramine, scopolamine) • Serotonin syndrome • Amoxicillin/erythromycin/clarithromycin • Anticonvulsants • Corticosteroids • Isoniazid **Withdrawal** • Baclofen • Benzodiazepines

Medication-induced psychosis is
- characterized by delusions or hallucinations that are temporally associated with the use of a new medication and rapid onset of symptoms while the medication is being used.

- **Glucocorticoids,** particularly at high doses, are often implicated in new-onset psychotic symptoms in patients who may have no current underlying psychiatric illness.

MANAGEMENT OF PSYCHOSIS

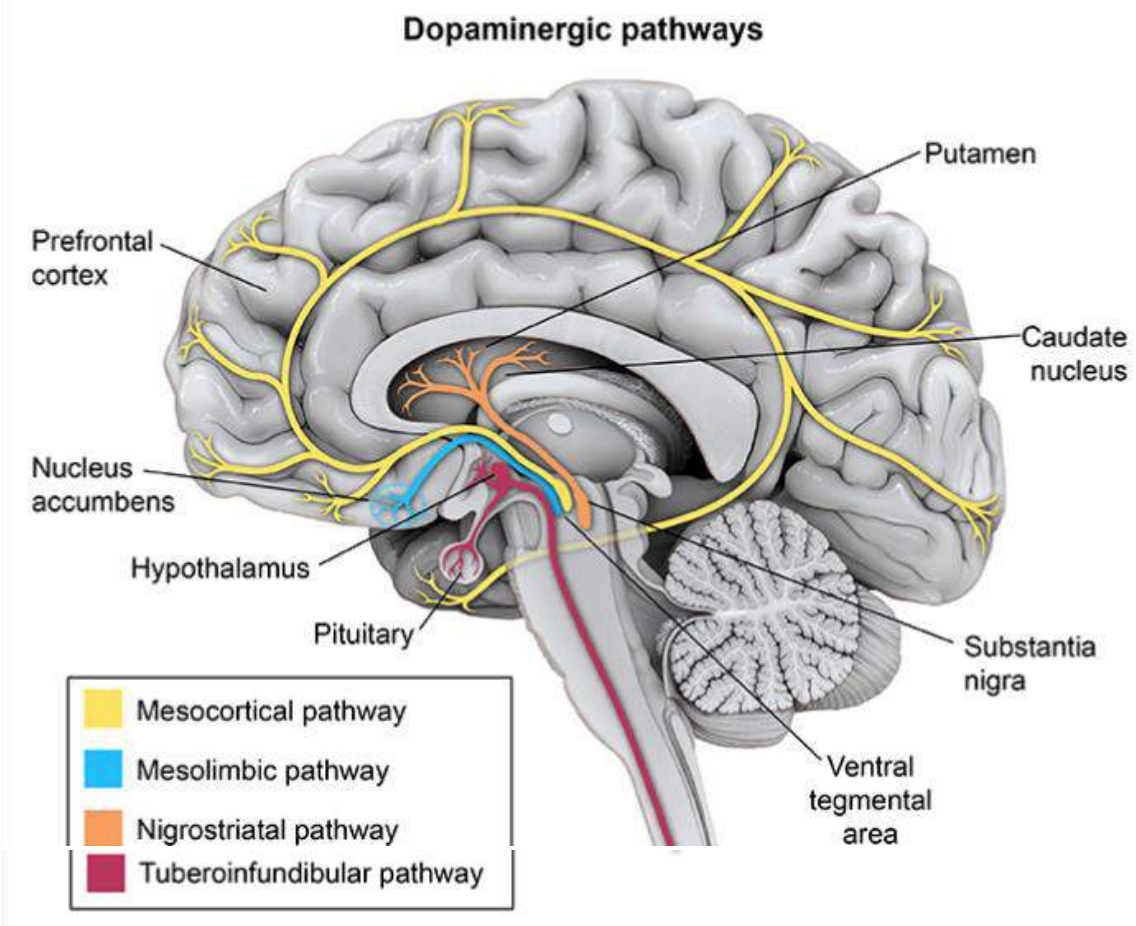


- Although antipsychotic medication is the primary treatment for schizophrenia, integrating psychosocial interventions into a broader treatment program can improve outcomes.
- Family counseling and psychoeducation have proven to be high-yield interventions in schizophrenia.
- For example, educating the patient's father about the symptoms of schizophrenia (eg, her social isolation and declining grades are not "laziness") can help reduce family stress.
- Patients with schizophrenia who have critical, hostile or over-involved family members→higher risk of relapse, while
- If the home atmosphere is stable and family stressors are kept to a minimum→ decreased risk of relapse

ANTIPSYCHOTICS

- **Long-acting injectables:**
  - Administered every 2-4 wks
  - Both 1st generation (haloperidol, fluphenazine) and 2nd generation (risperidone, paliperidone, olanzapine, aripiprazole) are available in long-acting injectable form
  - **Suitable candidates:** unstable illness in pts who live alone, have poor social support system, poor insight and frequent medication non-compliance—who have shown good response to oral medication

ANTIPSYCHOTIC EXTRAPYRAMIDAL EFFECTS



Antipsychotic medication effects (dopamine antagonism) in dopamine pathways	
Pathway	**Effect**
Mesolimbic	Antipsychotic efficacy
Nigrostriatal	Extrapyramidal symptoms: Acute dystonia, akathisia, parkinsonism
Tuberoinfundibular	Hyperprolactinemia

- Amenorrhea, gynecomastia, galactorrhea, ↓ libido resulting from prolactin ↑ is more common with high potency first generation antipsychotics (e.g. haloperidol and fluphenazine) and second generation anti-psychotics **paliperidone** (a metabolite of risperidone) and **risperidone**

➔ Prolactinomas can cause very high prolactin levels (>200 ng/ml), whereas medication-related hyperprolactinemia is typically 25-100 ng/ml with levels seldom above 200 ng/mL

➔ Some anti-hypertensives associated with hyperprolactinemia include: reserpine, methyldopa, verapamil

Antipsychotic extrapyramidal effects		
Extrapyramidal symptoms		**Treatment**
Acute dystonia 4 hr to 4 days	• Sudden, sustained contraction of the neck, mouth, tongue, eye muscles	• Benztropine or diphenhydramine neck torticollis, eye oculogyric crisis (forced, sustained elevation of the eyes in an upward position).
Akathisia Any time	• Subjective restlessness, inability to sit still	• Beta blocker (propranolol) or benzodiazepine (lorazepam)
Parkinsonism 4 days to 4 mo	• Gradual-onset tremor, rigidity, bradykinesia	• Benztropine or amantadine
Tardive dyskinesia 1-6 mo	• Gradual onset after prolonged therapy (>6 months): Dyskinesia of the mouth, face, trunk, extremities	• No definitive treatment (but clozapine may help) Valbenazine

Type of Dyskinesia	Symptoms
Oral and facial	Tongue protrusion and twisting Lip smacking, pouting, and puckering Retraction of the corners of the mouth Chewing movements
Limb	Limb twisting and spreading "Piano-playing" finger movements Foot tapping Dystonic extension of the toes
Neck and trunk	Torticollis Shoulder shrugging Rocking or swaying Rotary hip movements
Respiratory	Grunting noises

- Extrapyramidal side effects are more common with 1st generation antipsychotics as compared to 2nd generation (SGA). Out of SGA, risperidone is most likely to cause EPS, esp. at higher doses→ if dose reduction is not feasible→ give medicine in table above

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome	

Signs/ symptoms	• Fever sometimes >40 C
	• Mental status changes
	• Muscle rigidity (generalized)
	• Autonomic instability
	  ◦ Tachycardia/dysrhythmias
	  ◦ Labile blood pressure
	  ◦ Tachypnea
	  ◦ Diaphoresis

Precipitating factors	• Antipsychotics (typical & atypical) • Antiemetics (eg, promethazine, metoclopramide) • Antiparkinson (dopamine agonists) medication withdrawal • Infection • Surgery
Treatment	• Stop neuroleptics or restart dopamine agents • Supportive care (hydration, cooling) • Dantrolene or bromocriptine

Can develop over 1-3 days with delirium is often the 1st manifestation

Rhabdomyolysis, followed by myoglobinuria which can cause ARF—common complication.

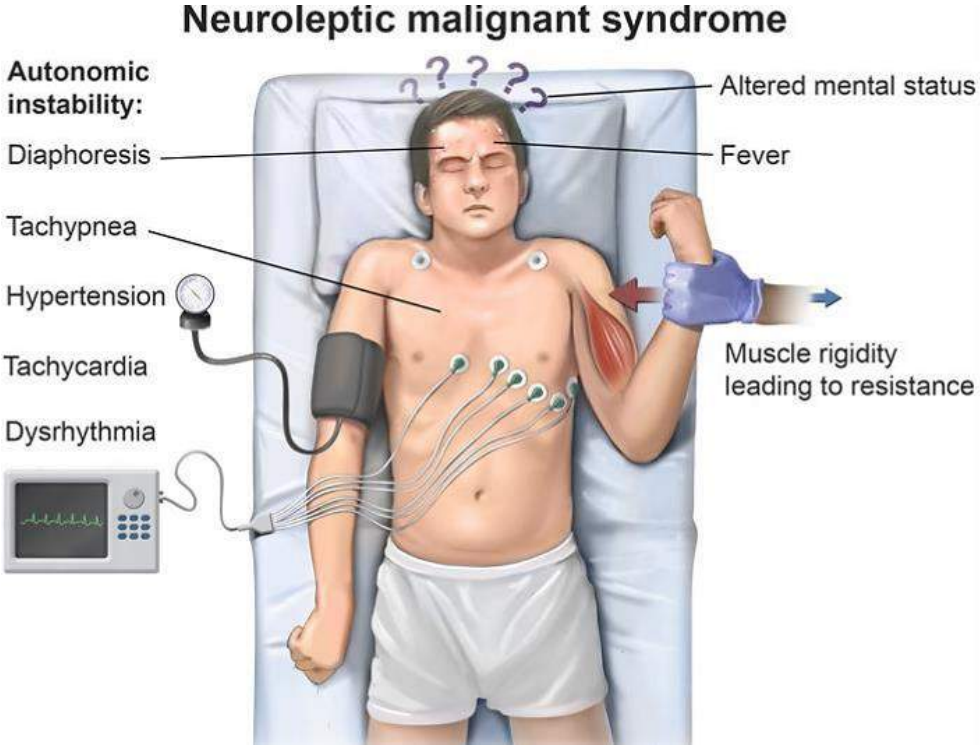
Leukocytosis

Associated with meds that block dopamine transmission- can occur at any time after treatment

Antipyretics, alkaline diuresis in case of rhabdomyolysis

And/or amantadine

- Monitor the pt in ICU
- **Difference from serotonin syndrome**: features of serotonin syndrome include:
  - Begins with: vomiting, diarhhea, restlessness and autonomic instability
  - Characterized by neuromuscular irritability and not rigidity i.e. tremors, hyperreflexia, myoclonus
  - Fever not as high as NMS
  - Waiting 2 weeks between the discontinuation of an MAOI (eg, phenelzine) and the start of a serotonergic antidepressant (eg, citalopram) is deemed sufficient to avoid the risk of developing serotonin syndrome



METABOLIC EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS

Metabolic effects of second-generation antipsychotics	
Metabolic syndrome	• Weight gain • Dyslipidemia • Hyperglycemia (including new-onset diabetes)
Highest risk drugs	• Clozapine • Olanzapine
Monitoring guidelines	Baseline & regular follow-up • Body mass index • Fasting glucose & lipids • Blood pressure • Waist circumference

BMI measured monthly—rest measured at baseline, then 3 months and then annually—earlier and more frequent monitoring needed in those with diabetes or who gained >5% of initial weight gain

OLANZAPINE

- Serotonin and dopamine antagonist but also has affinity for histamine, α-1 adrenergic and muscarinic receptors
- Most common side effects: sedation and weight gain
- Weight gain: due to antagonism of histamine (H1) and 5-HT2c receptors
- Sedation: due to antagonism of histamine receptor

CLOZAPINE TREATMENT GUIDELINES

Clozapine treatment guidelines	
Indications	• Treatment-resistant schizophrenia • Schizophrenia associated with suicidality
Adverse effects	• Agranulocytosis • Seizures • Myocarditis • Metabolic syndrome

Ileus and hypotension

- With the exception of clozapine, no antipsychotic is superior to other
- Least likely to cause extrapyramidal SE and not been shown to cause tardive dyskinesia
- **Treatment resistant definition:** poor response to at least 2 anti-psychotic trials
- Requires regular monitoring of WBC and absolute neutrophil counts due to risk of leukopenia (neutropenia) and agranulocytosis—weekly blood counts during first 6 mo of treatment

ARIPIPRAZOLE

- It is both antagonist and partial agonist at dopamine D2 receptors→ less likely to cause hyperprolactinemia

ZIPRASIDONE

- Associated with QT prolongation at higher doses

ANXIETY DISORDERS

Differential diagnosis of DSM-5 anxiety disorders	
Social anxiety disorder (social phobia)	Anxiety restricted to social & performance situations, **fear of scrutiny** & embarrassment
Panic disorder	Recurrent, **unexpected** panic attacks
Specific phobia	Excessive anxiety about a **specific object** or situation (phobic stimulus)
Generalized anxiety disorder	**Chronic multiple worries**, anxiety, tension

SOCIAL ANXIETY DISORDER

Social anxiety disorder (social phobia)	
Diagnosis	• Marked anxiety about ≥1 social situations for ≥6 months • Fear of scrutiny by others, humiliation, embarrassment • Social situations avoided or endured with intense distress • Marked impairment (social, academic, occupational) • Subtype specifier: Performance only
Treatment	• SSRI/SNRI • Cognitive-behavioral therapy • Beta blocker or benzodiazepine for performance-only subtype

β- blocker preferred. Benzo can cause sedation or affect cognition, avoid in substance abuse pt

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

- CBT: Techniques include social skills training, cognitive reframing of anxious thoughts, and systematic desensitization.

PANIC DISORDER

Panic disorder	

Clinical features	• Recurrent & unexpected panic attacks with ≥4 of the following:
	  ○ Chest pain, palpitations, shortness of breath
	  ○ Trembling, sweating, nausea
	  ○ Dizziness, paresthesias
	  ○ Derealization, depersonalization
	  ○ Fear of losing control, dying
	• Worry about additional attacks, avoidance behavior

Treatment	• Immediate: Benzodiazepines • Long-term: SSRI/SNRI &/or cognitive behavioral therapy

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

Panic disorder

DSM-5

1. Recurrent & unexpected panic attacks with ≥4 of the following:
   - Palpitations
   - Sweating
   - Trembling or shaking
   - Shortness of breath or smothering sensation
   - Choking sensations
   - Chest pain or discomfort
   - Nausea or abdominal distress
   - Dizziness or light-headedness
   - Chills or heat sensations
   - Paresthesias
   - Derealization or depersonalization
   - Fear of losing control or "going crazy"
   - Fear of dying
2. At least 1 attack followed by 1 or both of the following for >1 month:
   - Worry about additional panic attacks or consequences
   - Changes in behavior related to attacks (ie, avoidance)
3. Panic attacks not attributable to another mental illness or substance abuse

Treatment of panic disorder

- Immediate: Benzodiazepines
- Long-term: Selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor &/or cognitive behavioral therapy

e.g. lorazepam—once sx controlled, benzo should be tapered off due to risk of dependence

- Dx is mainly clinical, but drug screening, monitoring of vitals, ECG, cardiac enzymes should be performed to rule out serious disorder

COMORBIDITIES OF PANIC DISORDER

- Major depression—Studies have shown that about 60% of patients with panic disorder have had >1 lifetime episodes of major depression.
- Bipolar disorder,
- Agoraphobia (fear of public places)—Approximately 40% of patients meet the criteria for agoraphobia
- Substance abuse.
- Also ↑ risk of suicide attempts and suicidal ideations.

SPECIFIC PHOBIA

Specific phobia	
History & clinical features	• Marked anxiety about a **specific** object or situation (the phobic stimulus) for >6 months • Common types: Flying, heights, animals, injections, blood • Avoidance behavior (bridges, elevators, refusing work requiring travel) • Common, 10% of population • Usually develops in childhood; can develop after traumatic event
Treatment	• CBT **Behavioral therapy** (exposure, systematic desensitization) is treatment of choice • Short-acting benzodiazepines may help acutely (therapist unavailable, insufficient time) but have a limited role

GENERALIZED ANXIETY DISORDER

Generalized anxiety disorder	

DSM-5 criteria	• Excessive worry, anxiety (multiple issues) ≥6 months
	• Difficult to control
	• ≥3 of the following symptoms:
	  ○ Restlessness/feeling on edge
	  ○ Fatigue
	  ○ Difficulty concentrating
	  ○ Irritability
	  ○ Muscle tension
	  ○ Sleep disturbance
	• Significant distress or impairment
	• Not due to substances, another mental disorder, or medical condition

Treatment	• First-line
	  ○ Cognitive behavioral therapy
	  ○ SSRIs or SNRIs
	• Second-line
	  ○ Benzodiazepines
	  ○ Buspirone

RF-CIMS

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

- Buspirone—used in non-depressed pt and in the absence of panic sx

BENZODIAZEPINES

- Benzo—should not be used in pt with comorbid depression, substance abuse
- Should be used sparingly in elderly due to slow metabolism and accumulation → confusion and ↑ risk of falls
- Another adverse effect of benzodiazepines is paradoxical agitation. Paradoxical agitation is characterized by increased agitation, confusion, aggression, and disinhibition, typically within an hour of administration. Although paradoxical reactions to benzodiazepines are relatively uncommon (<1%), they are important to recognize as increasing the dose of the benzodiazepine will only worsen the patient's condition. Discontinuing is the most appropriate next step in management if pt develops paradoxical agitation

- Abrupt cessation of **alprazolam,** a short-acting benzodiazepine, is associated with significant withdrawal symptoms, including **generalized seizures** and confusion.

- **Benzodiazepine intoxication** can result in altered mental status, **ataxia,** and **slurred speech**. they lower vitals rather than elevate them (bradycardia, hypotension,hyporeflexia) & **mild respiratory depression** are seen, co-ingestion with other sedative-hypnotics should be suspected in case of **severe** resp. dep (mainly alcohol).

- Furthermore, while alcohol and phenytoin intoxication also share similarities with benzodiazepine overdose, they can be distinguished by the presence of nystagmus.

OBSESSIVE COMPULSIVE DISORDER

Obsessive-compulsive disorder	
Diagnostic criteria	**Obsessions** • Recurrent intrusive, anxiety-provoking thoughts, urges, or images • Attempts to suppress or neutralize with other thoughts or actions (compulsions) • No relation to another mental or substance use disorder **Compulsions** • Response to obsessive thoughts with repeated behaviors or mental acts • Excessive behaviors intended to reduce anxiety or avoid dreaded outcome • Behaviors not connected realistically with preventing anxiety/feared event Obsessions &/or compulsions consume >1 hr/day, cause significant distress, or interfere with daily routine or social functioning
Treatment	• Cognitive behavioral therapy (exposure & response prevention) &/or a high-dose selective serotonin reuptake inhibitor • Clomipramine or antipsychotic augmentation for treatment nonresponse • Deep-brain stimulation for treatment of severe or refractory cases

TRICHOTILLOMANIA

Trichotillomania (hair pulling disorder)	
DSM-5	• Recurrent hair pulling resulting in hair loss • Repeated attempts to decrease/stop hair pulling • Significant distress or impairment • Not due to a medical/dermatological condition (eg, alopecia areata) • Not due to another mental disorder (eg, body dysmorphic disorder)
Treatment	• Cognitive behavioral therapy (habit reversal training)

- DSM-5 classifies it as OCD-related disorder to reflect ↑ing evidence of shared features with OCD and higher rates of comorbidity in pts with a personal or FH of OCD
- Commonly affected areas: scalp, eyebrows and eyelids
- More common in girls and women
- Trichophagia (swallowing of hair) and subsequent formation of trichobezoars can lead to abdominal pain and bowel obstruction.

HOARDING SYNDROME

- New disorder in DSM-5
- Distinct from obsessive-compulsive disorder.
- Characterized by **accumulation of a large number of possessions** that may clutter living areas to the point that they are unusable. Patients experience intense distress when attempting to discard possessions regardless of their actual value. Social isolation due to embarrassment (e.g., being unable to invite people to their homes) may also occur. Extreme cases may be associated with unsanitary conditions and fire risk due to blocked exits.
- **Cognitive-behavioral therapy (CBT)** specifically targeted to hoarding behaviors is the most effective treatment. Specific techniques include education, motivational interviewing, skills training in organization and decision-making, cognitive restructuring of dysfunctional thoughts, and gradual exposure to discarding possessions. Although selective serotonin reuptake inhibitors (SSRIs) are often tried based on their efficacy in treating obsessive-compulsive disorder, their efficacy in treating hoarding behavior without obsessive-compulsive disorder is limited. SSRIs can be considered as an adjunct to CBT and can be helpful in treating comorbid depression and anxiety disorders

POST-TRAUMATIC STRESS DISORDER (PTSD)

Post-traumatic stress disorder	
Clinical features	• Exposure to life-threatening trauma • Nightmares, flashbacks, intrusive memories • Avoidance of reminders, amnesia for event • Emotional detachment, negative mood, decreased interest in activities • Sleep disturbance, hypervigilance, irritability • Duration ≥1 month → acute stress disorder (from 3 days to 1 month)
Treatment	• Trauma-focused cognitive-behavioral therapy • Antidepressants (SSRIs, SNRIs)

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

- Sexual assault pts (and also military veterans) are at ↑ed risk of PTSD, along with risk of developing major depression and contemplation of suicide actual attempt. also at increased risk for medical problems, including sexually transmitted disease, pelvic pain, fibromyalgia, functional gastrointestinal disorders, and cervical cancer, which may be linked to an avoidance of pelvic examinations.
- Some PTSD symptoms may appear immediately after the trauma; however, there is often a delay of months, or even years, before full criteria for the diagnosis are met.

the first step in ASD / PTSD is "**educate the patient about range of reactions to trauma**", especially when he insists that he is "**not interested in talking**" ... **Board classic !!!**

DEPRESSION

DEPRESSED MOOD DIFFERENTIAL DIAGNOSIS

Differential diagnosis of depressed mood		
Major depressive disorder	**Adjustment disorder with depressed mood**	**Normal stress response**
• ≥2 weeks • ≥5 of 9 symptoms: Depressed mood & SIGECAPS • Significant functional impairment • No lifetime history of mania • Not due to drugs or medical condition	• Identifiable stressor • Onset within 3 months of stressor • Marked distress • Significant functional impairment • Does not meet criteria for another DSM-5 disorder	• Not excessive or out of proportion to severity of stressor • No significant functional impairment

SIGECAPS = **S**leep disturbance, loss of **I**nterest, excessive **G**uilt, low **E**nergy, impaired **C**oncentration, **A**ppetite disturbance, **P**sychomotor agitation/retardation, and **S**uicidal ideation.

ADJUSTMENT DISORDER

- Sx rarely last >6 mo after stressor ends
- Stressor can be single or multiple
- Involves emotional or behavioral symptoms (e.g. anxiety, depression, disturbance of conduct)
- **Rx:** psychotherapy → focuses on developing coping mechanisms and improving individual's response to and attitude about stressful situation

MAJOR DEPRESSION

Signs & symptoms of major depression - SIGECAPS
• **S**leep (increased or decreased) • **I**nterest deficit (anhedonia) • **G**uilt (worthless, hopeless) • **E**nergy deficit • **C**oncentration deficit • **A**ppetite (increased or decreased) • **P**sychomotor retardation or agitation • **S**uicidality

4/8 + depressed mood or anhedonia (loss of interest in activities that were previously enjoyable)

Patients with depression often present to a primary care physician with **headaches** or other **physical complaints** (eg, fatigue, insomnia, nonspecific aches and pains). The physician should consider depression in the differential diagnosis and specifically **inquire** about **depressive symptoms** (depressed mood, anhedonia). If the patient is suffering from depression, physical symptoms will likely improve with adequate treatment.

↑ cortisol
↓ REM latency (the time from sleep onset to REM sleep)

MAJOR DEPRESSIONS AND GRIEF REACTION

Major depressive episode	Grief reaction (bereavement)
• Five of the following 9 symptoms: Sleep disturbances, appetite change, low energy, psychomotor changes, low mood, anhedonia, guilt, focus/concentration difficulty, suicidal ideation • Low mood or anhedonia must be present • May occur in response to a variety of stressors, including loss of loved one • Duration ≥2 weeks • Social & occupational dysfunction • Suicidality related to hopelessness & worthlessness	• Normal reaction to loss • Feelings of loss & emptiness • Symptoms revolve around the deceased • Functional decline less severe • "Waves" of grief at reminders • Worthlessness, self-loathing, guilt & suicidality less common • Sad feelings are more specific to deceased • Thoughts of dying involve joining the deceased • Intensity decreases over time (weeks to months)

Melancholic depression

- Subtype of major depression characterized by anhedonia, absent mood reactivity, depressed mood (typically worse in the morning), insomnia or early-morning awakening, loss of appetite with weight loss, excessive guilt, and psychomotor agitation or retardation.
- This subtype, and its psychomotor changes, is more common in older adults.
- Contrasted with atypical depression

Atypical depression

- Involves hypersomnia, increased appetite, rejection sensitivity, and leaden paralysis (heavy feelings in limbs)

Major depression with psychotic features

- First-line treatment of psychotic depression consists of an antidepressant plus an antipsychotic or electroconvulsive therapy (ECT). Because ECT is generally faster than pharmacotherapy, it is used to achieve a rapid response in depressed geriatric patients who are unable to eat and drink, psychotic, or actively suicidal.

S leep changes: increase during day or decreased sleep at night
I nterest (loss): of interest in activities that used to interest them
G uilt (worthless): depressed elderly tend to devalue themselves
E nergy (lack): common presenting symptom (fatigue)
C ognition/**C** oncentration: reduced cognition &/or difficulty concentrating
A ppetite (wt. loss); usually declined, occasionally increased
P sychomotor: agitation (anxiety) or retardations (lethargic)
S uicide/death preocp.

DYSTHYMIA

Persistent depressive disorder (dysthymia)	

DSM-5	• Chronic depressed mood **≥2 years** (1 year in children/adolescents)
	• No symptom-free period for >2 months
	• Presence of at least **2** of the following:
	  ○ Poor appetite or overeating
	  ○ Insomnia or hypersomnia
	  ○ Low energy or fatigue
	  ○ Low self-esteem
	  ○ Poor concentration or difficulty making decisions
	  ○ Feelings of hopelessness

Specifiers	• With **pure dysthymic syndrome**: Criteria for major depressive episode never met • With intermittent major depressive episodes • With persistent major depressive episodes: Criteria for major depressive episode met throughout previous 2 years

Cyclothymic disorder:

- chronic, mild fluctuating mood disturbance for ≥2 years duration.
- symptoms are mild and the patient does not have sufficient history to diagnose either a current or past major depressive or hypomanic/manic episode.

- Diagnosis requires ≥ 2 years duration (1 year in children) and insufficient number, severity, and pervasiveness to meet full criteriafor hypomanic or depressive episodes.

Qid: 1219

ANTIDEPRESSANTS

Antidepressant classification & major drugs	
SSRI - Selective serotonin reuptake inhibitor	• Fluoxetine • Paroxetine • Sertraline • Citalopram • Escitalopram • Fluvoxamine
SNRI - Serotonin & norepinephrine reuptake inhibitor	• Venlafaxine • Desvenlafaxine • Duloxetine
NDRI - Norepinephrine & dopamine reuptake inhibitor	• Bupropion
TCA - Tricyclic antidepressant	• Amitriptyline • Nortriptyline
MAOI - Monoamine oxidase inhibitor	• Phenelzine • Tranylcypromine
Other	• Mirtazapine • Trazodone • Vortioxetine

Benefits: helps smoking cessation, no weight gain no hypersomnia (activating effect), no sexual dysfunction. **CI:** seizure disorder, bulimia nervosa, anorexia nervosa, and use of MAOi in past 2 wks. **Caution needed:** abrupt withdrawal of sedative hypnotics and co-administration of other drugs that lower seizure threshold

Not 1st line due to ↑ SE profile. Give a 5 wk washout period after fluoxetine and before starting MAOI to avoid serotonin syndrome

- Parents of adolescent patients should always be notified when the patient is a risk to self or others or when starting psychotropic medication. If pt is not suicidal and simply wants to discuss his depression or obtain psychotherapy referrals, his request for confidentiality should be respected
- Patients with a single episode of major depressive disorder who respond to acute treatment should continue antidepressant treatment for an **additional 4-9 months (continuation phase treatment)**. There is a significantly increased risk of depressive relapse in patients who discontinue antidepressants earlier. The dose should be maintained at the level that achieved remission and not be reduced (i.e., the dose that gets the patient well keeps the patient well)
- Maintenance phase treatment is defined as continuing antidepressant medication past the initial continuation phase treatment. Maintenance for **1-3 years** is appropriate for patients with a history of multiple episodes (recurrent major depressive disorder), chronic episodes (>/=2 years), strong family history, or severe episodes (eg, suicide attempt). **Patients with a history of highly recurrent** (eg, >/=3 lifetime episodes) and very severe, chronic major depressive episodes should **continue maintenance treatment indefinitely**
- Should be tapered when discontinued
- **Failure of initial SSRI treatment:**
  1. Increase dose to max. therapeutic dose
  2. Adequate duration >/=6wks→ minimal or no improvement →

3. Switch to another **first-line antidepressant with a different MOA,** e.g. SNRI
4. Other options include: adding second agent (esp. in those with some benefit but not complete improvement) and either adding or switching to psychotherapy

- Pt undergoing chemotherapy→ low threshold of depression and starting SSRI→ 1st step in management: significant pain control
- **Mirtazapine S/E:** weight gain and sedation
- **Trazodone** is very sedating—used in insomnia related to depression

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy	
Indications	**Conditions treated** • Unipolar & bipolar depression • Catatonia • Bipolar mania **Specific indications** مهم • Treatment resistance • Psychotic features present • Emergency conditions o Pregnancy o Refusal to eat or drink o Imminent risk for suicide • Pharmacotherapy contraindicated due to comorbid medical illness or poor tolerability • History of ECT response
Safety	• No absolute contraindications • Increased risk o Severe cardiovascular disease, recent myocardial infarction o Space-occupying brain lesion o Recent stroke, unstable aneurysm

ECT = electroconvulsive therapy.

- Performed under general anesthesia
- One of the most common SE: amnesia:-
  - Can be retrograde (forgetting recent memories) – tends to last longer esp. of events occurring during ECT or
  - Anterograde (retaining new memories)—resolved rapidly
- ↑ risk of fractures esp. in osteoporotic pt—but not as common as amnesia—p.s. close monitoring of muscle relaxation with succinylcholine has ↓ incidence of bone fractures

Antidepressant discontinuation syndrome

Abrupt discontinuation or rapid taper of short half-life serotonergic antidepressants can result in psychological and physical symptoms

.

. **Pt**: dysphoria, fatigue, insomnia, and myalgias
Patient feel as if reemergence of the underlying disorder being treated
Sx begin within 2-4 days of the medication being abruptly stopped

Tx: re-institute the same antidepressant and taper the dose gradually over 2-4 weeks

Venlafaxine causes a dose dependant **HYPESRTENSION** , so BP should be monitored
UW: 15083

POSTPARTUM BLUES, DEPRESSION AND PSYCHOSIS

Postpartum blues, depression & psychosis			
	Postpartum blues	**Postpartum depression**	**Postpartum psychosis**
Prevalence	40%-80%	8%-15%	0.1%-0.2%
Onset	2-3 days (resolves within 10 days)	Within 4 weeks	Variable: Days to weeks
Symptoms	Mild depression, tearfulness, irritability	Moderate to severe depression, sleep or appetite disturbance, low energy, psychomotor changes, guilt, concentration difficulty, suicidal ideation	Delusions, hallucinations, thought disorganization, bizarre behavior
Treatment	Reassurance & monitoring	Antidepressants, psychotherapy	Antipsychotics, antidepressants Do not leave mother alone with infant (risk of infanticide)

BIPOLAR DISORDER

Bipolar & related disorders

Manic episode

- Symptoms more **severe**
- **1 week** unless hospitalized
- **Marked impairment** in social or occupational functioning or **hospitalization** necessary
- May have **psychotic features**; makes episode manic by definition

Hypomanic episode

- Symptoms **less severe**
- **≥4 consecutive days**
- Unequivocal, observable change in functioning from patient's baseline
- Symptoms not severe enough to cause marked impairment or necessitate hospitalization
- **No psychotic features**

Bipolar I

- **Manic episode(s)**
- Depressive episodes common, but not required for diagnosis

Bipolar II

- **Hypomanic episode(s)**
- ≥1 major depressive episodes required

Cyclothymic disorder

- At least **2 years** of fluctuating, mild hypomanic & depressive symptoms that do not meet criteria for hypomanic episodes or major depressive episodes

Acute mania	Qid: 2355
Clinical features	• Elevated, irritable, labile mood • Increased energy & activity, decreased need for sleep • Pressured speech, racing thoughts, distractibility • Grandiosity, risky behavior • Marked impairment, may have psychotic symptoms
Management	• Antipsychotics (first- & second-generation) • Lithium (avoid in renal disease) • Valproate (avoid in liver disease) • Combinations in severe mania (eg, antipsychotic plus lithium or valproate) • Adjunctive benzodiazepines for insomnia, agitation

e.g. risperidone because of its more rapid onset of action

Or carbamazepine—Lithium, valproate and carbamazepine—require gradual titration over several days

Manic episode

• ≥1 week (unless hospitalized) of persistently elevated or irritable mood & increased energy/activity
• ≥3 of the following symptoms (4 if mood is irritable only):
  ○ Decreased need for sleep
  ○ Grandiosity
  ○ Pressured speech
  ○ Racing thoughts (flight of ideas)
  ○ Distractibility
  ○ Hyperactivity/psychomotor agitation
  ○ Risky behavior (spending, investments, sexual indiscretions)
• Marked impairment typically necessitating hospitalization
• Psychotic features may be present
DIGFAST mnemonic: **D**istractibility, **I**mpulsivity/indiscretion, **G**randiosity, **F**light of ideas, **A**ctivity increase, **S**leep decrease, **T**alkativeness.

Guidelines for lithium therapy	
Indications	Mania due to bipolar disorder
Contraindications	• Chronic kidney disease • Heart disease • Hyponatremia or diuretic use
Baseline studies	• Blood urea nitrogen, creatinine, calcium, urinalysis • Thyroid function tests • ECG in patients with coronary risk factors
Adverse effects	**Acute** • Tremor, ataxia, weakness • Polyuria, polydipsia • Vomiting, diarrhea • Cognitive impairment **Chronic** • Nephrogenic diabetes insipidus • Thyroid dysfunction • Hyperparathyroidism

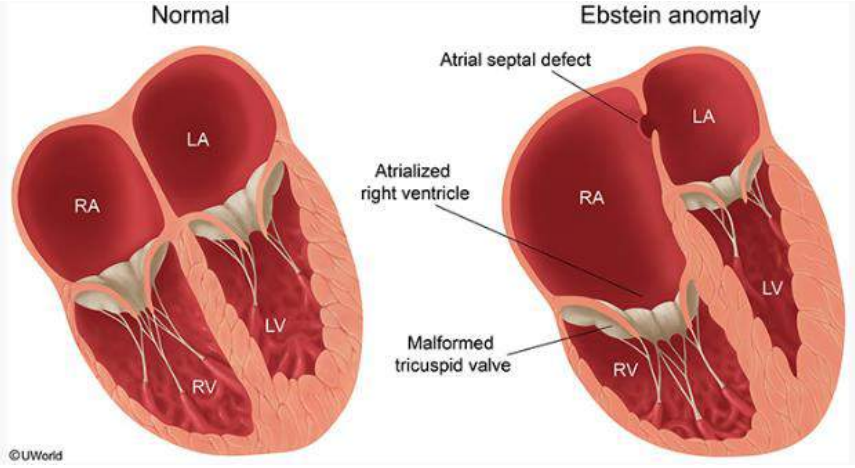
Should be reassessed periodically after starting med

Weight gain

Can also cause chronic tubulointerstitial nephropathy—rarely progress to ESRD

- Pregnant women should either avoid lithium or adjust the dose during pregnancy as it may cause complications in the first trimester (eg, Ebstein's anomaly) and later stages (eg, polyhydramnios, diabetes insipidus, floppy infant syndrome [transient neonatal neuromuscular dysfunction], goiter)
- Lithium has a narrow therapeutic index and can easily cause toxicity. Drug levels should be monitored every 6-12 months and 5-7 days after any dose changes or after starting other medications that can interact with lithium.

Common drugs affecting lithium levels
• Diuretics • Nonsteroidal anti-inflammatory drugs, except aspirin • Selective serotonin reuptake inhibitors • Angiotensin-converting enzyme inhibitors & angiotensin receptor blockers • Antiepileptics (eg, carbamazepine, phenytoin)



- If a pt has ↑ creatinine level, give valproate→ periodic LFT monitoring and platelet count is needed due to rare SE hepatotoxicity and thrombocytopenia

MANAGEMENT OF ACUTE BIPOLAR DEPRESSION

- **Commonly used meds:** 2nd generation antipsychotics **quetiapine** and **lurasidone** and anticonvulsant **lamotrigine.** Lithium, valproate and the combination of olanzapine and fluoxetine have also shown efficacy
- **Antidepressant monotherapy**—avoid as there is risk of precipitating mania—if necessary, use in combination with mood stabilizers (e.g. lithium, valproate, 2nd generation anti-psychotics→ ↓ risk of switch to mania
- Lamotrigene— greatest efficacy for bipolar depressive episode—can cause SJS in 0.1% pts

MAINTENANCE

- Lifelong illness→ require maintenance to ↓ risk of recurrence
- **Most require maintenance for many years**, but lifelong maintenance is indicated for those with severe course (i.e. highly recurrent episodes, suicide attempts, severe symptoms, and impairment requiring hospitalization)→ if pt wants to stop medicine→ strong therapeutic alliance, psychoeducation, and adjunctive psychotherapy can help the patient accept the chronic nature of the illness and enhance adherence→ if pts still insists on stopping medicine → slowly taper over wks to months and frequently monitor to identify early signs and sx of recurrence
- Maintenance treatment typically involves continuation of mood stabilizers used to treat the acute mood episode. Evidence-based options include **lithium, valproate, quetiapine, and lamotrigine**
- Patients with inadequate response to monotherapy and/or severe episodes (eg, psychotic features, aggression, high risk of suicide, frequent episodes with marked impairment requiring hospitalization) often require combination therapy. **Lithium or valproate combined with a second-generation antipsychotic** (eg, quetiapine) is recommended as first-line treatment
- If antidepressant is used in acute depression, it should be slowly tapered and discontinued in maintenance treatment

DISRUPTIVE MOOD DYSREGULATION DISORDER

- Individuals with disruptive mood dysregulation disorder display severe, pervasive irritability and poor frustration tolerance, resulting in frequent temper outbursts

SLEEP DISORDERS

Classified as:

1. Dyssomnias: insufficient, excessive or altered timing of sleep.

2. Parasomnias: Unusual sleep related behavior.

DYSSOMNIAS

1. Insomnia disorder:
   - Acute (<3 months)
   - Chronic (>3 months)

2. Sleep apnea (OSA, CSA, OHS)

3. Narcolepsy

4. Circadian rhythm disorders

PARASOMNIAS

1. Non REM disorders: **sleep walking, sleep terror.**

2. REM disorders: nightmare disorder, REM sleep behavior disorder.

REM SLEEP BEHAVIOR DISORDER

Features

- Repeated arousals during sleep associated with vocalization or complex motor behavior (dream enacting behaviors) occurring during REM, more often in the second half of the sleep episode
- Characterized by lack of muscle atonia during REM sleep
- No confusion or disorientation upon awakening
- Dream-enacting behaviors include:
  - Sleep talking
  - Yelling
  - Limb jerking
  - Walking and/or running
  - Punching and/or other violent behaviors
- Presenting complaint is often violent behaviors during sleep resulting in injury to the patient and/or to the bed partner.

- Happen in **old age**.
- may be a sign of **Neurodegeneration**

UW: 12208

SLEEP DISORDERS

POOR SLEEP HYGIENE

- Inadequate sleep hygiene is a sleep disorder due to performance of daily living activities that are inconsistent with the maintenance of good-quality sleep and full daytime alertness.
- Examples of poor sleep hygiene practices include poor sleep scheduling with variable wake and sleep times and frequent daytime napping; routine use of caffeine, alcohol, or nicotine especially in the period preceding sleep; engaging in mentally or physically stimulating activities too close to bedtime; and frequent use of the bed for activities other than sleep.

INSOMNIA DISORDER

- Insomnia for >/=3 nights a week for >/=3 months

NARCOLEPSY

- Narcolepsy pts are advised to maintain proper sleep habits, minimize alcohol, and avoid medications that can cause drowsiness and worsen symptoms. In addition, a number of medications can be used to treat the symptoms of narcolepsy.
    - **Modafinil (Provigil) and armodafinil (NuVigil)—** address excessive, uncontrollable, daytime sleepiness— considered chemically to be a novel stimulant— preferred treatment for narcolepsy
    - **Amphetamine stimulants** (eg methylphenidate, dextroamphetamine, methamphetamine)—have traditionally been used—not currently considered first-line treatment, due to risk of abuse, potential tolerance, and significant side effects.
    - **Sodium oxybate (Xyrem**)—reduces cataplexy. Due to the potential for abuse and illicit use, both sodium oxybate and amphetamines are regulated as controlled substances in the United States.

ADVANCED SLEEP PHASE SYNDROME

Circadian Rhythm Sleep Disorder

- A circadian rhythm disorder characterized by inability to stay awake in the evening (usually after 7 PM), making social functioning difficult. These patients frequently complain of early-morning insomnia due to their early bedtime

DELAYED SLEEP PHASE SYNDROME

- A circadian rhythm disorder characterized by inability to fall asleep at "normal" bedtimes such as 10 PM-midnight **"sleep-onset insomnia and excessive morning sleepiness"**. These patients often cannot fall sleep until 4-5 AM, but their sleep is normal if they are allowed to sleep until late morning. Unfortunately, societal pressures often make this impossible.
- Sleep is normal when they are allowed to set their own schedules
- They describe themselves as "night owls"
- **Onset:** usually in adolescence
- May respond to treatments such as light or behavioral therapy
- Accurate history and sleep diary are essential for making diagnosis

SHIFT WORK SLEEP DISORDER

- Shift work sleep disorder involves a recurrent pattern of sleep interruption due to shift work, causing difficulty in initiating and maintaining sleep and daytime sleepiness. This disorder is due to a work schedule that is incongruent with a normal circadian clock

AGE RELATED SLEEP CHANGES

- Sleep patterns tend to change in older individuals. As people age, they typically sleep less at night and nap during the day. The period of deep sleep (Stage 4 sleep) becomes shorter and eventually disappears

Older people also awaken more during all stages of sleep. These changes are normal and usually do not indicate a sleep disorder

NIGHT TERRORS

- Occur in non-REM sleep
- Child cannot be fully awakened during episode and lasts a few min.
- No memory of event
- Most common in children 2-12 and peak at 5-7 years—usually resolve spontaneously as child ages
- Can be triggered by acute stress, sleep deprivation, illness or meds that effect CNS

NIGHTMARE

- Occur during REM sleep, usually in middle of night and early morning
- Child fully asleep during nightmare and does not scream, cry or become tachycardic
- Fully alert when awakened
- Can recall nightmare

EATING DISORDERS

Eating disorders

Diagnosis	Clinical features	Treatment
Anorexia nervosa	• **BMI <18.5** • Intense fear of weight gain • Distorted views of body weight & shape	• Cognitive-behavioral therapy • Nutritional rehabilitation • **Olanzapine** if no response to above
Bulimia nervosa	• Recurrent episodes of binge eating • Binge eating followed by **compensatory behavior** to prevent weight gain • Excess worrying about body shape & weight • Maintains **normal body weight** (BMI 18.5-30)	• Cognitive-behavioral therapy • Nutritional rehabilitation • **SSRI** **(fluoxetine)**, often in combination with above
Binge-eating disorder	• Recurrent episodes of binge eating • **No compensatory behaviors** • Lack of control during eating	• Cognitive-behavioral therapy • Behavioral weight loss therapy • SSRI • Lisdexamfetamine, topiramate

SSRI = selective serotonin reuptake inhibitor.

Vegetarian diet is a normal behavior as long as the BMI & the body image are not affected.

ANOREXIA NERVOSA

- May have binge-eating/purging subtype—main difference is in the weight
  vomit / laxative

- Restrictive subtype: fasting and/or hyper-exercising
- **Hospitalization and acute stabilization**— highly recommended for dehydration, electrolyte disturbances (eg, hypokalemia, hypophosphatemia), bradycardia, or severe weight loss.
- Supervise meals, and some patients require nasogastric tube feeding. During the onset of anabolism, patients require close monitoring for **refeeding syndrome:** electrolyte depletion, arrhythmias, and heart failure, which can result from fluid and electrolyte shifts. Vitamin deficiencies should be assessed and supplemented if deficiencies are identified

BULIMIA NERVOSA

- Binges and inappropriate compensatory behavior must occur once a week for 3 months for diagnosis
- **Signs of bulimia**: hypotension, tachycardia, dry skin, menstrual abnormalities. Electrolyte abnormalities (e.g. hypokalemia, hypochloremia, metabolic alkalosis), erosion of dental enamel, and parotid hypertrophy who vomit frequently

Table 5.

American Academy of Pediatrics Criteria for Inpatient Hospitalization in Eating Disorders

Anorexia nervosa

Heart rate < 50 beats/min daytime; < 45 beats/min nighttime

Systolic blood pressure < 90 mm Hg

Orthostatic changes in pulse (> 20 beats/min) or blood pressure (> 10 mm Hg)

Arrhythmia

Temperature < 96°F 35 c

< 75% ideal body weight or ongoing weight loss despite intensive management BMI < 15

Body fat < 10%

Refusal to eat

Failure to respond to outpatient treatment

BODY DYSMORPHIC DISORDER

Body dysmorphic disorder	
Clinical features	• Preoccupation with ≥1 perceived physical defects • Defects are not observable or appear slight to others • Repetitive behavior or mental acts performed in response to the preoccupation • Significant distress or impairment • Specific insight (good, poor, absent/delusional beliefs)
Management	• Antidepressants (selective serotonin reuptake inhibitors) • Cognitive-behavioral therapy

DISSOCIATIVE DISORDERS

Dissociative disorders	

Depersonalization/ derealization disorder	• Persistent or recurrent experiences of 1 or both:
	  ○ Depersonalization (feelings of detachment from, or being an outside observer of, one's self)
	  ○ Derealization (experiencing surroundings as unreal)
	• Intact reality testing

Dissociative amnesia	• Inability to recall important personal information, usually of a traumatic or stressful nature • Not explained by another disorder (eg, substance use, post-traumatic stress disorder)
Dissociative identity disorder	• Marked discontinuity in identity & loss of personal agency with fragmentation into ≥2 distinct personality states • Associated with severe trauma/abuse

DISSOCIATIVE AMNESIA

The specifier "with dissociative fugue" is used when amnesia is associated with seemingly purposeful travel or bewildered wandering

SOMATIC SYMPTOM AND RELATED DISORDERS

Key features of somatic symptom & related disorders	
Somatic symptom disorder	Excessive anxiety & preoccupation with ≥1 unexplained symptoms
Illness anxiety disorder	Fear of having a serious illness despite few or no symptoms & consistently negative evaluations
Conversion disorder (functional neurologic symptom disorder)	**Neurologic** symptom incompatible with any known neurologic disease; often acute onset associated with stress
Factitious disorder	Intentional falsification or inducement of symptoms with goal to assume **sick role**
Malingering	Falsification or exaggeration of symptoms to obtain external incentives (**secondary gain**)

SOMATIC SYMPTOM DISORDER

Somatic symptom disorder	

Clinical features	• ≥1 somatic symptom(s) causing distress & functional impairment
	• Excessive thoughts or behaviors related to somatic symptoms
	  ○ Unwarranted, persistent thoughts about seriousness of symptoms
	  ○ Persistent anxiety about health or symptoms
	  ○ Excessive time & energy devoted to symptoms
	• ≥6 months duration

Management	• Regularly scheduled visits with same provider • Limit unnecessary workup & specialist referrals • Legitimize symptoms but make functional improvement the goal • Focus on stress reduction & improving coping strategies • Mental health referral if patient will accept

CONVERSION DISORDER

Conversion disorder (functional neurological symptom disorder)	
Common presenting symptoms	• Weakness &/or paralysis • Nonepileptic seizures • Movement disorders • Speech or visual impairment • Swallowing difficulty • Sensory disturbances • Cognitive symptoms
Diagnostic criteria	• Symptoms of altered neurological function - voluntary motor or sensory • Often precipitated by psychological stressor • Not feigned or intentionally produced (as in factitious disorder or malingering) • Findings incompatible with recognized neurological conditions • Symptoms cause significant social or occupational impairment
Stepwise treatment options	• Education & self-help techniques - first-line • Cognitive behavioral therapy - second-line • Physical therapy for motor symptoms

- Pts can be hysterical or strangely indifferent to their symptoms i.e "La belle indifference"
- D/D requires extensive workup to rule out possible underlying medical causes

PSEUDOCYESIS

- Uncommon condition in which a woman presents with many signs and symptoms of pregnancy such as amenorrhea, enlargement of the breasts and abdomen, morning sickness, weight gain, sensation of fetal movement and reported positive urine pregnancy test per the patient. Ultrasound, however, will reveal a normal endometrial stripe and the pregnancy test in office will be negative.
- Usually seen in women who have a strong desire to become pregnant.
- It has been suggested that the depression caused by this need is behind the occurrence of some hormonal changes mimicking those of pregnancy.
- This is a form of conversion disorder
- Management requires psychiatric evaluation and treatment.

PATHOLOGIC GAMBLING

- More common in males
- Defined as a persistent and maladaptive gambling behavior that usually results in a preoccupation with gambling and arranging for the means to indulge in it
- These patients might gamble increasing amounts of money to achieve the desired excitement and can resort to illegal behavior to finance their activities. Attempts to reduce gambling behavior are typically unsuccessful and result in jeopardized relationships and financial instability
- When confronted about the issue, pathologic gamblers are usually dishonest and evasive.

- Gambling can also be used as a means of escaping from problems or relieving unhappiness

PSYCHOTHERAPIES

Psychotherapies			
Modality	**Duration**	**Typical patient**	**Focus**
Interpersonal psychotherapy	Time limited	Relationship conflicts, life role transitions, grief	• "The here and now" • **Current relationships** & conflicts
Supportive psychotherapy	Ongoing	Lower functioning, in crisis, psychotic, cognitively impaired	• Therapist as guide • Reinforce coping skills • Listen & foster understanding • Build up adaptive **defense mechanisms**
Psychodynamic psychotherapy	Ongoing	Higher functioning, persistent patterns of dysfunction, more neurotic	• Unconscious conflicts cause symptoms • Explore **past relationships/conflicts** • Utilize **transference** • Break down **defense mechanisms**
Motivational interviewing	Variable	Substance use disorder	• Address **ambivalence** to change • Nonjudgmental • Enhance motivation to change • Acknowledge resistance
Cognitive-behavioral therapy	Time limited	Persistent maladaptive thoughts, avoidance behavior, ability to participate in homework	• Identify & challenge **maladaptive** thoughts • Change emotions & behavior coming from thoughts • Behavioral techniques (breathing, exposure, goal-setting, visualization)
Dialectical behavioral therapy	Variable	Borderline personality disorder, self injury	• Acceptance & change • Improve emotion regulation, mindful awareness, distress tolerance • Manage self harm • Group therapy component
Biofeedback	Variable	Prominent physical responses accompany psychiatric symptoms	• Improve awareness & control over physiological reactions • Lower stress levels • Integrate mind & body

SUICIDE

Suicide risk & protective factors	
Risk factors	• Preexisting psychiatric disorders • Hopelessness, impulsivity • Previous suicide attempts or threats • Divorced or separated • Elderly white men • Unemployed or unskilled • Physical illness • Family history of suicide • Family discord • Access to firearms • Substance abuse
Protective factors	• Social support/family connectedness • Pregnancy • Parenthood • Religion & participation in religious activities

Suicide assessment – ideation, intent & plan
Evaluate **ideation** • Wish to die, not wake up (passive) • Thoughts of killing self (active) • Frequency, duration, intensity, controllability Evaluate **intent** • Strength of intent to attempt suicide; ability to control impulsivity • Determine how close patient has come to acting on a plan (rehearsal, aborted attempts) Evaluate **plan** • Specific details: method, time, place, access to means (eg, weapons, pills), preparations (eg, gathering pills, changing will) • Lethality of method • Likelihood of rescue

Hospitalization to maintain safety is indicated for patients with active suicidal ideation that includes a plan and intent to act. Patients with suicidal ideation but no specific plan or intent need intensive outpatient treatment, but not necessarily hospitalization (e.g., treat the underlying disorder with medication and/or psychotherapy, increase the frequency of clinical contact, mobilize supports)

Assessment & management of suicidality	
Assessment	**SAD PERSONS** • **S**ex • **A**ge • **D**epression • **P**revious attempt • **E**tOH (or other substance) use • **R**ational thought loss (psychosis) • **S**ocial support (lack of) • **O**rganized plan • **N**o spouse or significant other • **S**ickness or injury
Management	**High imminent risk** (ideation, **intent & plan**) • Ensure safety: Hospitalize immediately (involuntarily if necessary) • Remove personal belongings & objects in room that may present self harm risk • Constant observation & security may be required to hold against will **High non-imminent risk** (ideation, intent, but **no plan to act in near future**) • Treat modifiable risk factors (eg, underlying depression, psychosis, substance abuse) • Recruit family or friends to support patient • Reduce access to potential means (eg, secure firearms, medications)

FIREARM INJURY

Firearm injury	
Risk factors	• Male adolescent • Behavior or psychiatric problems • Impulsive, violent, or criminal behavior • Low socioeconomic status
Prevention	• **Remove all firearms from the home** • Store firearms unloaded • Lock firearms & ammunition in separate containers

HOMICIDE RISK FACTORS

Homicide risk factors
• Young male • Unemployed • Impoverished • Access to firearms • Substance abuse • Antisocial personality disorder • History of violence or criminality • History of childhood abuse • Impulsivity

PERSONALITY DISORDERS

Key features of DSM-5 personality disorders	
A	
Paranoid	Suspicious, distrustful, hypervigilant
Schizoid	Prefers to be a loner, detached, unemotional
Schizotypal	Eccentric; odd thoughts, perceptions & behavior
B	
Antisocial	Disregard & violation of the rights of others
Borderline	Chaotic relationships, sensitivity to abandonment, labile mood, impulsivity, inner emptiness, self-harm
Histrionic	Dramatic, superficial, attention-seeking
Narcissistic	Grandiosity, lack of empathy
C	
Avoidant	Avoidance due to fears of criticism & rejection
Dependent	Submissive, clingy, needs to be taken care of
Obsessive-compulsive	Rigid, controlling, perfectionistic

ANTISOCIAL PERSONALITY DISORDER

Antisocial personality disorder	
Clinical features	• Violates rights of others, social norms, laws • Impulsive, irritable, aggressive (fights, assaults) • Consistently irresponsible, lies, is deceitful • Lack of remorse • Age ≥18 • Evidence of conduct disorder before age 15
Management	• Psychotherapy for milder forms (monitor for manipulation of therapeutic relationship) • Treat co-morbid psychiatric disorders (eg, substance use, depression)

- Failure to sustain consistent employment, self-appraisal and irresponsible work behavior

BORDERLINE PERSONALITY DISPORDER

Borderline personality disorder	
Diagnostic criteria	• Pervasive pattern of unstable relationships, self-image & affects & marked impulsivity, with ≥5 of the following features: ◦ Frantic efforts to avoid abandonment ◦ Unstable & intense interpersonal relationships ◦ Markedly & persistently unstable self-image ◦ Impulsivity in ≥2 areas that are potentially self-damaging ◦ Recurrent suicidal behaviors or threats of self-mutilation (eg, cutting) ◦ Affective instability (marked mood reactivity) ◦ Chronic feelings of emptiness ◦ Inappropriate & intense anger ◦ Transient stress-related paranoia or dissociation
Treatment	• **Primary treatment is psychotherapy** (several types effective; best evidence for dialectical behavior therapy) • Adjunctive pharmacotherapy to target mood instability & transient psychosis (second-generation antipsychotics, mood stabilizers) • Antidepressants if comorbid mood or anxiety disorder

- A history of **childhood trauma** (physical and sexual abuse, neglect) is common.
- **Insecure attachment** to the primary caregiver may underlie the unstable relationships and fears of abandonment that are commonly seen in the disorder.
- UW Qs had pt with borderline Sx + dissociative Sx = Hx of abuse.
UW: 15072

ACUTE DRUG TOXICITIES

Acute drug intoxication		
Drug	**Class**	**Clinical features**
Phencyclidine (PCP)	Hallucinogen	• Violent behavior • Dissociation • Hallucinations • Amnesia • **Nystagmus** (horizontal or vertical) • Ataxia
LSD	Hallucinogen	• **Visual hallucinations** • Euphoria • Dysphoric/panic • Tachycardia/hypertension
Cocaine	Stimulant	• Euphoria • Agitation • **Chest pain** • **Seizures** • Tachycardia/hypertension • Mydriasis
Methamphetamine	Stimulant	• Violent behavior, psychosis • Diaphoresis • Tachycardia/hypertension • Choreiform movements • Tooth decay, myadriasis
Marijuana (THC, cannabis)	Psychoactive	• **Increased appetite** • Euphoria • Dysphoria/panic • **Impaired time perception** • Dry mouth • **Conjunctival injection**
Heroin	Opioid	• Euphoria • **Depressed mental status** • **Miosis** • **Respiratory depression** • Constipation

High doses can cause severe HTN, seizure and life-threatening hyperthermia. Benzo used for severe psychomotor agitation

Can cause bradycardia or low BP, anxiety, psychosis, sweating, N/V. Overdose can cause MI, cardiac arrhythmia, seizure or stroke

INHALANTS ABUSE

- **Commonly abused inhalants:** Glue, nitrous oxide ("whippets"), amyl nitrite ("poppers") and spray paints
- **Way of abuse:** sniffing, huffing (inhaled from saturated cloth), bagging (bag over mouth or nose)

- **Signs of acute intoxication:**
  - Brief transient euphoria
  - LOC
  - Varys depending on specific chemical inhaled
  - Highly lipid soluble→ produce immediate effects→ lasts 15-45 minutes—rapidly eliminated from body—not commonly included in toxicology screen
  - They act as CNS depressants and can cause death
- Dermatitis ("glue sniffers rash")—due to chemical exposure—around mouth and nostrils
- LFTs—may be ↑ed with repeated use
- Boys age 14-17 are at highest risk—may go unnoticed as common household products are used

AMPHETAMINE INTOXICATION

- Commonly exhibit agitation, irritability, paranoia, or delirium. and psychosis.
- **Other Sx:** chest pain or palpitations and tachycardia, hypertension, diaphoresis, and mydriasis.
- **Other complications**: cardiac arrhythmias, seizures, hyperthermia, and intracerebral hemorrhage.
- Dx: clinical as laboratory tests, beyond a qualitative toxicology screen, are of limited utility
- Bath salt: amphetamine analog→ cause severe agitation and combativeness. Hyperthermia can occur due to physical exertion but not very severe

BATH SALTS

- Synthetic cathinones—consist of a large family of amphetamine analogs
- **MOA:** ↑ release or inhibit reuptake of NE, dopamine and serotonin
- Can cause myoclonus and rarely seizures
- **Most distinguishing feature of synthetic cathinone intoxication:** prolonged duration of effect. Delirium and psychosis due to bath salts **may last from days to weeks,** whereas the effects of intoxication with other amphetamines or hallucinogens are usually of much shorter duration. (PCP sx lasts for shorter duration—included in routine toxicology screen)
- Bath salts are usually sold as a white powder in small packages labeled as "plant food," "cleaners," or other substances.
- May be ingested orally, inhaled, or injected.
- Not related to the product Epsom salts or any other substances used in bathing.
- Routine toxicology screens do not test for bath salts.

MDMA/ECSTASY/MOLLY

- 3, 4-Methylenedioxy-methamphetamine (MDMA)—synthetic amphetamine with mild hallucinogenic properties.
- ↑ synaptic norepinephrine, dopamine, and serotonin.
- Neurotoxicity may develop with long-term use.
- MDMA is often used by college students during "**raves**" (large dance parties) to enhance euphoria and increase sociability, empathy, and sexual desire (not combative behavior)
- Intoxication may lead to **hypertension, tachycardia, hyperthermia, serotonin syndrome** (characterized by autonomic dysregulation, high fever, altered mental status, neuromuscular irritability, and seizures), **hyponatremia, and death**.
- Combining MDMA with other serotonergic drugs such as serotonergic antidepressants can increase the risk of serotonin syndrome
- Not detected by routine toxicology screens.

MARIJUANA INTOXICATION

- Cognitive effects include **slow reaction time**, incoordination, impaired short-term memory, and poor concentration. Some individuals, such as this patient, experience dysphoria, anxiety, and paranoia Perceptual disturbances such as auditory and visual hallucinations may also occur.
- **Psychomotor impairment** lasts beyond the timeframe of euphoria and can persist for up to a day, resulting in high risk of injury or death in motor vehicle accidents. Chronic abuse is also associated with **gynecomastia** in men.

WITHDRAWAL SYNDROMES

Common withdrawal syndromes

Substance	Symptoms	Examination findings
Alcohol	Tremors, agitation, anxiety, **delirium**, psychosis	**Seizures**, tachycardia, palpitations
Benzodiazepines	Tremors, anxiety, perceptual disturbances, psychosis, insomnia	
Heroin	Nausea, vomiting, abdominal cramping, muscle aches	**Dilated pupils**, **yawning**, piloerection, **lacrimation**, hyperactive bowel sounds
Stimulants (eg, cocaine, amphetamines)	Increased appetite, hypersomnia, **intense psychomotor retardation, severe depression ("crash")**	No significant findings
Nicotine	Dysphoria, irritability, anxiety, **increased appetite**	

ALCOHOL WITHDRAWAL SYNDROME

Alcohol withdrawal syndrome		
Manifestations	**Symptoms/signs**	**Onset since last drink (hours)**
Mild withdrawal	Anxiety, insomnia, tremors, diaphoresis, palpitations, gastrointestinal upset, intact orientation	6-24
Seizures	Single or multiple generalized tonic-clonic	12-48
Alcoholic hallucinosis	Visual, auditory, or tactile; intact orientation; stable vital signs	12-48
Delirium tremens	Confusion, agitation, fever, tachycardia, hypertension, diaphoresis, hallucinations	48-96

Usually develop in 12-24 hrs and resolve in 24-48 hrs

- Typically peak during 2nd day following cessation
- In any hospitalized pt with suspected h/o alcoholism, precautions should be taken to prevent sx of withdrawal. Due to the serious potential complications of alcohol withdrawal, the patient should be placed in a protective environment, and be treated with benzodiazepines, which are CNS depressants that will limit the effects of alcohol withdrawal. Chlordiazepoxide (Librium) is a benzodiazepine and a common choice of treatment for alcohol withdrawal.
- **Management of alcohol withdrawal seizures:**
  - Rule out other possible causes of seizures like infection, hypoxia, bleeding, metabolic derangement, preexisting seizure disorder→ confirmed→
  - Treat with benzodiazepine esp. intermediate acting **IV Lorazepam** is preferred in hospital setting—control symptoms and prevent progression to DT— also safe in possible liver disease and has no active metabolites. Chlordiazepoxide is very long-acting—not preferred in hospital setting and in pts with possible liver dis.
  - **Adjunctive therapy:** IV fluids, frequent monitoring of vitals, thiamine, folate and nutritional support
  - Phenobarbital—can be used as adjunct to benzo in treatment refractory alcohol withdrawal and withdrawal related seizures

HEROIN WITHDRAWAL

- Present within 6-12 hours, peak at 36-72 hours, and may continue for several days
- Very distressing but not life-threatening
- Restlessness and elevated pulse and BP (although usually not as elevated as alcohol withdrawal)

NEONATAL ABSTINENCE SYNDROME

- Neonates are frequently exposed to heroin and methadone. Methadone is given to heroin addict mothers to prevent uncontrollable withdrawal in infants
- Heroin does not cause dysmorphic facies but can cause IUGR, macrocephaly, SIDS and neonatal abstinence syndrome (NAS)

- **Sx of NAS**: irritability, high pitched cry, poor sleeping, tremors, seizures, sweating, sneezing, tachypnea, poor feeding, vomiting, and diarrhea.
- Usually presents within 48 hours after birth for heroin withdrawal and between 48 and 72 hours for methadone withdrawal— can be delayed up to four weeks.
- **Rx for NAS**: includes symptomatic care to calm the infant and help the infant sleep, such as swaddling, providing small frequent feeds, and keeping the infant in a low stimulation environment. Pharmacologic treatment should be used when supportive treatment does not control the infant's withdrawal symptoms. Morphine can be administered and systematically weaned to help control opiate withdrawal.

SMOKING CESSATION

- In addition to counseling, several meds are used to promote short and long term quit
- Bupropion is most commonly used—modestly effective at ↑ing quit rate
- TCAs are also moderately effective but not approved for this
- Varenicline—partial agonist of nicotinic Ach receptor—more effective than bupropion at ↑ing short and long term quit
- Efficacy of all meds can be enhanced by nicotine replacement therapy in appropriate pts

POINTERS

- Glucocorticoids can induce manic, depressive or psychotic episodes
- If a child/adolescent presents with recent changes in behavior, emotions and social circle→ suspect substance abuse even if pt denies→ perform urine toxicology screen but keep in mind that pt may be abusing substance not detected on routine toxicology screen (e.g. bath salts, K2, Salvia, household inhalants etc).
- In addition to substance use, other considerations of adolescent patients presenting with behavioral changes include: partner violence, date rape, physical or sexual abuse, and pregnancy.

KEY FACT

The most common sexual dysfunctions in men are erectile disorder and premature ejaculation. The most common in women are female sexual interest/arousal disorder and female orgasmic disorder.

- **Male hypoactive sexual desire disorder:** Absence or deficiency of sexual thoughts, desire, or fantasies for >6 months (occurs in <2% of men).
- **Female sexual interest/arousal disorder:** Absence or reduced sexual interest, thoughts/fantasies, initiation of sex, sexual excitement/pleasure, sexual arousal, and/or genital/nongenital sensations during sex for >6 months (unclear prevalence of DSM-5 disorder, but low sexual desire in up to 26–43% of women).
- **Erectile disorder:** Marked difficulty obtaining or maintaining an erection, or marked decreased in erectile rigidity for >6 months. Commonly referred to as *erectile dysfunction (ED)* or *impotence*. May be *lifelong* (never had one) or *acquired* (after previous ability to maintain erections).

LANGUAGE DISORDER

- persistent difficulties in **comprehension (receptive)** or **production (expression)** of spoken and written language.
- It may involve the rules (grammar, syntax, morphology), content (vocabulary), and/or functional use of language.

- **Tx**: structured language therapy

Childhood-onset fluency disorder

- AKA stuttering.
- impairment in the **fluency** of speech production.
- **Pt**: the speech is not clear nor fluent.

Question Id	Main Division	Sub Division	Notes
2659	Medicine	Cardiovascular System	hyperkalemia--> peaked T waves, followed by lengthening of PR and QRS intervals and eventually resulting in sine wave Rx: Calcium gluconate (also occasionally used for Beta blocker and CCB overdose)
2686	Medicine	Cardiovascular System	in HCM, there is diastolic heart failure. beta blockers slow heart rate and increase diastole time leading to increased time for filling ou of heart. hence, they are treatment of choice in hcm. calcium channel blockers like diltiazem can be used as alternative
2692	Medicine	Cardiovascular System	Alcoholic cardiomyopathy-->dialted cardiomyopathy-->Rx: total abstinence may reverse this condition if employed earlier in course cig. smoking cause coronary artery dis. and cessation should be encouraged in heart failure
2701	Medicine	Cardiovascular System	developing country--> rheumatic fever-->mitral stenosis--> inc. left atrial pressure--> increase pulmonary pressure--> exertional dyspnea,m nocturnal cough and hemoptysis hemoptysis in particular should raise suspicion of MS MS--> left atrial dilation-->atrial fibrillation--> thrombus-->embolize
2739	Medicine	Cardiovascular System	electrical alternans: amplitude of QRS varies from beat to beat specific for pericardial effusion cxr shows enlarged cardiac silhoutte echo confirms the diagnosis
2740	Medicine	Cardiovascular System	ACEi have survival benenfit in pts with CHF with severity ranging frim asymptomatic to severe. pts are typically started on low dose, which is then titrated upwards as pt tolerate cox improvement in mortality is does-dependent.they reduce preload and afterload as well as effects on local renin-angiotensin system
2742	Medicine	Cardiovascular System	epigastric pain with exertion n normal ecg--= exercise ecg--= negative--= GI endoscopy positive--= coronary angiography
3094	Medicine	Cardiovascular System	cig. smoking transiently raises BP but pts with chronic light to moderate smoking have lower blood pressure readings as compared to non-smokers

3158	Medicine	Cardiovascular System	in pts taking statins and higly elevated CPK, should stop taking statins as it can lead to rhabdomyolysis and renal failure. N-acetylcysteine: 1. dissolution of mucus 2. protection against contrast induced renal failure, 3. therapy for acetaminophen overdose
3777	Medicine	Cardiovascular System	NE is given to hypotensive pts to inc. BP but in some pts with dec. blood flow, vasoconstriction can result in ischemia and necrosis of distal fingers and toes (symmetric coolness and duskiness of fingertips), intestines (resulting in mesenteric ischemia) or kidney (causing renal failure). Cholesterol emboli--can occur in pts with atherosclerosis-->affect distal portion of digits (asymmetric), also called "blue toe syndrome"
3820	Medicine	Cardiovascular System	Metoprolol improve mortality in CHF, esp in NYHA classes II and III. carvedilol and bisoprolo are also beneficial. Spironolcatone was associated with 30% reduction in overall mortality at 24 months in pts with NYHA class III to IV HF who were receving ACEi and loop diuretic (RALES trial)
3881	Medicine	Cardiovascular System	clonic jerks can occur during any syncopal episode which is prolonged and associated with cerebral hypoxia, regardless of etiology. Features suggestive of seizure: + trigger (eg lack of sleep, emotional stress, loud music, flashing lights), + prodromal aura, head deviation or unusual body posturing, tongue laceration or prolonged postictal phase of confusion and disorientation
4101	Medicine	Cardiovascular System	diastolic and continuous murmurs are usualluy due to underlying pathology--> perform transthoracic echo midsystolic murmur in otherwise young asymptomatic adults are usually beingn and do not require further evaluation
4227	Medicine	Cardiovascular System	HMG-CoA reductase is intracellular enzyme. Captopril can cause immune mediated membranous glomerulonephritis. ACEi are kind of extracellular enzyme blocker

4238	Medicine	Cardiovascular System	tachycardia mediated myopathy: due to prolong periods of rapid ventricular rates in A. flutter, a. fib, VT, incessant atrial/junctional tachy, AV nodal reentrant tachy--> LV dilatation and myocaridal dysfunction in chronic cases-->Dx: ecg, echo and assess other causes of LV dysfunction Rx: aggressive rate and rhythm control with AV nodal blocking agents, antiarrhythmic drugs and catheter ablation of arrhythmia as it i reversible condition
4270	Medicine	Cardiovascular System	plasma BNP has recently become useful lab test to distinguish between CHF and other causes of dyspnea. Value >100pg/ml diagnoses CHF with sensitivity, specificity and predictive value of 90, 76 and 83, respectively
4291	Medicine	Cardiovascular System	excessive alcohol intake= >2drinks a day binge drinking= >/= 5 drinks in a row They lead to impaired BP control and should be counselled moderate alcohol intake= 1-2drinks a day for men and 1 drink a day for women--> dec. incidence of coronary heart dis. and cardiovascular mortality lifestyle modi:low salt,more fruits and veges,low fat,aerobic exer,wt loss 2* causes of htn should be sought in resistant htn (>3drugs of diff class), young (<30),obese,non african american pts
4346	Medicine	Cardiovascular System	pt with GERD if refractory to H2 receptor blockers and PPI--> surgical funcoplication or endoscopy treatment in 10-30% pts with 1mm ST depression will not have any significant coronary artery disease esp if appears near-maximal exertion without chest pain
4453	Medicine	Cardiovascular System	metoprolol SE like fatigue, depression, weight gain may resemble hypothyroidism but hepatic toxicity is uncommon unlike amiodarone
4454	Medicine	Cardiovascular System	pt taking digoxin should have regular blood drug levels checked if presnsts with toxicity sx, should check drug levels and also ecg and pt/inr to check life threatening arrythmia and coagulopathy

4650	Medicine	Cardiovascular System	costochondritis also worsens with movement and worsen with inspiration but reproducible with palpation
8927	Medicine	Cardiovascular System	Peripheral artery dis.: intermittent claudication, diminished pulses and abnormal (<1) ankle brachial index. people with PAD have increased risk of myocardial infarction and stroke within 5 years. only 1-2% develop critical limb ischemia with risk of amputation. they should be treated e' aggressive risk modification for prevention of cardiovascular morbidity and mortality
2468	Pediatrics	Cardiovascular System	VSD is the most common cardiac defect in Edward syndrome ASD and endocarddial cushion defect common in trisomy 21 supravalvular aortic stenosis in William's syndrome Conotruncal abnormalities (truncus arteriosus, tof, interrupted aortic arch)--associated with CATCH-22 syndromes like DiGeorge and velocardiofacial syndromes Congenital heart block-- in neonatal lupus PDA in congenital rubella coronary artery aneurysm--Kawasaki dis.
2371	Surgery	Cardiovascular System	AAA repair and bowel ischemia: C/F: abdominal pain and bloody diarrhea. fever and leukocytosis may also be present. this adverse effect can be minimized by checking sigmoid colon perfusion following placement of aortic graft
4507	Surgery	Cardiovascular System	arterial thrombosis is slowly progressive arterial embolus: acute. usually emboli originate from heart. from ventricles after MI and from atrial in atrial fib
2189	Medicine	Endocrine, Diabetes & Metabolism	serum osmolarity=2xNa mmol/L+glucose
2190	Medicine	Endocrine, Diabetes & Metabolism	intensive BP control is primary intervention to slow decline in GFR once azotemia develops in diabetic patient. recommended BP for diabetic pt with signs of nephropathy is 130/80mmHg
3499	Medicine	Endocrine, Diabetes & Metabolism	follicular thyroid CA--> early hematogenous spread to lungs, brain and bone papillary-->most common, slow spread, lymphatics. excellent prognosis even in presence of mets

3807	Medicine	Endocrine, Diabetes & Metabolism	Lung cancer screening: annual low dose CT scan in adults 55-80yo >/=30 pack-year smoking history who currently smoke or have quir in last 15 years. Cervial cancer screening: average risk: Pap smear every 3 years from age 21-29 from 30-65, pts with initial -ve testing may have either pap alone every 3 yr or combo of Pap and HPV testing every 5 yrs (preferred)
4134	Medicine	Endocrine, Diabetes & Metabolism	MILK-ALKALI SYNDROME: inc. intake of calcium and absorbable alkali.-->hypercalcemia, metabolic alaklosis and acute kidney injury, elevated bicarb due to inc. intake and dec renal excretion of bicarb
4161	Medicine	Endocrine, Diabetes & Metabolism	Pelvic fracture or urethral injury--> injury to parasympathetic nerve (arterial insufficiency may also be involved)--> erectile dysfunction venogenic ED--> after disruption of tunica albuginea (eg penile fracture)
4305	Medicine	Endocrine, Diabetes & Metabolism	Pt on Warfarin--> maintained INR-->acute stress like sepsis--> increase ACTH--> inc. adrenal blood flow--> adrenal hemorrhage (can also ocuur in meninogoccoccemia or Pseudomonas sepsis) ADRENOLEUKODYSTROPHY: congenital, young males (females can be carriers)--> accumulation of very long chain FA in adrenal gland--> adrenal insufficiency
4324	Medicine	Endocrine, Diabetes & Metabolism	most TSH- secreting pituitary adenomas are macroadenomas-->inc. TSH-->goiter cox of growth effect of TSH on thyroid follicles
4726	Medicine	Endocrine, Diabetes & Metabolism	increase risk of grave's ophthalmopathy: female sex, advancing age and smoking
8876	Medicine	Endocrine, Diabetes & Metabolism	osteoblastic bone mets can cause hypocalcemia due to use of calcium in bone formation
4149	Obstetrics & Gynecology	Endocrine, Diabetes & Metabolism	Estrogen is made from conversion of androgens by aromatase in granulosa cells of ovaries and peripheral fat. it is not produced by peripheral fat
4678	Obstetrics & Gynecology	Endocrine, Diabetes & Metabolism	post partum thyroiditis: autoimmune mediated destruction of thyroid-->occur within 1 year after delivery--> initially hyperthyroidism symptoms, later hypothyroidism
8882	Surgery	Endocrine, Diabetes & Metabolism	hypercalcemia-->short QT interval

2239	Medicine	Infectious Diseases	Acute epididymitis: fever, painful enlargement of testes & irritative voiding sx Sexually transmitted:adults,ass. with urethritis. chlamydia and gonococcus are causes Non-sexually transmitted:older pts., associated with UTI. E.coli most common cause. pseudomonas can also cause
2262	Medicine	Infectious Diseases	all pts. who are started on antiTB meds are also started on 10mg/day pyridoxine and those who have already developed peripheral neuropathy 100mg/day pyridoxine is given
2264	Medicine	Infectious Diseases	if a pt is suspected to have cerebral toxo, then sulfadiazine and pyrimethamine are given and brain biopsy is reserved for those who do not respond to treatment as if it does not respond, then it can be primary cns lymphoma. brain irradiation is needed for CNS lymphoma
2267	Medicine	Infectious Diseases	Pneumonia in HIV pt: if acute onset, high grade fever and pleural effusion--> suspect bacterial pneumonia. Pneumococcus being the most common one. due to impaired humoral immunity,other encapsulated bacteria should also be suspected Pneumocystis causes dry cough and dyspnea. CXR should b/l diffuse infiltrates; pleural effusion is not pesent
2268	Medicine	Infectious Diseases	Disseminated MAC infection: non-specfic symptoms e.g fever, cough, abdominal pain, diarrhea, night sweats, weight loss in the presence of splenomegaly and elevated alkaline phosphatase levels (reflecting MAC hepatosplenic involvement) in HIV pt with CD4 <50/mm3. Dx: blood culture/LN biopsy/BM biopsy. Rx: clarithro or azithromycin. Prophylaxis: azithro in HIV pt. with CD4 <50/mm3. DD: TB and CMV Pneumocystis prophylaxis: TMP-SMX (preferred) and Dapsone (alternative)
2269	Medicine	Infectious Diseases	Non-bloody diarrhea in HIV pt with low grade fever is caused by many organisms: Cryptosporidium, MAC (CD4<50), microsporidia, Giardia or Isospora belli. 1st step in diagnosis would be to perform a stool examination for culture, ova/parasite, C. diff Ag, and an acid fast stain for Cryptosporidium.
2270	Medicine	Infectious Diseases	CMV: fatigue, myalgia, arthralgia, fever, atypical lymphocytosis, negative monospot test and absence of LAD and pharyngitis.

2277	Medicine	Infectious Diseases	PML (progressive multifocal leukoencephalopathy): mode of transmission: unknown CF: hemiparesis, disturbance in speech, vision & gait, CN may be involved, focal neurological deficits. Area involved: cortical white matter common, brainstem and cerebellum also affected Dx:MRI non-enhancing demyelinating lesions, no mass effect Rx: none Survival time: 6mo Toxo: multiple in basal ganglia Primary CNS lymphoma: single & weakly enhancing, periventricular. EBV DNA in CSF is specific
2295	Medicine	Infectious Diseases	Lifetime risk of reactivation of latent TB infection in a person without any underlying disease is 5-10%. HIV significantly increases the risk of reactivation, with some studies estimating a reactivation risk of 10% per year. Antiretroviral therapy is not given in acute infection. it is started after acute infection resolves cox of risk of immune reconstitution syndrome.
2384	Medicine	Infectious Diseases	Hep B vaccination consists of recombinant hep B surface Ag. Pts with unknown vaccination Hx should receive both passive and active immunity. in pts who do not develop immunity with 1st 2 doses of hep B vaccine, a second vaccination course should be given
2968	Medicine	Infectious Diseases	amebic liver abscess- usually single, located in right lobe of liver, can cause pleuritic like pain if on superior surface. primary infection is colon-bloody diarrhea-->goes to liver via portal tract & form abscess. Mexico trip is imp in Dx Dx: stool examination for trophozoites, serology and liver imaging. aspirate from abscess is usually sterile. Rx: metronidazole
2981	Medicine	Infectious Diseases	INH hepatotoxicity is more ominous in pts >50yo, already with liver disease or drink alcohol daily. if S/S of INH hepatitis are observed, drug should be discontinued. however, if pt is young and appears healthy and AST/ALT raise but are <100 IU/L, then they respond well and drug should continue.

2986	Medicine	Infectious Diseases	fresh frozen plasma in conjunction with IV vitamin K is used in the management of coagulopathy more recent studies show that recombinan tuhman factor VIIa is more effective in treating coagulopathy than is FFP alone
2989	Medicine	Infectious Diseases	pulmonary cavitation in HIV pt. can be caused by: M. tuberculosis, atypical mycobacteria, Nocardia, gram negative rods, and anaerobes. Nocardia: lung most commonly involved site, manifest as nodules, a reticulonodular pattern, diffuse pulmonary infiltrate, abscess or cavity formation. Dx: difficult. presumptive Dx is made if partially acid fast, filamentous, branching rods are seen. Rx: TMP-SMX
2997	Medicine	Infectious Diseases	Invasive pulmonary disease caused by aspergillosis presents with fever, cough, dyspnea, or hemoptysis. CXR:rapidly progressing, dense consolidation. CT scan: pulmonary nodules with halo sign or lesions with air crescent. Aspergillus is ubiquitous; no specific geographic distribution Histoplasmosis: south-eastern, mid Atlantic and central US. Blastomycosis: south-central and north central US. pulm. infection asymptomatic/flu-like Coccidioidomycosis: Central & South america.
2998	Medicine	Infectious Diseases	coccidioidomycosis is common in southwestern US and Central and South America (Arizona/California). primary pulm. infection: non-specific feathures, such as fever, fatigue, dry cough, wt. loss & pleuritic chest pain. Cutaneous findings: erythema multiforme and erythema nododum as well as arthralgia are common. Blastomycosis: affects lungs, skin, bone, joints, & prostate.infection in immunocompetent in uncommon
3000	Medicine	Infectious Diseases	Adenopathy and systemic signs of infection are usually absent in sporotrichosis. ulcer is usually painless in cellulitis: systemic signs and adenopathy usually present
3011	Medicine	Infectious Diseases	Amoxicillin-clavulanate is the DOC for prophylaxis and treatment of infections caused by human bite as these are usually polymicrobial and thus coverage for G+ve, -ve and anaerobes should be provided. this is also a DOC for dig bites Comination of Clindamycin and Cirpofloxacin could be possible regimen in penicillin allergic pts.

3014	Medicine	Infectious Diseases	Viridans group include: S. sanguinis, S. mitis, S. oralis, S. mutans, S. sobrinus and S. milleri group
3103	Medicine	Infectious Diseases	CMV: intranuclear and intracytoplasmic inclusions HSV: intranuclear inclusions, volcano like small and deep lesions. cells show ballooning degeneration and eosinophilic intranuclear inclusions
3105	Medicine	Infectious Diseases	oral TMP-SMX should be given to all post-transplant pts. it prevents PCP, toxo, nocardiosis and other infections like UTI and pneumonia. ganciclovir or valganciclovir can prevent CMV. these pt.s should be vaccinated against influenza, penumococcus and hep B
3107	Medicine	Infectious Diseases	bright red, firm, friable, exophytic lesion in HIV pt--> bacillary angiomatosis
3172	Medicine	Infectious Diseases	arthritis of rheumatic fever is usually migratory and initially affects lower-extremity joints Mixed cryoglobulinemia usually associated with HCV. usually occur in association with chronic vasculitic syndrome characterized by palpable purpura, LAD, nephropathy and neuropathy
3246	Medicine	Infectious Diseases	HIV-infected pts carry inc. risk of progression to active TB. thus, all PPD + HIV pts (even if CXR is -) are given prophylactic Rx with isoniazid for 9 months and pyridoxine is added to prevent neuropathy. LFTS should be monitored in these pts cox of risk of hepatitis. test is + in HIV infected pts. when there is 5mm or mroe induration within 48-72 hours of intradermal injection of 5 tuberculin units. Alternative: 1.Pyrazinamide+rifampin/rifabutin for 2mo. 2.rifampin for 4m
3247	Medicine	Infectious Diseases	in 90% RMSF cases, rash occurs a few days after the onset of fever. leukopenia is also absent in RMSF.
3248	Medicine	Infectious Diseases	the most common cause of bloody diarhhea in the absence of fever is E.coli. EHEC causes inflammatory diarrhea syndrome with bloody stools and abdominal pain. Dx: confirmed with assay for Shiga toxin i stool. Stool culture can also identify toxin-producing strains. Rx: generally supportive; antibiotics not helpful and inc. risk of HUS

3250	Medicine	Infectious Diseases	clostridium perfringens is spore forming organism, spores germinate in foods like meats, poultry, and gravy. diarrhea occurs due to production of toxins in the gut
3253	Medicine	Infectious Diseases	Kaposi sarcoma: legs, face, oral cavity and genitalia, GI tract and lungs are involved lesions begin as papules ad later develop into plaques or nodules. color changes: light brown to violet, pts often have multiple lesions. may appear similar to purpura, angiomas, hematomas, nevi or dermatofibroma. DX: clinical, biopsy done for confirmation. Rx: HAART therapy also result in its regression. severe or refractory: systemic/intralesional chemo
3254	Medicine	Infectious Diseases	(Table)Rx of Cryptococcal meningoencephalitis: induction therapy with 2 wks of IV amphotericin B (AmB) and flucytosine, followed by fluconazole for consolidation-(8wks) and maintenance therapy (>/= 1 yr). intrathecal AmB may be considered as salvage therapy for pts who have failed systemic therapy or developed significant adverse effects to IV medications. Serial lumbar punctures may be required to reduce ICP, which is associated with increased morbidity and mortality.
3260	Medicine	Infectious Diseases	Malignant Otitis externa: ear discharge and severe ear pain that may radiate to TMJ and exacerbated by chewing. worsening of dis. despite use of topical antibiotics is an indicator of malignant dis. Examination shows granulation tissue in extrena auditoru meatus. DM and immunosuppression are risk factors. Most common cause: Pseudomonas aeruginosa
3261	Medicine	Infectious Diseases	HSV and VZV reactivation are the most common causes of idiopathic CN VII paly. the reactivation usually causes peripheral mononeuropathy e'out rash. Ramsay Hunt Syndrome: (herpes zoster oticus)-manifestation of VZV reactivation-triad of: ipsilateral facial paralysis, ear pain, and vesicles in auditory canal and external auricle.

3263	Medicine	Infectious Diseases	ERYSIPELAS: specific type of cellulitis. inflammation of superficial dermis, thereby producing prominent swelling. classic finding: sharply demarcated, erythematous, edematous, tender skin lesion with raised borders. Onset: abrupt. usually associated with systemic signs, including fever and chills. Legs most frequently involved site. Group A beta hemolytic strep most common cause. S. aureus, S. pneumoniae, Enterococci rare causes. H. influenza: cellulitis of face of child
3267	Medicine	Infectious Diseases	Typhoid: 1st week: fever 2nd wk: abdominal pain and salmon rash 3rd wk: HSM with abdominal complications (eg, intestinal bleeding, perforation)
3320	Medicine	Infectious Diseases	in parvovirus B19, rash is classically malar rash (on the face)
3422	Medicine	Infectious Diseases	Herpes zoster mostly involve dermatomes in T3-L3 distribution. Valacyclovir is the DOC. Acyclovir however, is less expensive and is also effective. Early antiviral therapy dec. duration of rash and associated pain, and is also thought to dec the likelihood of developing postherpetic neuralgia. Oral steroids can be combined with acyclovir (not valacyclovir) if initial symptoms are severe and pt has no CI for steroids. TCAs can be used to prevent/treat postherpetic neuralgia.
3425	Medicine	Infectious Diseases	LEPROSY: primarily affects nerves and skin. most coomonly affected sites: facem earsm wrists, buttocks, knees and eyebrows.in early part of dis., it may present as an insensate, hypopigmented plaque. progressive peripheral nerve damage results in muscle atrophy, with co nsequent crippling deformities of hands. Dx: acid-fast bacilli on skin biopsy. blood cultures are usually negative in leprosy

3530	Medicine	Infectious Diseases	LUDWIG ANGINA: rapidly progressive B/L cellulitis of submandibular & sublingual spaces Origin: from infected 2nd/3rd mandibular molar--typically by Streptococcus & anaerobes C/F:fever,dysphagia,odynophagia & drooling.Sx result from swelling of submandibular space & post. displacement of tongue Exam:firm induration of submandibular space;anaerobes can cause crepitus Death:from asphyxiation mostly-monitor for resp difficulty-intubate if needed Rx: antibiotic & tooth extracation
3583	Medicine	Infectious Diseases	Whipple disease: arthralgia develops before GI symptoms
3590	Medicine	Infectious Diseases	Cryptosporidium is the most common infectious diarrhea worldwide and commonly spread through drinking water, animal contact (horse breeding) and person to person contact. Self limited in immunocompetent and can cause severe chronic dis. in AIDS pt. Dx: stool exam with modified acid fast stain reveals cryptosporidial oocytes measuring 4-6um. Rx: supportive and antiretroviral therapy cox infection persists if CD4 count doesn't improve
3613	Medicine	Infectious Diseases	CMV Pneumonitis: d/d of any BMT recipient e' both lung and intestinal involvement. Risk factorS: immunosuppressive therapy, old age, sero+ before transplant Median time of dis after BMT: 45days(2wks-4mo) CXR: multifocal diffuse patchy infiltrate CT: parenchymal opacification/multiple small nodules Dx: bronchoalveolar lavage other manifestations in BMT pts: upper and lower GI ulcers, bone marrow suppression, arthralgia, myalgia, esophagitis GVHD: rash is almost always +

3674	Medicine	Infectious Diseases	brown recluse spider bites are characterized by a papule woth erythema at the site of the bite, followed by severe ulceration. Scabies: pruritic skin infection on volar wrist, intedigital web spaces, elbows, &/or penis. Burrowns made by the parasite appear as short, wavy lines in these regions and may be accompanied by papules, vesicles, pustules, or eczematous plaques. transmitted by close contact with another infected individual and not contact with sand
3675	Medicine	Infectious Diseases	dengue develops within 4-7 days of insect bite and does not occur after 2 weeks.
3825	Medicine	Infectious Diseases	S. gallolyticus (S. bovis biotype 1) is 1 of the 4 major species that belong to group D streptococci (also known as S bovis/S equinus complex). increased risk of colorectal CA and endocarditis in pts with infection due to S gallolyticus (S.bovis biotype 1) compared to pts with S. bovis biotype II infection
3917	Medicine	Infectious Diseases	CMV in AIDS pt: involve retina, CNS and GI. Dx: colonoscopy with biopsy (eosinophilic intranuclear and basophilic intracytoplasmic inclusions); serology and PCR may be + but don not prove end organ dis (eg, colitis). Rx: active CMV treated with ganciclovir, improvement and cure unlikely without antiretroviral therapy. perform ocular exam in pt of active CMV to rule out retinitis. HHV8 that cause HIV related KS is transmitted exclusively by same sex intercourse. fever - in KS
3928	Medicine	Infectious Diseases	Four members of Viridans group that can cause IE are: S. mitis, S. sanguis, S. mutans and S. salvarius. S. mutans also cause dental caries
3938	Medicine	Infectious Diseases	Table. PCP should be considered in HIV pt. who has dry cough, exertional dyspnea, and fever. CXR: B/L interstitial infiltrates. Hypoxia out of proportion to Xray findings. Elevated serum lactate dehydrogenase. NL WBC count (bacterial pneumonia-inc. WBC)Dx: demonstration of organism in sputum or bronchialveolar lavage aspirate. Rx: TMP-SMX for 21 days regardless of pneumonia severity. Steroids added if PaO2<70 mmHg or A-a >/=35mmHg. they dec. inflammation from dying organism.

4163	Medicine	Infectious Diseases	about 75% pts with IE have previously damaged heart valve, mitral valve being most common. Pts with mitral valve prolapse and associated regurgitation have 5-8 times higher risk of IE than those with a normal valve. aortic valve is 2nd most common esp in pts with congenital bicuspid valve and associated aortic stenosis
4167	Medicine	Infectious Diseases	intermittent catheterization is associated with a significantly lower risk of UTIs as compared to the use of indwelling catheters in pts with spinal cord injuries (neurogenic bladder). although each passage can introduce bateria into the bladder, indwelling catheters carry a greater risk because of the formation of biofilm along catheter wall that can reach bladder within 24 hours of insertion. generally, longer the catheterization, greater the risk of bacteriuria
4168	Medicine	Infectious Diseases	Diabetic patients are prone to chronic foot ulcers because of arterial insufficiency and peripheral neuropathy. Poor tissue perfusion-->immune system has difficulty combating infection. Thus, open ulcer is an ideal site of bacterial entry and infection of soft tissue can easily spread to include neighbouring bone. contiguous spread is the most likely mechanism of osteomyelitis in pts with arterial insufficiency
4354	Medicine	Infectious Diseases	Primary HIV and IM are distinguished on the basis of two points: rash (unless antibiotics are given) and diarrhea are less common in IM and tonsillar exudate is uncommon in primary HIV
4373	Medicine	Infectious Diseases	Bacillary angiomatosis(BA)-caused by Bartonella henselae and Bartonella quintana C/F: non-specific Sx e.g fever, wt loss, maialse & abdominal pain + characteristic lesion of skin and viscera. Classic cutaneous lesion-a large, pedunculated exophytic papuple e' collarette of scale-resembles a large pyogenic granuloma or cherry angioma. Dx: biopsy & microscopic identification of organism & angiomatous histology. Caution while taking biopsy due to risk of hemorrhage. Rx: antibiot
4388	Medicine	Infectious Diseases	septic emboli are usually located in periphery in case of IVDU legionella can also cause cavities in pneumonia, but they are most often found in immunosuppressed pts receiving corticosteroids

4417	Medicine	Infectious Diseases	CF: fever, night sweats, wt. loss. Nocardia can disseminate from lungs to involve brain and skin. pulm. nocardiosis is treated with TMP-SMX. in case of brain involvement, carbapenems are added for better coverage. when possible, abscesses should also be surgically drained. duration of therapy depends on response but is generally long (6-12months)
4418	Medicine	Infectious Diseases	INFLUENZA: abrupt onset fever, chills, malaise, myalgias, cough and coryza Epidemic ofetn in winters C/f: fever, variety of pulm findings like wheezes, crackles and coarse breath sounds Labs: leukopenia and proteinuria may be present CXR: normal or interstitial or alveolar pattern Dx: nasal swabs for influenza Ag are fastest way to confirm dx Rx: start within 48hrs to be effective neuraminidase inhibitors, oseltamivir & zanamivir-newest therapy Rimantidine & amantadine-only A
4478	Medicine	Infectious Diseases	HIV pts are susceptible to invasive infection with H. influenza. but usually caused by non-typable strains and Hib vaccination will not be helpful
4488	Medicine	Infectious Diseases	all pts presenting with PID should be counseled for safe sex practices and need for sexual partners from past 60days to be informed and treated as well. As these pts are at risk of other STDs, they should be advised HIV, RPR, pap smear and hepB surface Ag testing with patients consent. E' h/o IV drug abuse, hep C serology should be obtained
4517	Medicine	Infectious Diseases	secondary bacterial pneumonia after simple URTI is most commonly caused by S. pneumoniae, S. aureus, or H. influenzae. of these, only S. aureus is known to cause necrotzing bronchopneumonia resulting in pneumatocoeles leading to blood tinged sputum and multiple nodular infiltrates that can cavitate to cause small abscesses

4611	Medicine	Infectious Diseases	HIV patients should be tested for toxoplasma antibodies at the time of diagnosis of HIV as cerebral toxo occurs from reactivation of prior infection usually when CD4 count falls below 100. so in patients with antibodies against toxo should be given TMP-SMX which also prevents PCP. Fluconazole is used for prophylaxis against Cryptococcus neoformans and Coccidioides immitis in HIV+ pts who have had these diseases in the past. it is also used for frequent Candida infections
4656	Medicine	Infectious Diseases	1* syphilis: painless chancre-resolves in 3-6 wks 2* syphilis: non- pruruitic rash typically starts on trunk and extends to periphery, including palms and soles. Generalized LAD-v.common. constititional Sx are less severe. occurs wks to months after primary. requires high index of suspicion. RX: IM benzathine penicillin-Jarisch Herxheimer can occur within 24 hrs. allergic pts:doxycycline or azithromycin (Table) Coxsackie is not associated with LAD. more acute illness in RMSF
8880	Medicine	Infectious Diseases	eikenella corrodens is a gram -ve anaerobe and belongs to HACEK group. it is a common constituent of normal human oral flora. IE caused by this is seen in cases of poor dentition and/or periodontal infection, alongwith dental procedures that involve manipulation of the gingival or oral mucosa
8959	Medicine	Infectious Diseases	eosinophilic esophagitis: uncommon. Sx: dysphagia, heartburn, and refractory acid reflux. most pts typically have other atopic conditions (eg asthma, seasonal allergies). odynophagia is present chronically (months to years) rather than acutely as seen in this patient. Pill esophagitis: acute due to direct effect of med on esophageal mucosa. common meds ass. with this: potassium chloride, tetracycline, bisphosphonates, and NSAIDS.
10904	Medicine	Infectious Diseases	Pts receiving TNF antagonist should not be given live attenuated vaccines as there safety is not known in these pts.
11108	Medicine	Infectious Diseases	Opportunistic infections in HIV, increase inflammatory cytokines and can significantly increase the risk of KS development or exacerbation

2296	Pediatrics	Infectious Diseases	Mycoplasma causes atypical pneumonia. erythema multiforme is typical of M. pneumonia as compared to other causes of atypical pneumonia. on sputum Gram stain, only polymorphonuclear cells are seen and not the organism.
2406	Obstetrics & Gynecology	Pregnancy, Childbirth & Puerperium	Leg cramps and mild leg edema are common in pregnancy and occur in 1/3rd normal pregnancies. this is B/l. DVT is usually U/L e' feve, u/l leg pain, swelling, redness and calf tenderness. preeclampsia: b/l leg edema with HTN or proteinuria
2145	Medicine	Pulmonary & Critical Care	massive pulmonary embolism-->hypotension and/or acute right heart strain-->JVD and RBBB--> cardiogenic shock and CNS effects-->death within an hour--> if time permits--> confirm with CTA--> echo also shows abnormalities in massive PE-->Rx: respiratory and hemodynamic support, fibrinolysis. hemorrhagic complications frequent and surgery within 10days is a relative CI to fibrinolytic therapy
2297	Medicine	Pulmonary & Critical Care	PEEP: maintains airway pressure above atmospheric pressure at the end of expiration, preventing alveolar collapse, increasing FRC and dec. work of breathing ATELECTASIS: cough, dyspnea, and dec. oxygen saturation- does not lead to compression of mediastinum, so hypotension or other vital signs will be normal
2632	Medicine	Pulmonary & Critical Care	Squamous= sCa++mous
2702	Medicine	Pulmonary & Critical Care	ACUTE EOSINOPHILIC PNEUMONIA: fever, non-productive cough, tachypnea, dyspnea, and pleuritic chest pain CXR: diffuse reticular or ground glass opacities with associated pulmonary edema and pleural effusions IATROGENIC FLUID OVERLOAD: occurs if fluid intake is > 5L in pt without congestive heart failure

2919	Medicine	Pulmonary & Critical Care	AAT deficiency: can cause COPD, involve liver(eg neonatal hepatitis, HCC), and skin (panniculitis) pts e' liver dis. maybe asymptomatic up until endstage disease. cirrhosis 2nd common cause of death in these pts Dx: AAT levels and PFTs Rx: IV human AAT supplementation + bronchodilators + corticosteroids as needed. Severe lung disease-->lung transplantation. Hepatic failure-->liver transplantation
3022	Medicine	Pulmonary & Critical Care	normal JVP <10 cm H2O
3026	Medicine	Pulmonary & Critical Care	ACUTE ASTHMA ATTACK: Rx: inhaled albuterol and systemic steroids HIGH DOSE BETA-2 AGONISTS--> hypokalemia-->muscle weakness, arrythmias and EKG abnormalities, tremor, palpitations and headache--> check serum electrolyte panel
3031	Medicine	Pulmonary & Critical Care	ALPHA-1 ANTITRYPSIN DEFICIENCY: panacinar emphysema, lower lobes lucency, smokers in 30s, non-smokers in 40s, h/o unexplained liver disease (can cause neonatal hepatitis, cirrhosis, or HCC) Dx: AAT levels, PFTs Rx; IV supplementation with pooled human AAT
3050	Medicine	Pulmonary & Critical Care	EXERCISE INDUCED BRONCHOCONSTRICTION (EIB): due to masl cell degranulation triggered by passage of high volumes of dry, cold air-- can occur in asthmatics and ppl w/o asthma RX: beta agonists (albuterol) 10-20min b4 exercise (used intermittently ie <daily-1st line) or mast cell stabilizers (antileukotrienes-who don't tolerate albuterol) 15-20 min b4 exercise. combination in high performance athletes steroid inhalers/antileukotrienes for athletes who exercise daily
3400	Medicine	Pulmonary & Critical Care	ANAPHYLAXIS: type 1 HS reaction-- histamine mediated require immediate IM administration of epinephrine into the thigh-->alpha-1 to inc. vasoconstriction & beta 2 to relax bronchial smooth muscles and dec. vascular permeability adjunctive therapies: bronchodilators, antihistamines, steroids (3-5 day course to prevent relapse)& additional vasoconstricting agents (high-dose dopamine) IV has more S/E- reserved for rapidly decompensating pts or those who have not responded to IM
3433	Medicine	Pulmonary & Critical Care	must read 3433

3453	Medicine	Pulmonary & Critical Care	Large lung nodule size, spiculated borders, low density and eccentric calcification favor CA
3474	Medicine	Pulmonary & Critical Care	BRONCHIECTASIS: dilated central bronchi with thickened walls (larger than adjacent pulm. artery branches) C/F: similar to COPD, chronic productive cough often treated with repeated courses of antibiotic Hemoptysis is common complication--sometimes severe enough to require bronchial artery embolization Confirm diagnosis: CT scan
3579	Medicine	Pulmonary & Critical Care	GOODPASTURE'S DISEASE: common in young adult males Renal findings: nephritic range proteinuria (<1.5g/day), ARF & urinary sediment with dysmorphic red cells and red cell casts Pulmonary findings: SOB, cough & hemoptysis caused by pulm hemorrhage Systemic symptoms uncommon Ab against alpha-3 chain of type IV collagen
3580	Medicine	Pulmonary & Critical Care	eosinophilic granulomatosis with polyangiitis (EGPA)-- asthma (>95%), rhinosinusitis and peripheral eosinophilia aspirin exacerbated respiratory disease (AERD)-- cough, asthma, nasal congestion-- can be treated with aspirin desensitization
3606	Medicine	Pulmonary & Critical Care	WARFARIN AND GOAL INR: INR: ratio of pt. PT to standar internation reference PT warfarin dosing should be adjusted to maintain goal INR for condition being treated Idiopathic venous thromboembolism (VTE) or atrial fibrillation, goal INR is 2.5- acceptable range of 2.0 to 3.0 Prosthetic heart valve, goal INR 2.5 to 3.5 risk of bleeding increases substantially when INR is >4
3775	Medicine	Pulmonary & Critical Care	BRONCHOGENIC CYSTS: congenital due to abnormal development of foregut--> Sx dun develop until late childhood or early adulthood-->appearance: fluid-filled or air/fluid-filled cystic structures. common in MIDDLE MEDIASTINUM and uncommon in anterior mediastinum. Benign. may be seen on AP CXR and diagnosed on CT

3776	Medicine	Pulmonary & Critical Care	Pancoast syndrome: shoulder pain radiating to arm in ulnar distribution and is caused by tumor invasion of eighth cervical and first thoracic nerves
4036	Medicine	Pulmonary & Critical Care	glucocorticoids-->inc. circulating neutrophils and dec. eosinophils and lymphocytes
4039	Medicine	Pulmonary & Critical Care	Chest physiotherapy is indicated in broncheictasis and is of no benefit in acute exacerbations of COPD
4052	Medicine	Pulmonary & Critical Care	ANTERIOR MEDIASTINUM MASSES: thymoma, retrosternal thyroid, teratoma & lymphoma--> chest discomfort/heaviness, hoarseness, horner's, facial & upper limb edema can occur MIDDLE MEDIASTINUM: bronchogenic cyst, tracheal tumors, pericardial cysts, lymphoma, LN enlargement & aortic aneurysm of arch POST. MEDIASTINUM: all neurogenic tumors: meningocele, enteric cysts, lymphomas, diaphragmatic hernias, esophageal tumors & aortic aneurysm-->Dx: MRI
4097	Medicine	Pulmonary & Critical Care	CAP: cough +/- sputum, pleuritic chest pain, tachycardia/tachypnea & dyspnea. GI complains or mental status change may be present. Dx: clinical supported by CXR- normal early (<24hr), neutropenia, dehydration or atypical infections like P. jirovecii Mycoplasma: fever, dry cough, b/l perihilar infiltrates Testing for mycoplasma is not routinely performed as empiric antibiotic regimens (eg azithromycin, levofloxacin, moxifloxacin) cover these organisms
4115	Medicine	Pulmonary & Critical Care	Pneumocystis jiroveci-->PCP in IC pts (HIV and chemotherapy pts) incubation period=4-8 wks natural habitat= lungs & airborne transmitted S/S: atypical pneumonia--dyspnea, fever, dry cough-- tachypnea, tachycardia and cyanosis with minimal chest findings B/l diffuse interstitial infiltrates beginning in perihilar region on CXR Dissemination: to lymph nodes, spleen, liver and bone marrow ASPERGILLOSIS:solid mass surrounded by radiolucent crescent (Monod's/crescent sign)
4210	Medicine	Pulmonary & Critical Care	PCP in non-HIV pt: fever, dry cough and imaging shows diffuse and b/l interstitial infiltrates

4301	Medicine	Pulmonary & Critical Care	RECURRENT BACTERIAL INFECTIONS: selective Ig def. including IgA &/or IgG subfractions->GI & sinopulm inf Eg:selective def of IgG3 alone more common in adult females, ass. e' recurrent sinopulmonary & GI infections. Food allergies & autoimmine diseases may also be present IgA def and common variable immunodeficiency can also cause similar Sx. latter may be ass e' suppressed cell immunity & inc. risk of malignancy. Quantitative measurement of serum Ig levels help make diagnosis
4523	Medicine	Pulmonary & Critical Care	LARYNGEAL EDEMA/UPPER AIRWAY OBSTRUCTION:acute onset dyspnea,difficulty swallowing,scattered urticaria,use of accessory respiratory muscles during inspiration,stridor,harsh respiratory sounds from trachea,absence of wheezes EOSINOPHILIC PNEUMONIA:asthma-like sx for several days.PE;diffuse wheezes & fine inspiratory crackles i.e bronchial and interstitial involvement peripheral eosinophilia + LEUKOCYTOCLASTICVASCULITIS:cutaneous manifestations+ pulm infiltrates+ pleural eff
4570	Medicine	Pulmonary & Critical Care	CHF--> reduced ventilation-->hypoxia-->tahypnea-->hypocapnea--> respiratory alkalosis COPD--> hypercapnea and hypoxia--> respiratory acidosis
4613	Medicine	Pulmonary & Critical Care	Sudden onset chest pain, tachpneam dyspnea, tachycardia, small pleural effusion due to hemorrhage or inflammation, pleuritic chest pain, h/o prolonged immobilization--> Pulmonary embolism. Pleural effusion is exudative and grossly bloody in this.
4614	Medicine	Pulmonary & Critical Care	risk of TB is highest in those who have lived in US </= 5 years
4632	Medicine	Pulmonary & Critical Care	Ideal location of distal tip of endotracheal tube= 2-6 cm above carina. further progression can make it enter right main bronchus

4664	Medicine	Pulmonary & Critical Care	pH decreases approx. 0.08 for every 10mmHg acute rise in $PaCO_2$ chronic hypoventilation occur in COPD, obesity hypoventilation syndrome or neuromuscular causes inc. dead space ventilation-- main cause of hypercapnea in COPD--> worsens resp. acidosis minute ventilation= TV x RR
4665	Medicine	Pulmonary & Critical Care	Must read 4665
4689	Medicine	Pulmonary & Critical Care	Hodgkin lymphoma--> curable with chemo &/or radio. inc. risk of 2* malignancy in pts treated for HL (incidence: 10% within 20 yrs and 30% within 30 yrs) Most common 2* solid tumors: lungs (esp. in smokers), breast, thyroid, bone and gastrointestinal (eg, colorectal, esophageal, gastric tumors) In addition, HL pts treated with radiation, and/or chemo have an inc. risk of developing subsequent acute leukemia or non-HL Aspergillosis occurs in preexisting lung cavities
4690	Medicine	Pulmonary & Critical Care	PE: chest CT-->wedge shaped, pleural based opacification distal to completely occluded pulmonary a. CXR: may appear as Hampton hump Contrast enhanced CT--> pulmonary artery filling defect
4713	Medicine	Pulmonary & Critical Care	must read 4713
4717	Medicine	Pulmonary & Critical Care	immunosuppressed pt-->hypoxia and fever--> pneumonia (by typical and opportunistic organisms)--> V/Q mismatch and A-a gradient fever induces hyperdynamic state and an audible flow murmur (soft crescendo/descrescendo systolic murmur) may be heard
4770	Medicine	Pulmonary & Critical Care	option D explanation? dec. prefusion bt well ventilated-->> physiologic dead space poor ventilation+ well perfused-->physiologic shunting

8905	Medicine	Pulmonary & Critical Care	Aspirin- exacerbated respiratory disease-- cough and wheezing preceded by refractory chronic rhinosinusitis with associated nasal polyposis
11669	Medicine	Pulmonary & Critical Care	NEGATIVE PRESSURE PULMONARY EDEMA: occurs when a pt has upper airway obstruction (eg laryngospasm during extubation)--> large negative intrathoracic pressure (due to inspiration against obstruction)-->noncardiogenic pulmonary edema more common in young men or after head and neck surgery
2451	Pediatrics	Pulmonary & Critical Care	chest physiotherapy is indicated in pts with bronchiectasis for removing tenacious secretions and mucous plugs IM epinephrine--> anaphylaxis Nebulized racemic epinephrine--> for laryndotracheobronchitis (croup)
3459	Pediatrics	Pulmonary & Critical Care	Status asthmaticus not responding to treatment/ fatigue/ poor air movement ie silent chest/ altered mental status/ impending respiratory failure--> endotracheal intubation and mechanical ventilation Tracheostomy--> elective procedure usually--> to relieve upper airway obstruction and not to treat asthma which is lower airway disease
3531	Pediatrics	Pulmonary & Critical Care	Primary ciliary dyskinesia can also present similar to CF like recurrent sinopulmonary infections, nasal polyposis and digital clubbing but it is much less common than CF
3538	Pediatrics	Pulmonary & Critical Care	exhaled nasal nitric oxide-- screening test for primary ciliary dyskinesia
4638	Pediatrics	Pulmonary & Critical Care	Bee sting anaphylaxis: most imp recommendation --> carry self-injectable epinephrine all the time and proper education of pt also refer to an allergist for venom immunotherapy--> reduced repeat bee sting anaphylaxis risk from 30% to <5%

4831	Pediatrics	Pulmonary & Critical Care	RISK FACTORS FOR ARDS: prematurity, male sex, perinatal asphyxia, maternal diabetes and C. section without labor. insulin anatagonize cortisol and block maturation of sphingomyelin IUGR, maternal HTN and chronic IU stress from prolonged rupture of membranes--> dec. risk of RDS. IU stress stimulate early fetal lung maturity
2812	Surgery	Pulmonary & Critical Care	SEPTIC SHOCK: metabolic acidosis(dec. pH, primary dec. in bicarb) due to accumulation of lactic acid 2* to tissue hypoxia and anaerobic respiration 2* to hypotension Rx: correct underlying cause + restoration of tissue perfusion-- IV normal saline +/- vasopressor is 1st line for IV pressure + antibiotics for underlying infection
3220	Surgery	Pulmonary & Critical Care	trauma--> significant localized chest wall tenderness--> suspect rib fracture--usually not evident initially on CXR in 50% cases--> hypoventilation due to pain--> atelectasis and pneumonia--> Rx: pain management (most imp) and respiratory support (not intubation unless resp. decompensation) Oral agents like opiates &/or NSAIDS used--> if dint work-->intercostal nerve block e' long acting local anesthetic can be used-- pain relief without affecting resp. function unlike opiate
3731	Surgery	Pulmonary & Critical Care	DIAPHRAGMATIC RUPTURE: h/o blunt abdominal trauma/MVA-->inc. intraabdominal pressure-->avulsion/rupture of diaphragm (left>right), abnormal CXR, left lower lung opacity, elevated hemidiaphragm & mediastinal deviation Presentation in children can be delayed (weeks/years later)with expansion of diaphragmatic defect and herniation of abdominal organs Confirm with CT in pt with CXR suggestive of this
4229	Surgery	Pulmonary & Critical Care	Blunt abdominal trauma--> inc. intraabdominal pressure--> diaphragmatic rupture--> acute respiratory distress or smaller rupture e' delayed N/V--> elevation of hemidiaphragm may be the only finding on CXR--> USG or CT chest --> early recognition and repair and exploration of abdomen for other traumatic injuries due to high mortality rate

4537	Surgery	Pulmonary & Critical Care	MYOCARDIAL CONTUSION: usually asymptomatic. in symptomatic cases: cause arrythmia, heart failure, and chest pain. PCWP n SOB much high
4539	Surgery	Pulmonary & Critical Care	SBP < 90mmHg, HR>/=120 and RR >/=30, flat neck veins--> signs of Class II-III hemorrhagic shock, resulting from loss of around 30% blood volume HEMOTHORAX: Each hemithorax is capable of holding up to 50% of circulating blood volume. Massive hemothorax= >1.5L--> tracheal deviation+dullness to percussion--> can be due to laceration of lung parenchyma or damage to interncostal or internal mammary a.
4695	Surgery	Pulmonary & Critical Care	General anesthesia--> impair laryngeal defenses and residual anesthetic effect--> aspiration of gastric contents and hypoventilation respectively--within 1st few hours after surgery in perioperative unit usually-->sudden onset dyspnea, cough fever and rhochi/crackles on exam
4739	Medicine	Renal, Urinary Systems & Electrolytes	ventilation=tidal volume x respiratory rate intravascular volume contraction--> inc. aldosterone function to restore intravascular volume--> inc. urinary proton loss--> contraction alkalosis
2450	Medicine	Rheumatology/Orthopedics & Sports	neurosyphilis can cause arteritis causing a cerebrovascular event but typically accompanied by abnormal CSF cell count (lymphocytic pleocytosis, 10-100/mm3)
3148	Medicine	Rheumatology/Orthopedics & Sports	Popliteal cyst/Baker cyst: posterior extrusion of synovial fluid into gastricnemius or semimembranosus bursa
3170	Medicine	Rheumatology/Orthopedics & Sports	bone scans: diagnose infectious (eg osteomyelitis) or metastatic disease Aspiration of synovial fluid: for septic and crystal induced arthritis

8866	Medicine	Rheumatology/Orthopedics & Sports	Tendinopathy 2* to fluoroquinolones: Risk factors: age>60, female, normal BMI, concurrent corticosteroid use, h/o organ transplant Involved tendons: Achilles (most common), rotator cuff, hand, biceps, thumb & other tendon sites. C/f: pain/tenderness 2-6cm above post calcaneus in Achilles. Onset: within 24 hrs, with a median of 8 days Rx; stop drug at Sx onset, avoid exercise &/or use of affected area, seek medical care for Sx evaluation & changing to non-fluoro med
2486	Pediatrics	Rheumatology/Orthopedics & Sports	bucket handle fractures also known as classic metaphyseal lesions (corner lesions) and rib fractures are Xray findings in non-accidental trauma or child abuse