Internal Medicine Review

Done by :
Arwa Aljohany
Munira Almasaad
Batoul AlRuhaimi
Khulood Alwehaibi
Rawan Mishal

Content

Neurological Disorders

Lectures List

Neurological disorders	
1	Stroke - Recognize the clinical presentation of acute ischemic stroke and intracerebral hemorrhage. - Recognize common imaging findings of ischemic and hemorrhagic stroke. - Manage patient presenting with hyperacute and acute ischemic stroke. - Address risk factors for ischemic and hemorrhagic stroke.
2	Myasthenia Gravis - Understand the pathophysiology of MG, botulism and Lambert Eaton syndrome. - Recognize the presentation of MG and botulism. - Recognize the triggers for myasthenic exacerbations. - List methods for the diagnosis of MG. - List the management options for MG and MG crisis.
3	Multiple Sclerosis - Understand the demographic characteristics of MS. - Recognize the different clinical presentations and subtypes of MS. - Describe the diagnostic methods of multiple sclerosis. - List the treatment options of MS relapses. - Understand the concept of disease modifying therapies and goals of treatment.
4	Guillain-Barre syndrome - Recognize the presentation of GBS and typical findings on examination. - List the cause for GBS. - List methods for the diagnosis of GBS. - List the management options for GBS and importance of supportive management.
5	Parkinson disease - Describe the clinical features of Parkinsonism and PD. - Recognize the difference between PD and Parkinsonism. - List causes of Parkinsonism. - List the management options for PD.
6	Headache and migraine - List causes of primary and secondary headaches. - Describe the epidemiology of migraine. - Describe the clinical features of tension-type headache and migraine. - List red flags for headache. - Understand the management options for migraine (abortive, prophylactic, non-pharmacological)
7	Seizure disorders, epilepsy, and status epilepticus - Understand the definition of seizure, epilepsy and status epilepticus. - Differentiate between a seizure and syncope using semiology and historical clues. - Know the subtypes (generalized, partial, etc) and causes of seizures. - Know the role of investigations (EEG, MRI, etc) in a patient with a seizure. - Master the steps in the management of status epilepticus. - Know how to counsel a patient with a seizure (including triggers, precautions, etc)

Stroke

- Recognize the clinical presentation of acute ischemic stroke and intracerebral hemorrhage

❖ **Ischemic:**

1. Thrombotic stroke => The onset of symptoms may be rapid or step wise. Classically the patient awakens from sleep with the neurologic deficits
2. Embolic stroke
    a. The onset of symptoms is very rapid (within seconds), and deficits are maximal initially.
    b. Clinical features depend on the artery that is occluded. The **MCA is most commonly affected**, and neurologic deficits seen in MCA involvement include:
        - Contralateral hemiparesis and hemisensory loss.
        - Aphasia (if dominant hemisphere is involved)—for 90% of population this is left cerebral dominance.
        - Apraxia, contralateral body neglect, confusion (if nondominant hemisphere is involved).
3. Lacunar stroke—Clinical features are focal and usually contralateral pure motor or pure sensory deficits. Lacunar stroke includes four major syndromes:
    a. Pure motor lacunar stroke—if lesion involves the internal capsule.
    b. Pure sensory lacunar stroke— if lesion involves the thalamus.
    c. Ataxichemiparesis—incoordination ipsilaterally.
    d. Clumsy hand dysarthria.

❖ **Hemorrhagic:**

a. Abrupt onset of a focal neurologic deficit that worsens steadily over 30 to 90 minutes
b. Altered Level Of Consciousness,stupor,or coma
c. Headache, vomiting
d. Signs of increased ICP

MNEMONIC

***MCA stroke can cause* CHANGes—**

Contralateral paresis and sensory loss in the face and arm
Hemiparesis
Aphasia (dominant)
Neglect (nondominant)
Gaze preference toward the side of the lesion

TABLE 5-1 Deficits Seen in Stroke

Distribution	Location and/or Type of Deficiency
Anterior cerebral artery	Contralateral lower extremity and face
Middle cerebral artery	Aphasia, contralateral hemiparesis
Vertebral/basilar	Ipsilateral: ataxia, diplopia, dysphagia, dysarthria, and vertigo Contralateral: homonymous hemianopsia with basilar—PCA lesions
Lacunar	
Internal capsule	Pure motor hemiparesis Dysarthria, clumsy hand
Pons Thalamus	Pure sensory deficit

PCA, posterior cerebral artery.

Note:
Most people (about 90%) have the left cerebral hemisphere dominant, and are therefore right-handed.
The frontal lobe of the dominant hemisphere contains Broca's area (the area for production of speech). Therefore, if a right-handed person gets a stroke involving his left cerebral hemisphere, he is likely to have right-sided hemiplegia (paralysis) and aphasia (loss of the power of speech).

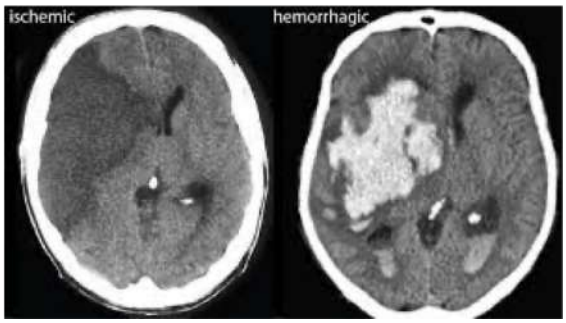
- Recognize common imaging findings of ischemic and hemorrhagic str

Brain imaging (CT or MRI)

a. CT scan of the head without contrast is preferred at most centers due to availability and time constraints, and it differentiates an ischemic from a hemorrhagic infarction. **Ischemic strokes appear as dark areas** on the CT scan (**hemorrhagic strokes appear white**). It may take 24 to 48 hours to visualize an infarct on CT.

b. MRI of the brain is more sensitive than CT; it identifies all infarcts, and does so earlier than CT scan. Ninety-five percent of infarcts identified on MRI within 24 hours.

c. The brain imaging modality can be combined with neurovascular imaging at some centers (e.g., CT with CTA, MRI with MRA).



- Address risk factors for ischemic and hemorrhagic stroke.

The risk factors for stroke are the same as those for myocardial infarction: hypertension, diabetes, hyperlipidemia, and tobacco smoking.

❖ Risk factors of Ischemic Stroke:

a. The most important risk factors are **age** and **HTN**. Others include smoking, DM, hyperlipidemia, atrial fibrillation, coronary artery disease (CAD), family history of stroke, previous stroke/TIA, and carotid bruits.

b. In younger patients, risk factors include oral contraceptive use, hypercoagulable states (e.g., protein C and S deficiencies, antiphospholipid antibody syndrome), vasoconstrictive drug use (e.g., cocaine, amphetamines), polycythemia vera, and sickle cell disease.

❖ Risk factors of Hemorrhagic Stroke:

HTN is the most most most important risk factor, Excessive ETOH use, Smoking, Obesity and physical inactivity, Age, Ethnicity/Race, Medications Such as warfarin, anticoagulation drugs, and Aspirin, Sympathomimetics. Like amphetamine and cocaine.

TABLE 2.10-5. Modifiable and Nonmodifiable Risk Factors for Stroke

Modifiable Risk Factors	Nonmodifiable Risk Factors
"Live the way a **COACH SHoulDD**":	**FAME**:
CAD	**F**amily history of MI or stroke
Obesity	**A**ge > 60
Atrial fibrillation	**M**ale gender
Carotid stenosis	**E**thnicity (African-American, Hispanic, Asian)
Hypercholesterolemia	
Smoking	
Hypertension (highest risk factor)	
Diabetes	
Drug use (cocaine, IV drugs)	

ABCD2 score

prognostic scores for stroke risk after TIA

Risk Factor	Points
Age	
≥ 60 years	1
Blood pressure	
Systolic BP ≥ 140 mm Hg *OR* Diastolic BP ≥ 90 mm Hg	1
Clinical features of TIA (*choose one*)	
Unilateral weakness with or without speech impairment *OR*	2
Speech impairment without unilateral weakness	1
Duration	
TIA duration ≥ 60 minutes	2
TIA duration 10-59 minutes	1
Diabetes	1
Total ABCD² score	0-7

Risk of stroke after TIA* according to the ABCD2

Risk group	Score	Prevalence of stroke		
		2 days	7 days	90 days
Low	0-3	1.0%	1.2%	3.1%
Moderate	4-5	4.1%	5.9%	9.8%
High	6-7	8.1%	12%	18%

The ABCD2 score is often used as a risk stratification tool to identify patients at highest risk of early stroke (validated to predict stroke risk within 2 days) that require emergency assessment.

- Age
- Blood pressure elevation shortly after TIA Clinical features of stroke
- Clinical presentation
- Duration of TIA symptoms
- Diabetes

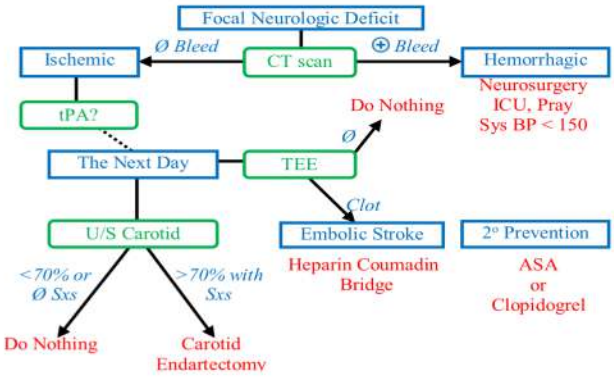
- Manage patient presenting with hyperacute and acute ischemic stroke.

❖ **Therapeutic approach :**

- Treat all eligible patients with reperfusion therapy for acute ischemic stroke within recommended time frames.
- Continue supportive care for ischemic stroke including neuroprotective measures.
- Initiate secondary prevention of recurrent ischemic stroke.
- Start antiplatelet treatment with aspirin or clopidogrel within 24–48 hours after symptom onset.
- Treat underlying conditions: e.g., atrial fibrillation, carotid artery stenosis
- Reduce modifiable risk factors: e.g., smoking, hypertension, hyperlipidemia, diabetes
- Monitor and treat any complications.
- Provide early rehabilitation and mobilization.

1. **Acute—Supportive treatment** (airway protection, oxygen, IV fluids) is initiated.
    a. Early recognition of the cause of stroke is unreliable, and early treatment is critical. Therefore, choos therapies that have broad efficacy and safety.
2. **Thrombolytic therapy (t-PA)**
    a. If administered within 4.5 hours of the onset of an acute ischemic stroke, improved clinical outcome is seen at 3 months.
    b. Do not give t-PA if the time of stroke is unknown, if more than 4.5 hours have passed, or if the patient has any of the following:
        i. uncontrolled HTN
        ii. bleeding disorder
        iii. taking anticoagulants
        iv. history of recent trauma or surgery.

    These patients are at increased risk for hemorrhagic transformation. If t-PA is given, there is risk of intracranial hemorrhage. Therefore, **do not give aspirin for the first 24 hours**, perform frequent neurologic checks (every hour), and carefully monitor BP. (Keep BP <185/110 mmHg.)



b) **Mechanical thrombectomy**
Description: physical retrieval or aspiration of the occluding thrombus via the femoral artery using a stent retriever and/or an aspiration catheter
Inclusion criteria :

- Age ≥ 18 years
- Acute large artery occlusion causing a stroke: e.g., proximal artery occlusion in anterior cerebral circulation (M1) or occlusion of the internal carotid artery (within 6 hours of stroke onset)

- **Reducing subsequent stroke risk**

Further therapeutic goals consist of identifying and treating risk factors and underlying conditions to prevent recurrent stroke.
-**Antiplatelet therapy**

- Starting within first 24–48 hours after symptom onset
- Aspirin OR Clopidogrel

-**Long-term antiplatelet therapy**

- Indicated in patients with noncardioembolic stroke to reduce the risk of recurrence.
- Choose an agent based on individual risk factors, e.g., aspirin, clopidogrel, or combination therapy.

Cardioembolic sources

- Atrial fibrillation or atrial flutter: anticoagulation with warfarin or direct oral anticoagulant is indicated.
- Patent foramen ovale: Initiate antiplatelet therapy and refer to neurologist and cardiologist to consider PFO closure.

Neuroprotective measures:

Follow standard measures, including the following specific targets for acute ischemic

- Targeted temperature management: treat any temperature > 38°C
- Glucose management for secondary brain injury prevention
- Hypoglycemia: Treat if blood glucose is < 60 mg/dL.
- Hyperglycemia: Treat to maintain blood glucose levels in a range of 140 to 180 mg/dL

Supportive care

- Dysphagia screening: Keep patient NPO until the risk of aspiration has been assessed.
- VTE prophylaxis: in addition to antiplatelet therapy and hydration
- Early rehabilitation and mobilization
- Start normal enteral diet within 7 days if possible.
- Order physiotherapy, occupational, and speech therapy.
- Screen for depression.

BP control:

In general, do not give antihypertensive agents in the first 24 hours unless one of the following three conditions is present:

a. The patient's BP is very high (systolic>220, diastolic>120, or mean arterial pressure >130 mmHg).

b) The patient has a significant medical indication for antihypertensive therapy.

Examples include:

- Acute MI Aortic dissection Severe heart failure Hypertensive encephalopathy

c. The patient is receiving t-PA—aggressive blood pressure control is necessary to reduce the likelihood of bleeding.

For future stroke prevention,

- control dyslipidemia with statins with HDL >40 and LDL <100, control diabetes with Insulin, bG <125 (HgbA1C <7%), continue cardiovascular exercise, and daily ASA. These will decrease the risk of stroke.
- In the condition where there's a carotid dissection or carotid stenosis >70% and symptoms, a carotid endarterectomy may be performed.

Myasthenia Gravis

- Understand the pathophysiology of MG, botulism and Lambert Eaton syndrome.

1- Myasthenia Gravis is an autoimmune disorder—Autoantibodies are directed against the nicotinic acetylcholine receptors of the neuromuscular junction, which leads to a reduced **postsynaptic** response to acetylcholine and results in significant muscle fatigue.

2-Botulinum toxin blocks the release of acetylcholine from **presynaptic** axon terminals into the synaptic cleft, irreversibly inhibiting neurotransmission.

3-Lambert–Eaton Myasthenic Syndrome
Associated with **small cell lung cancer**
Caused by autoantibodies directed against **presynaptic** calcium channels
Clinical features include proximal muscle weakness and hyporeflexia
Distinguished from myasthenia gravis in that symptoms **improve with repeated muscle stimulation**

KEY FACT

Lung mass with weakness = Eaton-Lambert syndrome (in a patient with SCLC) until proven otherwise

Myasthenia gravis vs. Lambert-Eaton myasthenic syndrome

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
Associated diseases	• Thymoma	• Small-cell lung cancer
Weakness	• Starts with weakness of the extraocular muscles • Worsens with exercise and throughout the day	• Starts with weakness of proximal limb muscles • Improves with exercise and throughout the day
Reflexes	• Normal	• Reduced or absent
Repetitive nerve stimulation (RNS)	• Decremental response	• Incremental response
Autonomic dysfunction	• None	• Common
Response to cholinesterase inhibitors	• Symptomatic relief	• No response

- Recognize the presentation of MG and botulism.

❖ **Myasthenia Gravis Presentation:**

1. Skeletal muscle weakness—with preservation of sensation and reflexes.

   a. Weakness is exacerbated by continued use of muscle and improved by rest. Symptoms worsen toward the end of the day (due to fatigue).

   b. Involved muscles vary and may include the following:
   - Cranial muscles: extraocular muscles, eyelids (ptosis), facial muscles (facial weakness, difficulty in chewing, slurred speech).
   - Limb muscles (proximal and asymmetric).

2. Ptosis, diplopia, and blurred vision—**most common initial symptoms.**

3. Generalized weakness, dysarthria, and dysphagia.

4. The condition progresses slowly with periodic exacerbations. Myasthenic crisis is a medical emergency that occurs in 15% of patients. Diaphragm and intercostal fatigue result in respiratory failure, often requiring mechanical ventilation.

❖ **Botulism Presentation:**

1. The severity of illness ranges widely, from mild, self-limiting symptoms to rapidly fatal disease.

2. Abdominal cramps, nausea, vomiting, and diarrhea are common.

3. The hallmark clinical manifestation is **symmetric, descending flaccid paralysis**. It starts with dry mouth, diplopia, and/or dysarthria. Paralysis of limb musculature occurs later.

Recognize the triggers for myasthenic exacerbations.

Sometimes associated with exacerbating factors, including:

1. **Medications**
    a. Muscle relaxants
    b. Beta blockers
    c. Benzodiazepines
    d. Antibiotics– Aminoglycosides, fluoroquinolones
    e. Antiarrhythmics–quinidine, procainamide, and lidocaine
    f. Low-potency antipsychotics
    g. Tricyclic antidepressants
    h. D-penicillamine
2. **Pregnancy**
3. **Stress**
4. **Infection**

List methods for the diagnosis of MG.

Suspected cases of MG are generally confirmed via EMG and AChR antibodies.
Chest CT to rule out thymoma

1. **Acetylcholine receptor antibody** test is the test of choice (most specific). (**Best initial**)

2. EMG shows a **decremental** response to repetitive stimulation of motor nerves. (**Most accurate**)

3. **A CT scan of the thorax can rule out thymoma**. Thymoma is present in only 10% to 15% of patients, but the thymus is histologically abnormal in 75% of patients.

4. Edrophonium (Tensilon) test–anticholinesterase (AChE) medications cause marked improvement of symptoms, but a high false-positive rate limits utility.
Used to diagnose MG before AChR antibody test became the common method
Symptoms improve rapidly after administration of a short-acting acetylcholinesterase inhibitor.
High false positive rate

5. Simpson test
Provocation test used to reproduce eyelid fatigue
Positive if looking upward for > 1 minute (without lifting the head) provokes eyelid fatigue

6. Ice test: ice pack placed on one eye for 5 minutes → temporary improvement of eyelid fatigue

- List the management options for MG and MG crisis.

1. **AChE inhibitors**—for example, pyridostigmine.
   a. Inhibiting AChE increases concentration of acetylcholine at the synapse by decreasing the breakdown of acetylcholine.
   b. This is a symptomatic benefit only.

1. **Thymectomy**.
   a. This provides a symptomatic benefit and complete remission in many patients, even in the absence of a thymoma.
   b. Although usually benign, thymoma is an absolute indication for thymectomy.

1. **Immunosuppressive drugs.**
   a. Use corticosteroids for patients with a poor response to AChE inhibitors.
   b. Azathioprine and cyclosporine are alternative third-line agents.

1. **Plasmapheresis** removes antibodies to acetylcholine receptors. Use it if all else fails or if the patient is in respiratory failure.

1. **IV immunoglobulin therapy** is now sometimes used for acute exacerbations.

1. Monitor **serial forced vital capacities.** A forced vital capacity of 15 mL/kg (about 1 L) is generally an indication for intubation. Patients in myasthenic crisis have a low threshold for intubation—do not wait until the patient is hypoxic.

Acute myasthenic crisis presents with severe, overwhelming disease with profound weakness or respiratory involvement. It is treated with **IVIG or plasmapheresis.**

Multiple Sclerosis

- Understand the demographic characteristics of MS.

Epidemiology:

- Sex: Female > Male (3:1)
- Age of onset: 20–40 years of age
- Ethnicity: ↑ prevalence among the white population
- Prevalence: 50-300 per 100 000 people (greater among people who live further from the equator) (MS is more common in white women who live in colder climates)

Etiology:

- The etiology of multiple sclerosis is unclear; it is believed to develop in genetically predisposed people who have been exposed to certain environmental factors.

Genetic predisposition:

- Presence of HLA-DRB1*15 allele increases the risk of MS.
- Presence of HLA-A*02 allele appears to be protective against MS.
- 35% disease concordance among monozygotic twins
- 3–4% disease concordance among first-degree relatives

Environmental risk factors:

- Low vitamin D levels (insufficient intake, decreased exposure to UV radiation)
- Cigarette smoking
- Pathogens: EBV, HHV 6
- Obesity early in life

- Recognize the different clinical presentations and subtypes of MS.

Clinical features:

1. **Constitutional symptoms**
   Fatigue
   Headache
1. **Optic neuritis**
   Most often the earliest manifestation, Typically unilateral, Can be painful
   Impaired vision and color blindness
   Relative afferent pupillary defect (Marcus Gunn pupil)
1. **Internuclear ophthalmoplegia** (INO) as a result of a lesion in the medial longitudinal fasciculus (MLF)
   Ipsilateral medial rectus weakness but an intact convergence reflex
   Disconjugate, lateral gaze nystagmus in the contralateral eye
   More frequently bilateral than unilateral
1. **Demyelination of spinal cord tracts**
   - Lhermitte sign: a shooting electric sensation that travels down the spine upon flexion of the neck
   - Pyramidal tract lesion: upper motor neuron weakness
     - Spasticity
     - Hyperreflexia
     - Positive Babinski sign
   - Involvement of the dorsal spinal column
     - Loss of vibration and fine-touch sensation
     - Numbness, paresthesias
     - Sensory ataxia usually involving the trunk or one or more limbs
   - Neuropathic pain
   - Absent abdominal reflex
1. **Cerebellar involvement**: Charcot neurological triad:
   - Scanning speech
   - Nystagmus
   - Intention tremors
1. **Cranial nerve palsies**
   - Diplopia
   - Trigeminal sensory neuralgia
   - Facial palsy
1. **Autonomic dysfunction**
   - Bowel and bladder neurogenic disorders
   - Impaired sexual function
1. **Changes in mental state**
   - Depression, emotional changes
   - Memory deficits, impaired concentration
1. **Uhthoff phenomenon** a reversible exacerbation of neurological symptoms following an increase in body temperature, e.g., physical exertion, a warm bath, or fever

- List the treatment options of MS relapses
- Understand the concept of disease modifying therapies and goals of treatment

1. **Treatment of acute attacks.**
   a. High-dose **IV corticosteroids** can shorten an acute attack. Oral steroids have not shown the same efficacy.
   b. **Plasma exchange** may be used for patients with a poor response to steroids.
   c. Studies have shown that treatment of acute exacerbations does not alter the outcome or course of MS.
   d. Most acute attacks resolve within 6 weeks with or without treatment.

1. **Disease-modifying therapy.**
   a. There are many newer therapies, and management options are evolving. Therapy should be started early to avoid progressive, irreversible disability.
   b. The older injection therapies are effective and include **interferon-based** therapies (e.g., interferon B-la) or glatiramer.
   c. **Natalizumab** is a very effective infusion therapy, especially for those with active disease, though it increased the risk of progressive multifocal leukoencephalopathy.
   d. If convenience is a priority, then oral options include dimethyl fumarate, teriflunomide, and fingolimod.

1. **Symptomatic therapy:**
   a. Baclofen or dantrolene for muscle spasticity.
   b. Carbamazepine or gabapentin for neuropathic pain.
   c. Treat depression if indicated.

- There is no cure for MS. There are two primary goals:
  - Prevent relapses
  - Relieve symptoms of acute exacerbations
- IV steroids help hasten recovery of the acute episode in MS but do not result in any improvement in long-term outcome.

Summary of multiple sclerosis therapy

Indication	Clinically isolated syndrome (CIS)	Relapsing remitting MS (RR-MS)	Secondary progressive MS (SP-MS)	Primary progressive MS (PP-MS)
Treatment of acute exacerbation	• First line: high-dose **IV glucocorticoids** (methylprednisolone) • Second line: **plasmapheresis** • Alternative for patients who do not respond to or do not tolerate corticosteroid therapy: adrenocorticotropic hormone (ACTH) gel [24]			

Prevention of exacerbations	• Interferon therapy (IFN-β)
	• Glatiramer acetate
		• Low- and intermediate efficacy
		  ◦ Glatiramer acetate
		  ◦ Interferon therapy (IFN-β)
		  ◦ Dimethyl fumarate
		  ◦ Teriflunomide
		  ◦ Fingolimod
		• High efficacy
		  ◦ Natalizumab
		  ◦ Ocrelizumab
		  ◦ Alemtuzumab
		  ◦ Cladribine
		  ◦ Ofatumumab
			• Interferon therapy (IFN-β)
			• Siponimod
			• Ocrelizumab
			• Rituximab
			• Mitoxantrone
				• Ocrelizumab
				• Ofatumumab
				• Rituximab
				• Supportive therapy is essential.

Medication	Mechanism of action	Route of application	Indications	Side effects
Interferon beta	• Suppresses T cell activity → ↓ proinflammatory cytokines and ↓ lymphocyte invasion of the CNS	• SC	• All forms of MS	• Injection site necrosis • Flu-like symptoms • Liver dysfunction • Thrombotic microangiopathy • Depression
Glatiramer acetate (copolymer-1)	• Acts as a decoy for T cells instead of neuronal myelin • Decreases activity of proinflammatory Th1 lymphocytes		• RR-MS	• Chest pain • Hypersensitivity reactions • Lipoatrophy
Mitoxantrone	• A strong, non-selective immunosuppressant	• IV	• RR-MS	• Bone marrow suppression • Myocardial toxicity • Secondary acute myeloid leukemia (AML)
Dimethyl fumarate	• An immunomodulator that protects nerve cells through its anti-inflammatory effect	• PO	• RR-MS	• Lymphopenia • Flushing • Gastrointestinal symptoms (nausea, diarrhea) • Progressive multifocal leukoencephalopathy
Teriflunomide	• Inhibits pyrimidine synthesis, which has an antiproliferative and anti-inflammatory effect • Less activated lymphocytes enter the CNS			• Headache • Alopecia • Diarrhea • Liver dysfunction
Fingolimod	• A sphingosine-1-phosphate analog that decreases lymphocyte invasion of the CNS	• PO	• RR-MS	• Hemophagocytic lymphohistiocytosis (HLH)
Siponimod Ozanimod	• Selective agonists of subtypes 1 and 5 of sphingosine-1-phosphate receptors that cause sequestration of lymphocytes in lymph nodes		• CIS • RR-MS • Active SP-MS	• Headache • Hypertension • Elevation of transaminases • Bradycardia
Alemtuzumab	• A monoclonal antibody against the superficial antigen CD52, which is found on the surface of immune cells (T-cells, B-cells, NKT cells, and monocytes) • As a consequence, both B- and T-lymphocytes numbers decrease drastically.	• SC/IV	• RR-MS	• Secondary, B-cell mediated autoimmune phenomena (e.g., formation of autoantibodies, ITP, glomerulonephritis)
Natalizumab	• An antibody against α4-integrin (decreases lymphocyte invasion of the CNS)	• IV	• RR-MS	• Risk of progressive multifocal leukoencephalopathy in patients with (latent) JC virus infection
Ocrelizumab	• An antibody against CD20 that depletes premature and mature B-cells.	• IV	• RR-MS • PP-MS • SP-MS	• Injection site reactions • Upper respiratory infections • Hepatitis B virus reactivation • Immune suppression
Ofatumumab		• SC	• RR-MS	

Guillain barre syndrome

- Recognize the presentation of GBS and typical findings on examination

Initial symptoms

- Back and limb pain
- Paresthesias affecting distal extremities

Advanced symptoms

- **Ascending paralysis**
  - Bilateral flaccid paralysis
  - Spreads from the lower to the upper limbs in a “stocking-glove” distribution

- **Landry paralysis:** involvement of the respiratory muscles → respiratory failure
- **Muscle reflexes**
  - Reduced or absent
  - Commonly beginning in the lower limbs

- **Paresthesias**
  - Peripheral, symmetric
  - Usually affecting hands and feet

- **Neuropathic pain:** develops in about ⅔ of affected individuals

- **Autonomic dysfunction**
- Cardiovascular:
  - **Arrhythmia**
  - Blood pressure dysregulation: ↑ or ↓
  - Voiding dysfunction
  - Intestinal dysfunction

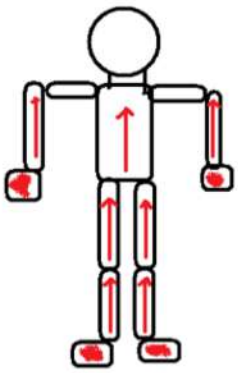
- **Cranial nerve involvement**
  - Facial diplegia due to frequent bilateral facial nerve involvement
  - Also affects glossopharyngeal nerve (IX) and vagal nerve (X)

MNEMONIC

The 4 “A’s” of Guillain-Barré syndrome—

Acute inflammatory demyelinating polyradiculopathy
Ascending paralysis
Autonomic neuropathy
Albuminocytologic dissociation (increased albumin in CSF)

- List the cause for GBS



Antibodies against myelin in the peripheral nerves begin most distally and work its way up. The demyelination is not permanent

- About ⅔ of GBS patients experience symptoms of an upper respiratory or gastrointestinal tract infection 1–4 weeks prior to onset of GBS.

Associated pathogens

- Campylobacter jejuni: campylobacter enteritis is the **most common** disease associated with GBS.
- Zika virus
- Cytomegalovirus: **most common virus** associated with GBS
- Epstein-Barr virus
- HIV
- Influenza
- SARS-CoV-2
- Mycoplasma pneumoniae
- Vaccination
- May also occur in Hodgkin disease, lupus, after surgery, or after HIV seroconversion

List methods for the diagnosis of GBS

Diagnosis
1- clinical presentation
2- LP
- CSF showing High proteins, normal cell count “albuminocytological dissociation”

3-Nerve conduction study
- ↓ Nerve conduction velocity (NCV) due to demyelination

4- Serological screening
- To identify potential pathogens

List the management options for GBS and importance of supportive management

1- **Supportive management**
- Monitor cardiac and respiratory function: in some cases, ICU treatment and intubation may be indicated
- Prevent decubitus ulcer and/or thrombosis (esp. pulmonary embolism)
- DVT prophylaxis “subcutaneous heparin / enoxaparin, stockings”
- respiratory Distress “intubation”
- Low BP “fluid bolus”
- pain “gabapentin / carbamazepine”
- high BP “short acting agent (e.g., labetalol, esmolol, or nitroprusside) to prevent abrupt hypotension”

2- **Intravenous immunoglobulins**
contraindicated in renal failure, IgA Deficiency
3- **Plasmapheresis**
In adults: equivalent outcome as IV immunoglobulins
In children: only recommended in children with rapidly progressing or severe disease
4- **do NOT give steroids**

Parkinson disease

- Describe the clinical features of Parkinsonism and PD.

Parkinsonism: a triad of signs (bradykinesia , rigidity, and resting tremor) that is consistent with impairment of the extrapyramidal system.

Clinical Features of PD:
1. **Pill-rolling tremor at rest** (worsens with emotional stress). Tremor goes away when performing routine tasks.
2. **Bradykinesia**—slowness of voluntary movements.
3. **Rigidity** is characteristic. "Cogwheel Rigidity" refers to ratchet-like jerking, which can be elicited by testing the tone in one limb while the patient clenches the opposite fist.
4. **Poor Postural Reflexes**; difficulty initiating the first step,and walking with small shuffling steps; stooped posture.
5. Masked (expressionless) facies; decreased blinking.
6. Dysarthria And Dysphagia, micrographia (small handwriting).
7. Impairment Of Cognitive Function (dementia) in advanced disease.
8. Autonomic dysfunction can lead to orthostatic hypotension, constipation, increased sweating, and oily skin.
9. Personality Changes Present In Early Stages. Patients Become Withdrawn, apathetic, and dependent on others. Depression is common and can be significant—causes worsening of parkinsonian symptoms.
10. Follows progressive course—significant disability usually presents within 5 to 10 years; indirectly leads to increased mortality.

The clinical features of Parkinson disease can be remembered with the mnemonic TRAP: Tremor, Rigidity, Akinesia, Postural instability.

Recognize the difference between PD and Parkinsonism.

Parkinson disease (PD) is a neurodegenerative condition that involves the progressive depletion of dopaminergic neurons in the basal ganglia, particularly the substantia nigra.
Parkinsonism refers to symptoms and signs of Parkinson disease

List causes of Parkinsonism.

Medication:

- Neuroleptic drugs (chlorpromazine, haloperidol, perphenazine)
- Metoclopramide (dopamine antagonist)
- Reserpine
- Flunarizine
- Amiodarone
- Valproate
- Lithium

Metabolic disorders: (eg. Wilson disease, hemochromatosis, Niemann-Pick disease)

Toxins: (Manganese, carbon monoxide, carbon disulfide)

Cerebrovascular disease (vascular parkinsonism): subcortical arteriosclerotic encephalopathy

CNS infections

- Viruses: e.g., HSV, HIV
- Bacteria: e.g., Treponema pallidum, Mycoplasma tuberculosis
- Protozoa: e.g., Toxoplasma gondii, Plasmodium spp.
- Prion agents: Creutzfeldt-Jakob disease

List the management options for PD.

No cure—goals are to delay disease progression and relieve symptoms.

1. Carbidopa-levodopa (Sinemet)—**drug of choice** for treating parkinson's symptoms.
    a. It ameliorates all the symptoms Parkinson disease. It is the **most effective** if all the antiparkinsonian drugs.
    b. is the mainstay of therapy for (>70 or non functioning) individual
    c. Side Effects:

- Dyskinesias (involuntary, often choreic movements) can occur after 5 to 7 years of therapy. This is a major concern, and may warrant delay in initiating carbidopa-levodopa for as long as possible.
- Nausea/vomiting, anorexia, HTN, hallucinations.
    a. Levodopa Does Showan "on–off" phenomenon (over the course of the day) during treatment, which leads to fluctuations in symptoms. This is due to dose– response relationships. It often occurs in advanced disease.

1. Dopamine-receptor agonists (bromocriptine,pramipexole).
    a. Mainstay of therapy for young, functional people (<70, maintained function).
    b. Pramipexole Is The Most Commonly Used.
    c. These can be useful for sudden episodes of hesitancy or immobility (described as "**freezing**").

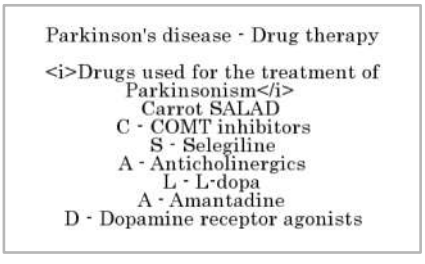
2. Selegiline—inhibits MAO-B activity (increased dopamine activity) and reduces metabolism of levodopa. It is an adjunctive agent, and is often used in early disease. It has mild symptomatic benefit.

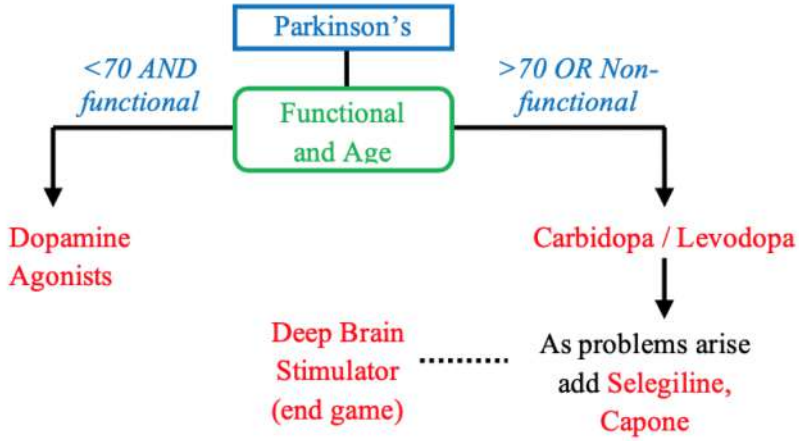
3. Amantadine (antiviral agent)—mild benefit, mostly for early or mild disease.

4. Anticholinergic Drugs (Trihexyphenidyl And Benztropine)
    a. These may be particularly helpful in patients with **tremor as a major finding**. Do not use in older patients or demented patients.

5. Amitriptyline => useful in treatment Parkinson disease both as an anticholinergic agent and as an antidepressant.

6. Surgery (deep brain stimulation) => if patient does not respond to medicationsorin patients who develop severe disease before age 40 years.





Drug	*Mechanism*	*Indications*	*Side Effects*
Amantadine		Functional >60 years old	
Carbidopa Levodopa	Dopamine Agonists	Nonfunctional	HoTN, Psychosis
Selegiline	MAO-B Antagonist	Nonfunctional Exacerbate	Delays Progression
Capones	COMT Antagonist	Nonfunctional Exacerbation	Delays Progression
Bromocriptine	Dopamine Agonist	Functional <60 years old	-

Headache and migraine

List causes of primary and secondary headaches.

Primary headaches:

- Tension headache
- Migraine headache
- Cluster headache

Secondary headaches:

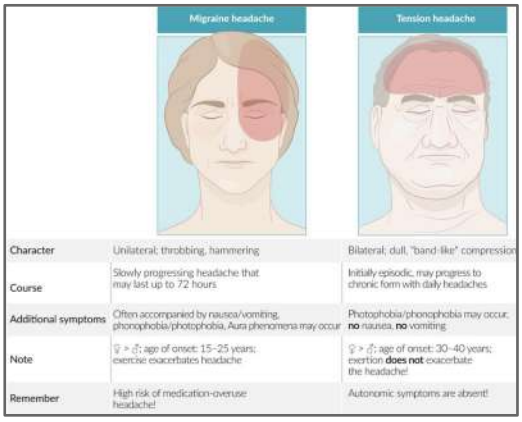
- Meningitis
- Intracranial hemorrhage
- Subarachnoid hemorrhage
- Subdural hematoma
- Epidural hematoma
- Cerebral venous sinus thrombosis
- Giant cell arteritis
- Hypertensive crisis
- Ischemic stroke
- Intracranial space-occupying lesions (e.g., brain tumors)
- Concussion (e.g., mild traumatic brain injury)
- Trigeminal neuralgia
- Medication overuse headache

Describe the epidemiology of migraine.

- Prevalence: ~ 17% of females and ~ 6% of males
- Peak incidence: 30–39 years
- Migraine is the second most common type of headache.

- Describe the clinical features of tension-type headache and migraine

Types of primary headaches		
	Tension headache	**Migraine headache**
Sex	• ♀ > ♂	• ♀ > ♂
Duration	• **30 minutes** to a couple of days	• **4–72 hours**
Frequency	• Occasionally to daily • Episodic or chronic	• Occasionally to several times a month
Localization	• **Holocephalic** or bifrontal	• 60% are unilateral.
Character	• Dull, nonpulsating, band-like or vise-like pain • Constant	• **Pulsating**, boring/hammering pain
Intensity	• Mild to moderate	• Moderate to severe
Additional symptoms	• Maximum of one autonomic symptom (phonophobia, or photophobia) • No nausea, vomiting, or aura • Tightness in the posterior neck muscles • Pericranial tenderness	• **Nausea, vomiting** • Hyperacusis • Photophobia • Phonophobia • **Preceding aura** • Prodrome
Triggers/exacerbating factors	• Stress • Lack of sleep, fatigue • Routine activities (e.g., climbing stairs) do not exacerbate symptoms.	• Stress • Fluctuation in hormone levels: oral contraceptives, menstruation • Certain types of food (e.g., those containing tyramines or nitrates such as processed meat, chocolate, cheese) • Exacerbated by exertion
Diagnostic findings	• Clinical diagnosis	• Clinical diagnosis [2] • Neuroimaging: typically normal findings [8][9]



- List red flags for headache.

TABLE 4

SNNOOP10 Mnemonic for Red Flag Symptoms in Patients with Headache

Sign or symptom	Potential cause of headache
Systemic symptoms (e.g., fever, rash, myalgia, weight loss)	Intracranial infection or nonvascular condition; carcinoid tumor, pheochromocytoma
Neoplasm diagnosis (current or history)	Brain neoplasm or metastasis
Neurologic deficit or dysfunction (e.g., focal deficits, seizure, cognitive or consciousness changes)	Intracranial disorder
Onset sudden or abrupt*	Subarachnoid hemorrhage, cranial or cervical vascular lesion
Older age (> 50 years)	Giant cell arteritis, cervical or intracranial lesions
Painful eye plus autonomic features	Posterior fossa; pituitary, cavernous sinus, or ophthalmic condition; Tolosa-Hunt syndrome
Painkiller overuse or new medication	Medication overuse headache, medication adverse effect or incompatibility
Papilledema	Intracranial condition, intracranial hypertension
Pathology of immune system	HIV or opportunistic infection
Pattern: new headache or change in pattern of established headache	Intracranial condition
Position exacerbates or relieves pain	Intracranial hypotension or hypertension
Posttraumatic onset (acute or chronic)	Subdural hematoma, vascular condition
Precipitated by sneezing, coughing, or exercise	Posterior fossa or Arnold-Chiari malformation
Pregnancy or puerperium	Cranial or cervical vascular condition, hypertension/preeclampsia, cerebral sinus thrombosis, epidural-related headache
Progressive and atypical presentation	Nonvascular intracranial condition

*—Recurrent "thunderclap" headaches suggest reversible cerebral vasoconstriction syndrome.

Adapted with permission from Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. *2019;92(3):136.*

- Understand the management options for migraine (abortive, prophylactic, non-pharmacological).

	Tension	Migraine	Cluster
Acute Management			
First line	- Ibuprofen - Acetaminophen	**No vomiting:** - **Mild:** "ibuprofen/ Acetaminophen" - **Severe:** "oral triptans / Sumatriptan-naproxen" **vomiting:** - **Non oral:** SC/ nasal Sumatriptan, non oral antiemetic agent	- O2 100% "most effective" - subcutaneous /nasal triptan "Do not offer paracetamol, NSAIDs, or oral triptans"
Prophylaxis			
First line	- Antidepressant "amitriptyline"	- propranolol "CI in asthma and COPD" - Metoprolol - amitriptyline "Avoid in MAOIi, MI, Seizure"	- Verapamil
Second line	- Mirtazapine - Venlafaxine	- topiramate "CI in pregnant 🤰" - candesartan - gabapentin	

Nonpharmacological :

- Lifestyle modifications
- Exercise in moderation
- Maintain a healthy diet
- Identify and try to avoid potential triggers
- Follow a regular sleeping schedule

Seizures

- Understand the definition of seizure, epilepsy and status epilepticus.

Seizure: an excessive and/or hypersynchronous activity of cortical neurons that results in transient neurological symptoms

Acute symptomatic seizure (provoked seizure): a seizure that occurs at the time or soon after the onset of an acute systemic or CNS condition. Examples include:

- Within 1 week of stroke, traumatic brain injury (TBI), anoxic encephalopathy, or intracranial surgery
- Subdural hematoma
- Acute CNS infection
- Exacerbation of multiple sclerosis or other autoimmune diseases
- Metabolic disturbances
- Drug/alcohol intoxication or withdrawal

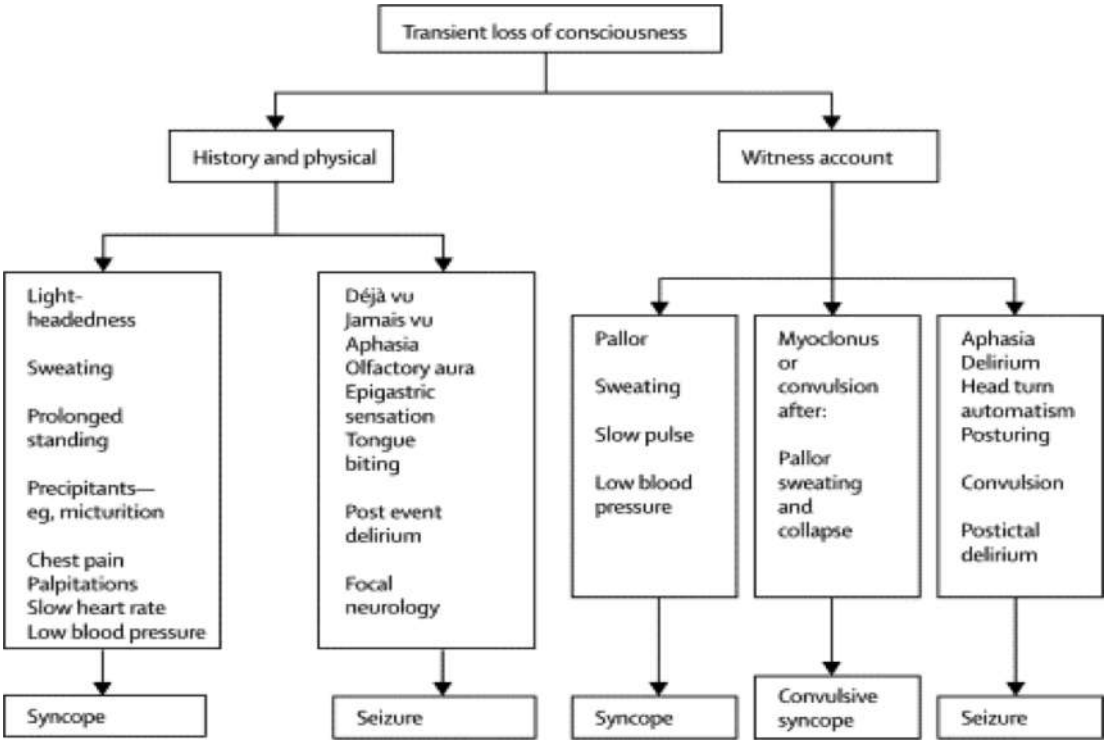
Reflex seizure: a seizure constantly evoked by a particular stimulus (trigger) that lowers seizure threshold (e.g., flashing lights)

Unprovoked seizure: a seizure that occurs in the absence of an identifiable cause or beyond the specified interval after an acute CNS condition

Epilepsy: a chronic neurologic disorder characterized by a predisposition to seizures as defined by one of the following:
Two or more unprovoked or reflex seizures separated by more than 24 hours
One unprovoked or reflex seizure in an individual with a high risk of subsequent seizures (e.g., after traumatic brain injury, stroke, CNS infections)

Status epilepticus (SE) is a seizure that lasts ≥ 5 minutes or a series of seizures in rapid succession without recovery in the interictal period, which increases the risk of long-term consequences such as neuronal injury and functional deficits.
The time threshold after which a seizure is considered SE differs according to the type of a seizure:
≥ 5 minutes for tonic-clonic seizures
≥ 10 minutes for focal seizures with impaired consciousness
10–15 minutes for absence seizures

- Differentiate between a seizure and syncope using semiology and historical clues.



Seizure	Syncope
Aura, focal symptoms, olfactory hallucinations, automatism (ex. lip smacking) before	Prodromal presyncope, palpitations, diaphoresis before
Myoclonic jerks *before* LOC	Myoclonic jerks *after* LOC
Usually between 1-2 minutes	Brief, generally <1 minute
EMS vitals: usually BP & HR generally elevated (exception: rare types of temporal lobe seizure can cause bradycardia)	EMS vitals: could have low BP & HR
Post-ictal confusion	Rapid recovery
More often horizontal deviation or flickering of eyelids, blank stare	Vertical deviation (rolling back), can also see flickering of eyelids
Eyes open	Usually eyes closed or rolled back
Lateral tongue biting	

- Know the subtypes (generalized, partial, etc) and causes of seizures.

1. Focal seizures (formally partial seizures)

- Originate in one brain hemisphere
- Usually caused by focal structural abnormalities
- Symptoms depend on the anatomical location of the lesion or disturbance within the brain.

—accounts for 70% of patients with epilepsy older than 18 years of age. It begins in one part of the brain (typically the temporal lobe) and initially produces symptoms that are referable to the region of the cortex involved.

a. Simple partial seizure.

- **Consciousness remains intact**. The seizure remains localized but may evolve into a complex partial seizure
- May involve transient unilateral clonic–tonic movement.
- Some have **an aura** and may verbalize during the attack; **no postictal period**
- EEG—**spike and sharp** waves or **multifocal spikes**
- Treatment—phenytoin and other anticonvulsants

b. Complex partial seizure.

- **Consciousness is impaired**; postictal confusion.
- **Automatisms** (last 1 to 3 minutes)—purposeless, involuntary, repetitive movements (such as lip smacking or chewing); patients may become aggressive if restraint is attempted.
- Olfactory or gustatory hallucinations.
- Interictal EEG—**anterior temporal lobe shows sharp waves or focal spikes**
- **MRI—many will show abnormalities in temporal lobe**
- Treatment—**carbamazepine (drug of choice)** and other add-ons

Table 17.10 The commoner types of seizure

Generalized seizure types
Bilateral abnormal electrical activity with bilateral motor manifestations and impaired consciousness
Absence seizures (petit mal) Generalised tonic–clonic seizures (grand mal) Myoclonic seizures Tonic seizures Akinetic seizures
Partial seizure types
Electrical activity starts in one area of the brain
Simple partial seizures (without impaired awareness, e.g. Jacksonian seizures) Complex partial seizures (with impaired awareness) Partial seizures evolving to tonic–clonic seizures Apparent generalized tonic–clonic seizures, with ECG but not clinical evidence of focal onset
Unclassifiable seizures
Seizures that do not fit a category above

KEY FACT

If a patient presents with uncontrollable twitching of his thumb and is fully aware of his symptoms, think simple partial seizures.

KEY FACT

If an adult patient presents with an episode of lip smacking associated with an impaired level of consciousness and followed by confusion, think complex partial seizures.

2. Generalized seizure

1. Generalized-onset seizures

- Symptoms are produced by bilateral cerebral cortex disturbances.
- Start with loss of consciousness.
- Patients do not recall the seizure.
- characterized by **loss of consciousness.** Involves disruption of electrical activity in the entire brain.

a. Tonic–clonic (grand mal) seizure

-bilaterally symmetric and without focal onset.

-Begins with sudden loss of consciousness—a fall to the ground.

- **Tonic phase**—The patient becomes rigid; trunk and limb extension occurs. The patient may become apneic during this phase.
- **Clonic phase**—This is musculature jerking of the limbs and body for at least 30 seconds.

-The patient then becomes flaccid and comatose before regaining consciousness.

-Postictal confusion and drowsiness are characteristic and can last for hours, although 10 to 30 minutes is more typical.

-Other features may include tongue biting, vomiting, apnea, and incontinence

Treatment—**valproic acid, phenobarbital, phenytoin, carbamazepine**

b. Absence (petit mal) seizure.

- **Sudden cessation of motor activity or speech with blank stare and flickering eyes**
- **More in girls; uncommon <5 years of age**
- Episodes are brief (lasting a few seconds) but may be quite frequent (up to 100 times per day).
- Impairment of consciousness but no loss of postural tone or continence, and **no postictal confusion**. **no aura**
- Minor clonic activity (eye blinks or head nodding) in up to 45% of cases.
- **EEG—3/second spike and generalized wave discharge**
- **Treatment—ethosuximide (drug of choice),** valproic acid (second line)

KEY FACT

Petit mal seizures may be described with the classic EEG finding of 3-per-second spike-and-wave discharges.

KEY FACT

If a patient presents with clonic movements associated with loss of consciousness and incontinence, think tonic-clonic (grand mal) seizures.

❖ **Causes of seizures:**

VITAMINS		
Vascular	Stroke, AVM, Hemorrhage	FND + Risk Factors
Infxn	Encephalitis, Meningitis	Seizure + Fever
Trauma	MVA, TBI	h/o Trauma
Autoimmune	Lupus, Vasculitis, Arthritis	Rash, Purpura, ANA
Metabolic	Na, Ca, Mg, O_2, Glucose	CMP, ABG, Mg, Phos
Idiopathic	"Everybody Gets One"	1st Time Seize
Neoplasm	Mets vs Primary	h/o Cancer, headache
Sychiatric	Faking it, Iatrogenic	Faking it / Hand Drop

❖ **Seizure triggers:**

Seizure triggers are stimuli that can precipitate seizures both in people with and without epilepsy.

- Excessive physical exertion
- Alcohol consumption
- Fever (febrile seizures)
- Sleep deprivation
- Flashing lights (e.g., strobe lights, video games)
- Music
- Hormonal changes (e.g., at different phases of the menstrual cycle, after menopause)

- Know the role of investigations (EEG, MRI, etc) in a patient with a seizure.

❖ **Diagnosis:**

1. If the patient has a known seizure disorder (epileptic), **check anticonvulsant levels** –This is usually the only test that is needed. Because therapeutic anticonvulsant levels are variable, one dose may be toxic for one patient and therapeutic for another. Therefore, take the range given in laboratory reports as a general guideline.

2. If the patient history is unclear or if this is the patient's first seizure:

a. **Laboratory screening**: to identify metabolic disorders and infectious diseases, if suspected
CBC, **electrolytes**, **blood glucose**, LFTs, renal function tests, serum calcium, urinalysis, **Toxicology screening.**

b. EEG

- Performed in individuals who present with first seizure, with insufficient information for seizure classification, and/or treatment-refractory seizure
- Although the EEG is the most helpful diagnostic test in the diagnosis of a seizure disorder, an abnormal EEG pattern alone is not adequate for the diagnosis of seizures.
- A normal EEG in a patient with a first seizure is associated with a lower risk of recurrence

During the seizure (ictal) :

- **Epileptiform discharges** (e.g., spikes, sharp waves, spike waves) are usually detected.

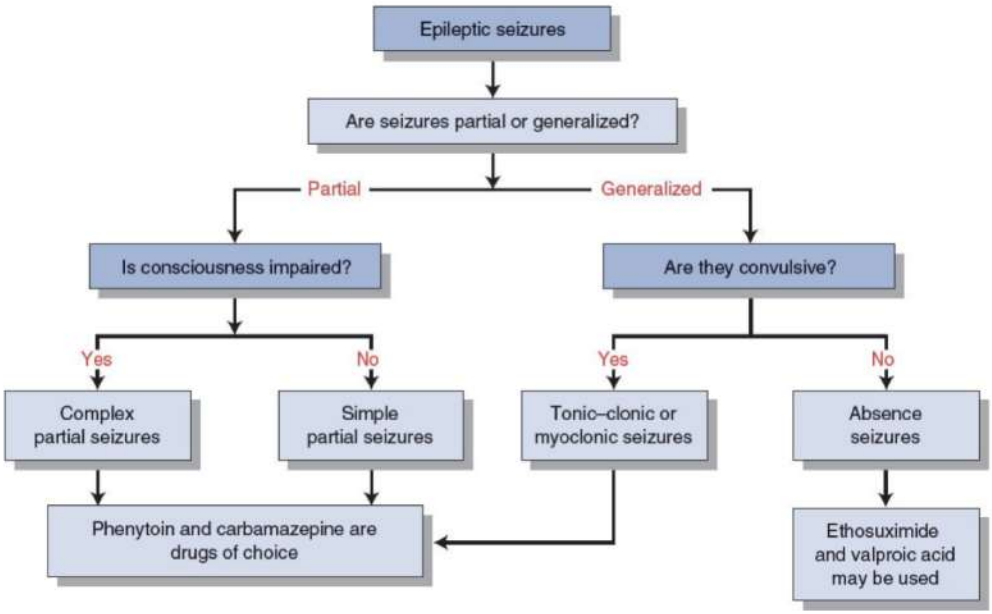
c. CT scan of the head–to identify a structural lesion.

d. MRI of the brain–with and without gadolinium (first without). An important part of the workup of a patient with a first seizure. More sensitive than a CT scan in identifying structural changes, but not always practical (e.g., in an unstable patient).

e. LP and blood cultures–if patient is febrile.

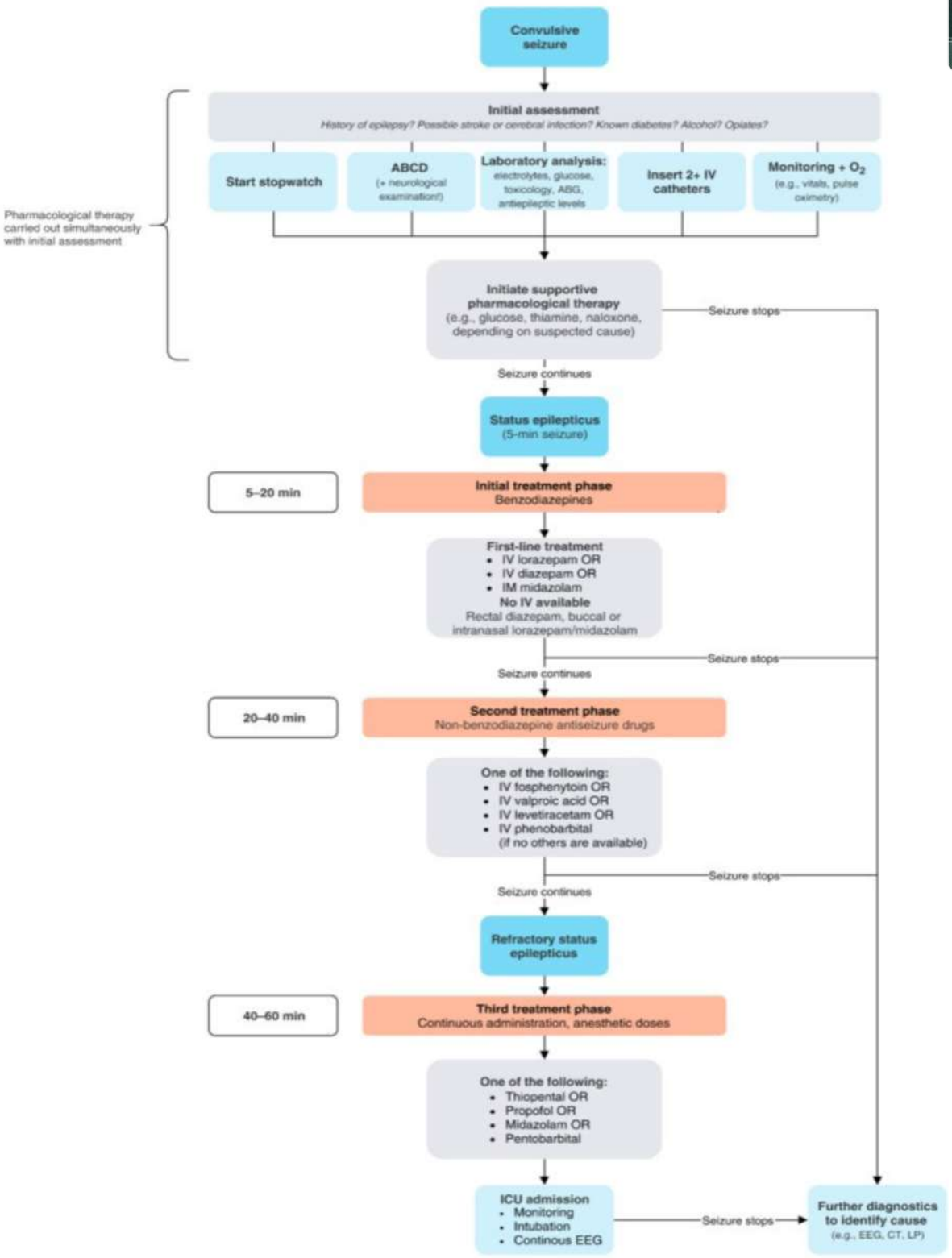
f. Angiography: if vascular cause (e.g., cerebral arteriovenous malformation) is suspected

❖ **Treatment:**



- For all seizures, ABCs take priority: Secure airway and roll patient onto his side to prevent aspiration.
- Do not treat patients with a single seizure. Antiepileptic drugs are started if EEG is abnormal, brain MRI is abnormal, patient is in status epilepticus.

- Master the steps in the management of status epilepticus.



- Know how to counsel a patient with a seizure (including triggers, precautions, etc)

- Acknowledging the event
- Explanation of what a seizure is (and is not)
- Possible etiology and prognosis
- Purpose and limitations of tests
- Lifestyle considerations (safety, occupation, seizure threshold)
- Driving
- Seizure first aid
- Role of medication
- Medication action and side effects (if appropriate)
- Psychological implications
- Next steps and when to call for help

Oncology Disorders

Lectures List

Oncology disorders	
1	Lung cancer - Recognize the risk factors for lung cancer. - Identify common presentations of lung cancer - To be able to apply lung cancer screening in high risk individual
2	Gastroenterological malignancies - Recognize the risk factors for GI tract cancers. - Understand rationale behind diagnostic testing and their utility/limitation in the diagnosis of GI malignancies - Able to understand and outlines basic management for common GI malignancies (Colorectal, Pancreatic, esophageal and liver) - To be able to apply cancer screening in community population.
3	Oncology Urgencies and Emergencies (include TLS, Spinal cord compression, and SVC syndrome) - Understand and recognize oncologic urgencies and emergencies can associated with hematological and solid tumor - Able to understand pathophysiology and outlines basic management and prevention strategy for tumor lysis syndrome - Able to understand clinical presentation and know common causes and outlines basic management for Spinal cord compression and superior vena cava syndrome.

Lung cancer

- Recognize the risk factors for lung cancer.

❖ **Risk factors:**

- Cigarette smoking
  - accounts for >85% of cases There is a linear relationship between pack-years of smoking and risk of lung cancer.
  - Weaker association with lung adenocarcinoma
- Second-hand smoke
- Asbestos
  - Common in shipbuilding and construction industry, car mechanics, painting
  - Smoking and asbestos in combination synergistically increase the risk of lung cancer
- Radon (2nd leading cause of lung cancer)
  - high levels found in basements
- COPD
  - an independent risk factor after smoking is taken into account
- Environmental air pollution
- Family history (genetic predisposition)
- Other risk factors: pulmonary scarring, previous radiation, pulmonary fibrosis, chronic infections (e.g., tuberculosis, HIV)

- Identify common presentations of lung cancer

❖ **Clinical Features:**

1. **Local manifestations** (squamous cell carcinoma is most commonly associated with these symptoms)
   a. Airway involvement can lead to cough, hemoptysis, obstruction, wheezing, dyspnea
   b. Recurrent pneumonia (postobstructive pneumonia)
2. **Constitutional symptoms**
   a. Anorexia, weight loss, weakness
   b. Usually indicative of advanced disease

3. **Local invasion**
    a. Superior vena cava (SVC) syndrome
        i. Caused by obstruction of SVC by a mediastinal tumor More commonly occurs with **SCLC**
        ii. Findings: facial fullness; facial and arm edema; dilated veins over anterior chest, arms, and face; jugular venous distention (JVD)
    b. Phrenic nerve palsy
        i. Destruction of phrenic nerve by tumor; phrenic nerve courses through the mediastinum to innervate the diaphragm
        ii. Results in hemidiaphragmatic paralysis
    c. Recurrent laryngeal nerve palsy
        i. causes hoarseness
    d. Horner syndrome
        i. due to invasion of cervical sympathetic chain by an apical tumor.
        ii. Symptoms: unilateral facial anhidrosis (no sweating), ptosis, and miosis.
    e. Pancoast tumor Superior sulcus tumor
        i. an apical tumor involving C8 and T1–T2 nerve roots, causing shoulder pain radiating down the arm Usually **squamous cell cancers**
        ii. Symptoms: pain; upper extremity weakness due to brachial plexus invasion; associated with Horner syndrome 60% of the time
    f. Malignant pleural effusion
        i. Prognosis is very poor—equivalent to distant metastases

4. **Metastatic disease** (most common sites are)
    a. Brain, bone, adrenal glands, liver

5. **Paraneoplastic syndromes**
    a. Syndrome of inappropriate ADH:
        i. usually associated with **small cell carcinoma** (10% of SCLC patients)
    b. Cushing syndrome:
        i. due to ectopic ACTH secretion, typically associated with **small cell carcinoma**
    c. Hypercalcemia:
        i. commonly due to PTH-like hormone secretion, most commonly **squamous cell carcinoma**
    d. Hypertrophic pulmonary osteoarthropathy:
        i. associated with both **adenocarcinoma** and **squamous cell carcinoma**; severe long-bone pain may be present, and leads to digital clubbing.
    e. Eaton–Lambert syndrome:
        i. most common in **SCLC**; clinical picture is similar to that of myasthenia gravis, with proximal muscle weakness/fatigability, diminished deep tendon reflexes, paresthesias (more common in lower extremities)

- To be able to apply lung cancer screening in high risk individual

❖ **Diagnosis:**

1. **CXR**
   a. Most important radiologic study for diagnosis, but not used as a screening test
   b. Demonstrates abnormal findings in nearly all patients with lung cancer

2. **CT scan of the chest with IV contrast**
   a. Very useful for staging
   b. Can demonstrate extent of local and distant metastasis
   c. Very accurate in revealing lymphadenopathy in mediastinum
   d. Consider CT of abdomen to screen for metastases to adrenal glands and liver

CXR may show pleural effusion, which should be tapped; the fluid should be examined for malignant cells. Regardless of the findings on CXR or CT scan, pathologic confirmation is required for definitive diagnosis of lung cancer.

❖ **Lung cancer screening:**

- Annual screening with low-dose CT imaging
  - Associated with a decrease in lung cancer-specific mortality
- The U.S. Preventive Services Task Force (USPSTF) recommendation Indicated in patients aged 50–80 years with a history of smoking (≥ 20 pack-years) within the past 15 years
- Screening should be discontinued if:
  - the patient quit smoking more than 15 years ago or
  - has a health problem that lowers the life expectancy or limits their ability or willingness to have curative lung surgery.

Gastroenterological Malignancies

- Recognize the risk factors for GI tract cancers.

❖ **Risk Factors of colon cancer:**

1. Age
   a. everyone over the age of 50 years is at increased risk
2. Adenomatous polyps
   a. These are premalignant lesions, but most do not develop into cancer.
   b. Villous adenomas have higher malignant potential than tubular adenomas.
   c. The larger the size, and the greater the number of polyps, the higher the risk of cancer.
3. Personal history of prior CRC or adenomatous polyps
4. Inflammatory bowel disease (IBD)
   a. Both ulcerative colitis (UC) and Crohn disease pose an increased risk for CRC, but UC poses a greater risk than Crohn disease.
   b. Incidence of CRC is 5% to 10% at 20 years and 12% to 20% at 30 years with UC.
   c. Begin surveillance colonoscopy for CRC 8 years following the diagnosis of IBD.
5. Family history
   a. Multiple first-degree relatives with CRC.
   b. Any first-degree relative diagnosed with CRC or adenoma under age 60.
6. Dietary factors
   a. High-fat, low-fiber diets associated with a higher risk of CRC
7. Major polyposis syndromes
   a. Familial adenomatous polyposis (FAP)

❖ **Hepatocellular Carcinoma (Malignant Hepatoma) Risk Factors:**

1. Cirrhosis, especially in association with alcohol or hepatitis B or C; HCC develops in 10% of cirrhotic patients.
2. Chemical carcinogens: for example, aflatoxin, vinyl chloride, Thorotrast
3. AAT deficiency
4. Hemochromatosis, Wilson disease
5. Schistosomiasis
6. Hepatic adenoma (10% risk of malignant transformation)
7. Cigarette smoking
8. Glycogen storage disease (type 1)

❖ **Risk factors for pancreatic cancer:**

1. Cigarette smoking (most clearly established risk)
2. Chronic pancreatitis
3. Diabetes
4. Heavy alcohol use
5. Exposure to chemicals—benzidine and β-naphthylamine

❖ **Risk factors for esophagus cancer:**

1. GERD and Barrett esophagus are main risk factors
2. alcohol and tobacco may not be as important as in SCC.

- Understand rationale behind diagnostic testing and their utility/limitation in the diagnosis of GI malignancies.

❖ **Diagnosis of CRC:**

1. Fecal occult blood testing (FOBT)
    a. has poor sensitivity and specificity
    b. all patients with positive FOBT need a colonoscopy regardless.
2. Fecal immunochemical tests (FIT)
    a. detect human hemoglobin and are more specific for colorectal cancer (CRC) than FOBT.
    b. also require colonoscopy if positive.
3. Digital rectal examination
4. Colonoscopy
    a. Most sensitive and specific test; the diagnostic study of choice for patients with a positive FOBT
    b. Diagnostic and therapeutic (e.g., biopsy, polypectomy)
5. Flexible sigmoidoscopy
    a. Can be used to reach the area where approximately 50% to 70% of polyps and cancers occur (with a 60-cm scope)
6. Barium enema
    a. Any abnormal finding needs to be evaluated by colonoscopy.
7. Carcinoembryonic antigen (CEA)
    a. useful for establishing baseline
    b. monitoring treatment efficacy, and recurrence surveillance.
    c. prognostic significance: Patients with preoperative CEA>5 ng/mL have a worse prognosis
8. Clinical staging is done with CT CAP and by physical examination (ascites, hepatomegaly, lymphadenopathy).

❖ **Diagnosis of liver cancer:**

1. Liver biopsy required for definitive diagnosis
2. Laboratory tests: hepatitis B and C serology, LFTs, coagulation tests
3. Imaging studies: ultrasound, CT CAP; MRI or MRA if surgery is an option (provides more detail about the anatomy of the tumor)
4. alpha fetoprotein (AFP)
    a. useful as a screening tool
    b. and is also helpful in monitoring response to therapy.

❖ **Diagnosis of pancreatic cancer:**

1. ERCP
    a. most sensitive test for diagnosing pancreatic cancer.
    b. distinguish cancer of the head of the pancreas from tumors of the CBD, duodenum, ampulla, and lymphomas, which have more favorable prognosis.
2. CT scan
    a. preferred test for diagnosis and assessment of disease spread
3. Tumor markers.
    a. CA 19-9 (sensitivity of 83% and specificity of 82%).
    b. CEA (sensitivity of 56% and specificity of 75%).

❖ **Diagnosis of esophageal cancer:**

1. Barium swallow is useful in evaluation of dysphagia.
2. Upper endoscopy with biopsy and brush cytology is required for definitive diagnosis.
3. Transesophageal ultrasound
    a. helps determine the depth of penetration of the tumor
    b. most reliable test for staging local cancer.
4. Full metastatic workup (e.g., CT scan of the chest/abdomen, CXR, bone scan).

- Able to understand and outlines basic management for common GI malignancies (Colorectal, Pancreatic, esophageal and liver).

❖ Treatment for CRC:

1. Surgery is the only curative treatment of CRC. Surgical resection of tumor containing bowel as well as resection of regional lymphatics
2. CEA level should be obtained before surgery
3. Utility of adjuvant therapy (chemotherapy or radiation therapy) depends on the stage of tumor

Radiation therapy is not indicated in the treatment of colon cancer, although it is used in treating rectal cancer

❖ Treatment for liver cancer:

1. Liver resection
2. Liver transplantation if diagnosis is made early
3. If unresectable
    a. consider transcatheter arterial chemoembolization (TACE)
    b. radiofrequency ablation
    c. or selective internal radiation therapy.

❖ Treatment for pancreatic cancer:

1. Surgical resection (Whipple procedure) is the only hope for a cure; however, only a minority of tumors are resectable (roughly 10%). The prognosis is grim even after resection, with a 5-year survival rate of 10%.
2. If the tumor is unresectable and biliary obstruction is present, perform PTC or ERCP with stent placement across the obstruction for palliation.

❖ Treatment for esophageal cancer:

1. Palliation is the goal in most patients because the disease is usually advanced at presentation.
2. Surgery (esophagectomy) may be curative for patients with disease in stage 0, 1, or 2A.
3. Chemotherapy plus radiation before surgery has been shown to prolong survival more than surgery alone.

- To be able to apply cancer screening in community population

❖ **Colorectal Cancer Screening/surveillance**:

1. **Average-risk patients** 50 to 75 years of age—any of the following (USPSTF 2008 guidelines):
    a. Colonoscopy every 10 years
    b. Flexible sigmoidoscopy every 5 years and fecal occult blood test every 3 years
    c. Fecal occult blood test every year

2. **Moderate-risk patients**
    a. Patients with single or multiple polyps, personal history of CRC, initial colonoscopy; repeat at 3 years—if normal, then colonoscopy every 5 years
    b. Family history of CRC or adenomatous polyps in first-degree relatives colonoscopy at age 40 or 10 years younger than the youngest case in family; if normal, repeat in 3 to 5 years

3. **High-risk patients**
    a. Families with familial adenomatous polyposis—genetic testing at age 10; consider colectomy if positive genetic testing or polyposis is confirmed; if not, colonoscopy every 1 to 2 years beginning at puberty
    b. Families with hereditary nonpolyposis CRC—genetic testing at age 21; if positive, colonoscopy every 2 years until age 40, and then every year thereafter
    c. Patients with ulcerative colitis—colonoscopy 8 years after disease onset, then every year

❖ **Breast cancer:**

- mammogram every 2 years for women 50 to 74 years of age
- routine screening every year starting at the age of 40
- Recommendations for clinical breast examination (CBE) and breast self examination (BSE) vary based on expert group recommendations; USPSTF states that there is insufficient evidence to recommend for or against CBE, and some groups (e.g., WHO) recommend against BSE

❖ **Cervical cancer:**

- Start at age 21, irrespective of sexual history
- Ages 21 to 29, Pap smear every 3 years
- Ages 30 to 65, Pap smear every 3 years or Pap smear + HPV testing every 5 years
- Can discontinue screening at age 65 if adequate negative prior screening (3 negative Pap smears or 2 negative Pap smears with negative HPV testing within the previous 10 years, with the most recent test within the previous 5 years)

❖ **Ovarian cancer:**

- Routine screening is not recommended

Overview [4][5]

Condition	Test	Population		Frequency
		Risk Group	Age group	
Colorectal cancer	• Colonoscopy	• General population	• 45–75 years	• Every 10 years
		• Individuals without signs or symptoms of colorectal cancer and with an average risk for colon cancer (e.g., adenomatous polyps, individuals with inflammatory bowel disease, no prior diagnosis of colorectal cancer)	• All age groups, beginning 8 years after diagnosis	• Every 1–2 years
		• Individuals with familial adenomatous polyposis (FAP)	• 10 years	• Every year
		• Individuals with Lynch syndrome (HNPCC)	• 20 years	• Every 1–2 years
	• Sigmoidoscopy	• General population	• 50 years	• Every 5 years
	• Fecal occult blood test	• General population	• 50 years	• Every year
Breast cancer	• Mammography	• Women	• 50–74 years	• Every 2 years
Lung cancer	• Low dose chest CT scan	• Smokers ≥ 20 pack year • Current smoker or ex-smoker for 15 years	• 50–80 years	• Every year up to 3 consecutive times
Cervical cancer	• Pap smear	• Women	• 21–29 years	• Every 3 years
	• Pap smear with high-risk HPV testing	• Women	• 30–65 years	• Every 5 years

Oncology Urgencies and Emergencies

- Understand and recognize oncologic urgencies and emergencies can associated with hematological and solid tumor

Most oncologic emergencies can be classified as metabolic, hematologic, structural, or treatment related.

❖ **Metabolic related:**

- Tumor lysis syndrome:
  - A potentially life-threatening oncologic emergency resulting from the rapid destruction of tumor cells, which leads to a massive release of intracellular components, e.g., potassium (K^+), phosphate (PO_4^{3-}), and uric acid, that can damage the kidneys and cause renal failure.
- Hypercalcemia of malignancy
- Syndrome of inappropriate antidiuretic hormone (SIADH)

❖ **Hematologic:**

- Febrile neutropenia:
  - Neutropenia: ANC < 500/µL **OR** expected to decrease to < 500/µL within 48 hours
  - Fever: single oral temperature ≥ 38.3°C (101°F) **OR** ≥ 38°C (100.4°F) for at least 1 hour
- Hyperviscosity syndrome:
  - triad of mucosal bleeding, visual changes, and neurologic symptoms.
- Leukostasis:
  - a medical emergency characterized by tissue hypoxia and hypercoagulability due to an excessive number of immature leukocytes causing microvascular obstruction

❖ **Structural:**

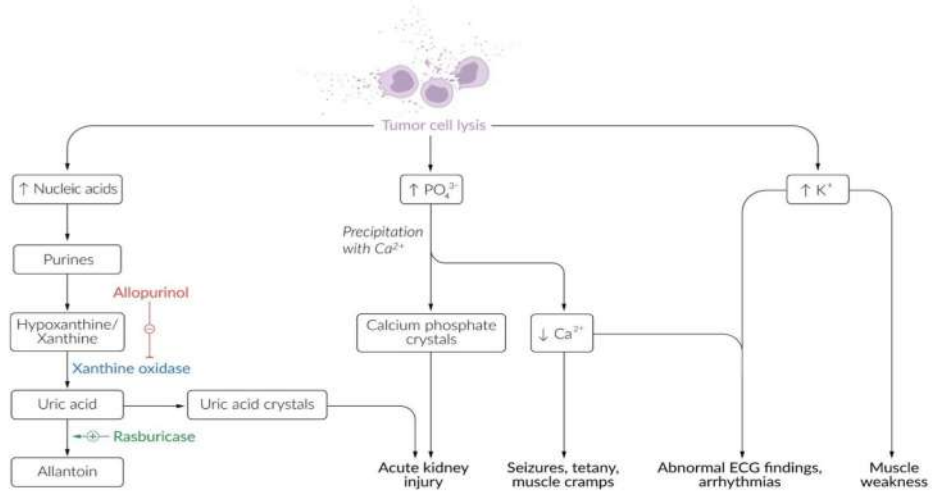
- Superior vena cava syndrome
- Spinal cord compression
- Malignant pericardial effusions

- Able to understand pathophysiology and outlines basic management and prevention strategy for tumor lysis syndrome

❖ **Pathophysiology:**

- Tumor cell lysis → release of intracellular components (e.g., K+, PO43-, nucleic acids) into the bloodstream
- ↑ Nucleic acid → conversion to uric acid → hyperuricemia → urate nephropathy and risk of acute kidney injury
- ↓ Ca2+ secondary to PO43- binding → hypocalcemia → neuronal excitability → risk of seizures
- Hyperphosphatemia: PO43- binds Ca2+ and forms calcium phosphate crystals that obstruct renal tubules → acute kidney injury
- Hyperkalemia: changes in resting membrane potential → risk of cardiac arrhythmias

Think of **"PUKE calcium"** to remember the electrolytes affected in tumor lysis syndrome: **P**hosphorus, **U**ric acid, and potassium (K^+) are **E**levated; **Calcium** is decreased.



❖ **Prevention:**

- To avoid Tumor Lysis Syndrome prophylaxis with vigorous hydration
- pretreat with Allopurinol. If the uric acid levels have already risen, lessen the burden of uric acid with Rasburicase.

❖ **Management:**

- Identify patients with established TLS and those at high risk (e.g., hematological malignancy, chemotherapy)
- Start intensive fluid therapy, uric acid reduction, and correction of electrolyte imbalances.
- Consider notifying ICU, nephrology, and oncology early on.

1. Fluid management
    a. Hydration is the mainstay of TLS prophylaxis and treatment.
2. Electrolyte imbalances
    a. Monitor electrolytes regularly, as they can be also be affected by fluid therapy.
    b. **Hyperkalemia**: cardiac monitoring and standard therapy for hyperkalemia if $K+ \geq 6$ mEq/L, e.g., glucose and insulin (rapid action)
    c. **Hyperphosphatemia**: hydration and possibly oral phosphate binders, e.g., sevelamer
    d. **Hypocalcemia**: Treat only if symptomatic and give the lowest calcium dose to relieve symptoms
3. Hyperuricemia
    a. Allopurinol
        i. Indicated as prophylaxis in patients at low to intermediate risk
    b. Rasburicase:
        i. recombinant uricase that catalyzes the breakdown of uric acid to allantoin
        ii. Indications
            1. Treatment of established TLS
            2. Prophylaxis for intermediate to high-risk patients
            3. Contraindications: G6PD deficiency, which can precipitate hemolytic anemia
    c. Urinary alkalinization: no longer routinely recommended

- Able to understand clinical presentation and know common causes and outlines basic management for Spinal cord compression and superior vena cava syndrome.

1. Spinal cord compression:

❖ Etiology:

- Acute onset (within minutes to hours): vertebral fracture, acute disc herniation, hematoma
- Insidious onset
- days to weeks: Abscess, primary tumor, metastasis
- months to years: Slow-growing primary tumors, degenerative spine changes (e.g., spondylosis)

❖ Clinical features:

- depend on the location of the spinal compression
- Common features: back pain, radicular pain (follows dermatomal distribution of affected nerve), and neurological deficits below the level of the lesion (first sensory abnormalities, followed by motor and/or bladder/bowel dysfunction)

❖ Treatment:

- Immediate management
  - IV glucocorticoids: reduce pain, swelling, and inflammation → immediate decompression; bridge time until surgery can be performed
  - Opioids for further pain control if necessary
- Surgical management: definitive treatment
  - Decompression surgery
  - Stabilization surgery
- Radiation therapy:
  - indicated if tumor is inoperable and following surgery; controls local tumor growth and significantly reduces pain

2. Superior vena cava syndrome

❖ Etiology:

Conditions that obstruct the SVC intraluminally (e.g., neoplastic invasion, thrombosis) or due to extraluminal compression (e.g., Pancoast tumors, mediastinal masses). The etiology of SVC syndrome is the basis for its classification.

- Malignant SVC syndrome (most common)
  - Non-small cell lung cancer (NSCLC)
  - Small cell lung cancer (SCLC)
  - Non-Hodgkin lymphoma (NHL)
  - Less common: metastatic cancer (usually breast cancer), germ cell tumors, thymoma, mesothelioma
- Nonmalignant SVC syndrome
  - Most commonly caused by thrombosis associated with an intravascular device (e.g., dialysis catheter, pacemaker wire)
  - Can also be due to other conditions that cause compression of the SVC

❖ **Clinical features:**

- Hemodynamic symptoms
  - Edema of the upper extremities and face (facial plethora)
  - Prominent venous pattern on the chest, face, and upper extremities
  - Jugular venous distension
  - Orthostatic hypotension
  - Syncope
  - Renal failure
- Symptoms and signs of congestion of the neck
  - Dyspnea
  - Cough and hoarseness
  - Stridor
  - Dysphagia
- Neurological symptoms
  - Headache
  - Dizziness
  - Confusion and mental obtundation
  - Visual impairment

❖ **Management:**

- Patients with severe or life-threatening SVC syndrome require emergency treatment (e.g., invasive venography with stent placement)
- Definitive treatment depends on the underlying condition.
  - Malignant SVC syndrome: tumor-specific management
  - Nonmalignant SVC syndrome: directed therapy if possible, anticoagulation if thrombosis is present

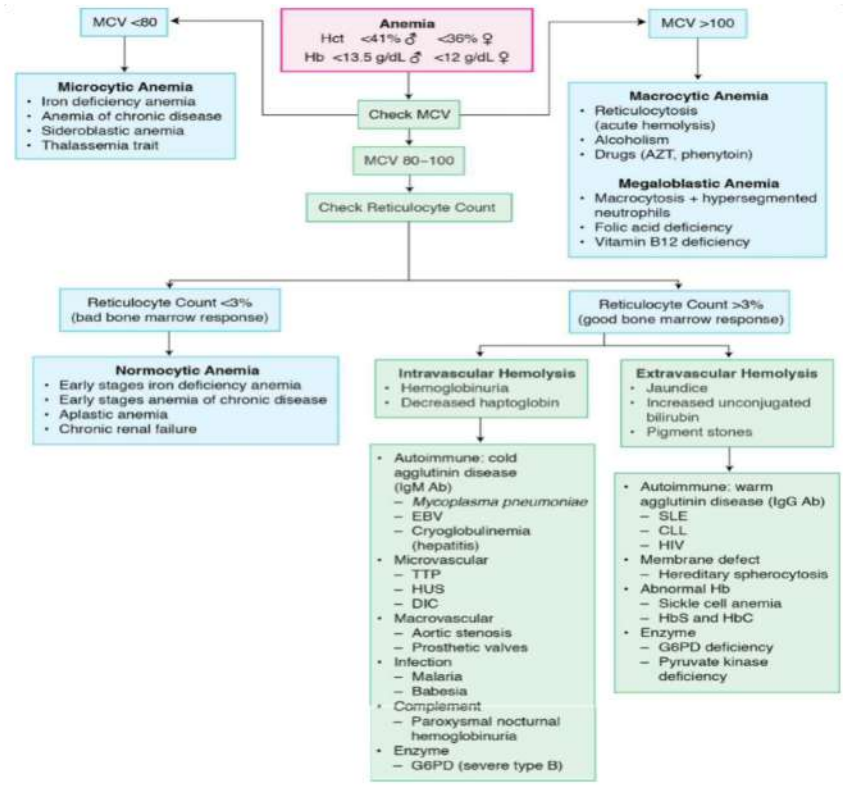
Hematological Disorders

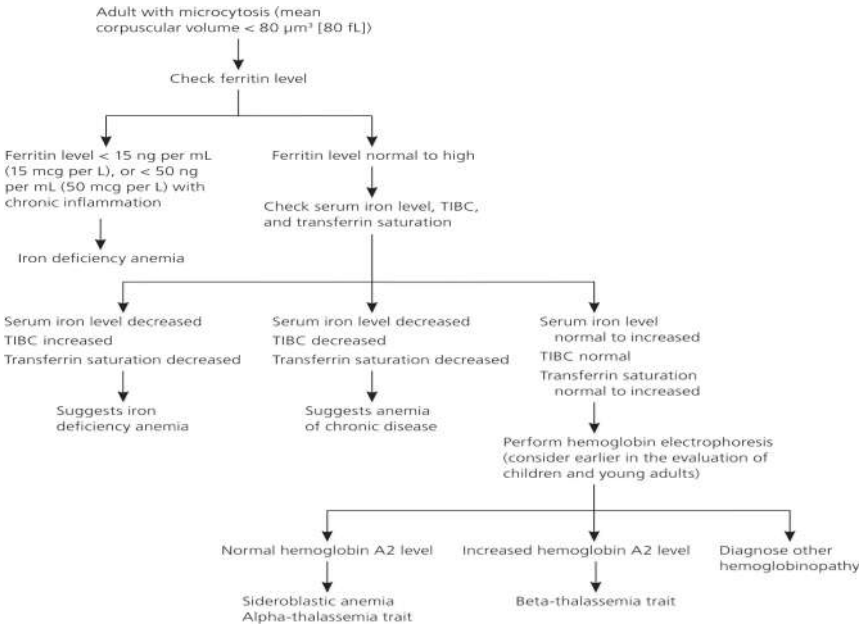
Lectures List

Hematological disorders	
1	**Anemia and sickle cell disease** - To be able to approach an anemic patient and differentiate between different causes based on hematological, biochemistry and electrophoresis studies. - To be able to manage patient with anemia. - To understand the pathophysiology of hemoglobinopathy in sickle cell disease and thalassemia. - Learn approach patients with vaso-occlusive crisis and identify acute chest syndrome. - Learn approach to Bi-cytopenia and pancytopenia and recognize hematologic emergency (blasts, HUS/TTP) and basic managements
2	**Blood product and Transfusion medicine** - To recognize common blood transfusion reactions. - To be able to manage patients with anaphylaxis.
3	**Hematological malignancies (Lymphomas, leukemias, Multiple myeloma)** - To identify common presentation of patients with lymphomas, leukemia and multiple myeloma - To be able to list a work-up plan to establish the diagnosis of lymphoma, leukemia and multiple myeloma - Recognize patients presenting with leukemias and be able to differentiate between the types.
4	**Bleeding disorders** - To learn different between platelets disorders V. Coagulation disorders and How to differentiate between them clinically and laboratory. - Understand approach to patient with bleeding - Enlist differential diagnosis for an isolated or combined coagulation profile prolongation
5	**Venous thrombosis (DVT/ PE)** - Identify patients at risk of hypercoagulable states - Identify patients presenting with acute deep vein thrombosis and initiate work-up plan - And basic of management. - To be able to identify patients with PE and establish the management.
6	**Myeloproliferative disorders** - To identify common presentation of patients with Myelofibrosis, Primary thrombocythemia, Polycythemia Rubra Vera and chronic Myelogenous Leukemia - To be able to list a work-up plan to establish the diagnosis of Myelofibrosis, Primary thrombocythemia, Polycythemia Rubra Vera and chronic Myelogenous Leukemia

Anemia and sickle cell disease

- To be able to approach an anemic patient and differentiate between different causes based on hematological, biochemistry and electrophoresis studies.





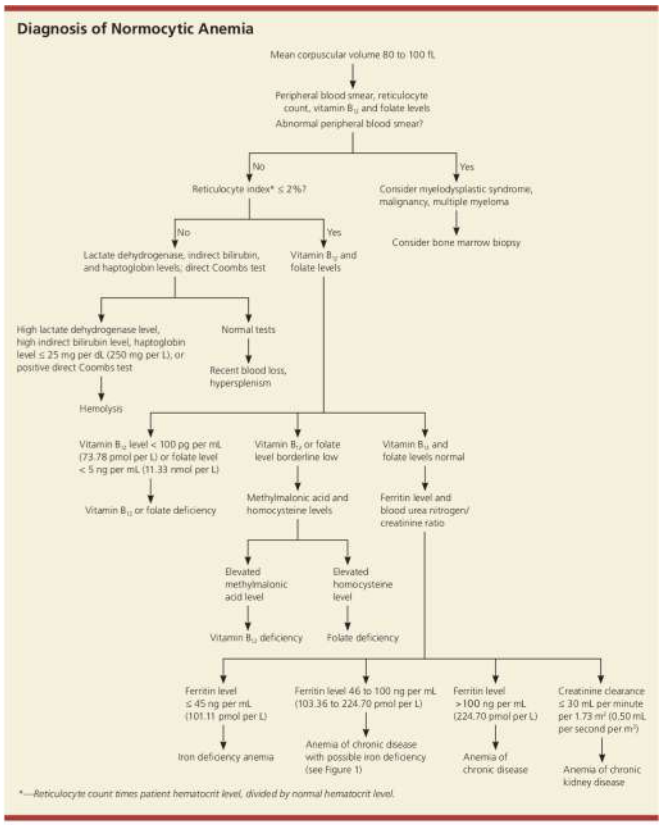
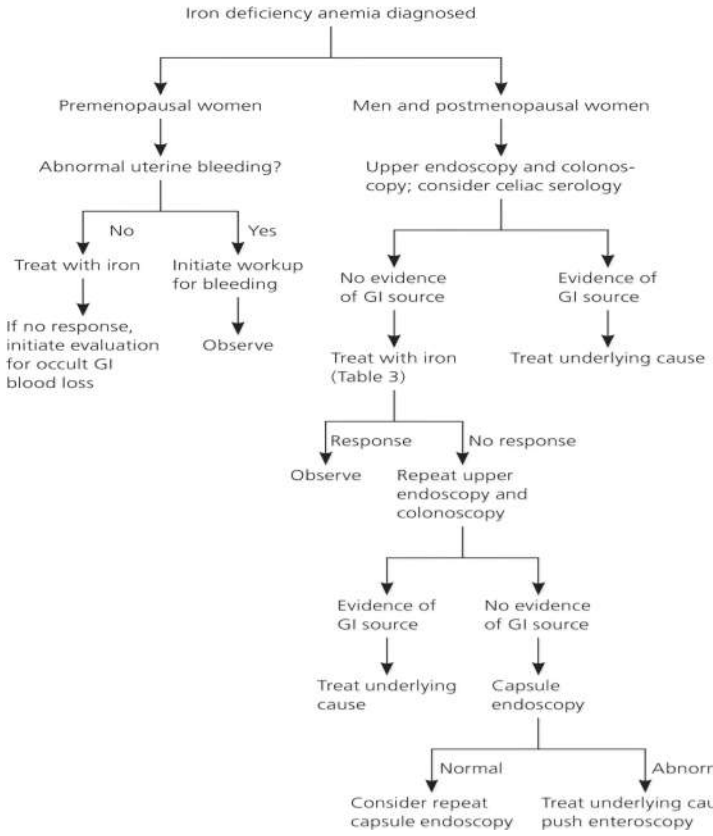
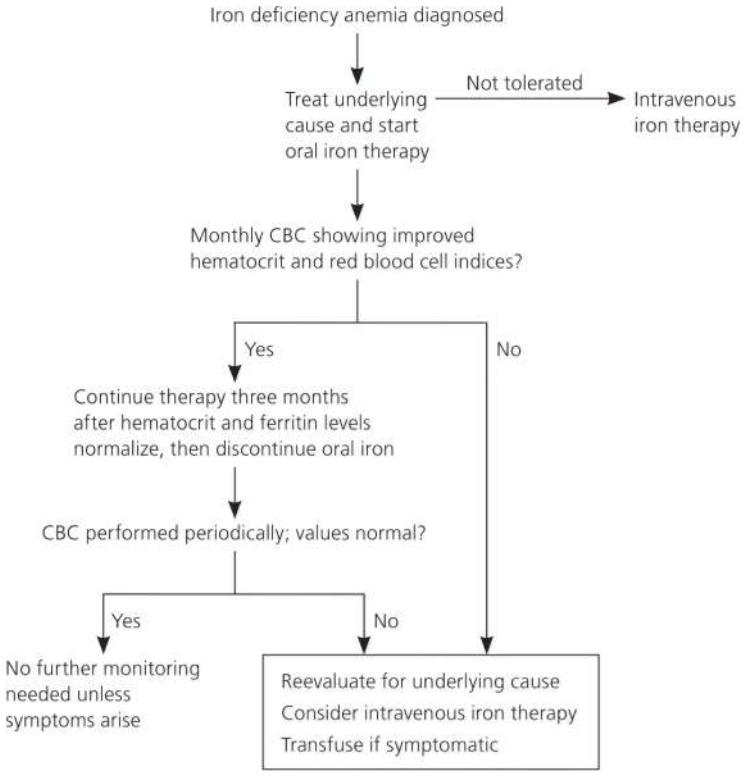


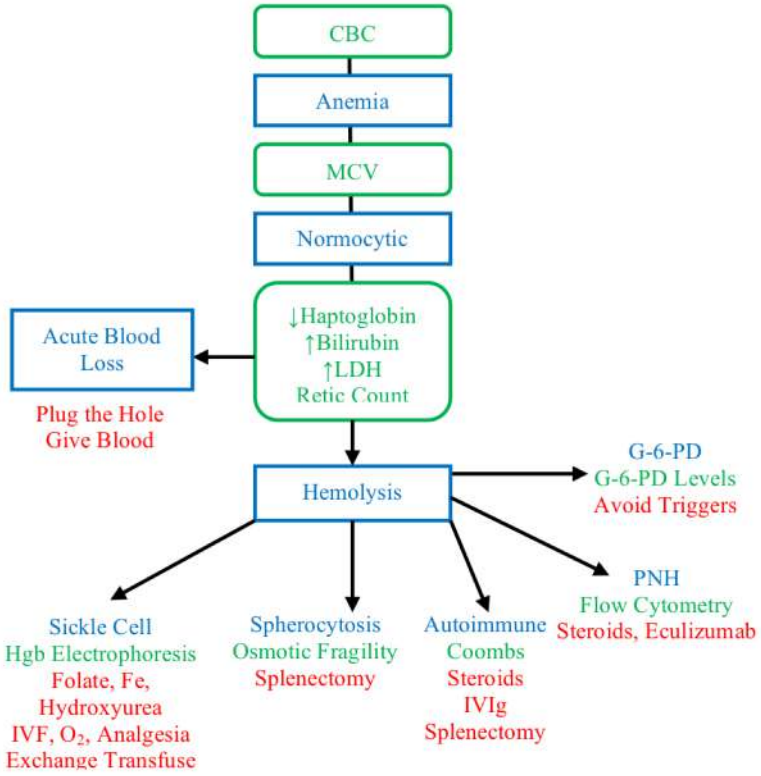
Figure 2. Algorithm for the diagnosis of normocytic anemia.

Important findings	
Iron deficiency anemia	Decrease ferritin, serum iron, transferrin saturation Increase TIBC
β-Thalassemia	elevated Hb F and HbA2 target cells on Peripheral blood smear
Sideroblastic Anemia	increased serum iron, serum ferritin, normal TIBC, normal/elevated TIBC saturation ringed sideroblasts in bone marrow
Anemia of Chronic Disease	low serum iron, normal-to-low TIBC/serum transferrin increased serum ferritin
Aplastic Anemia	Pancytopenia Bone marrow biopsy reveals hypocellular marrow
Vitamin B12 Deficiency	Blood smear reveals megaloblastic anemia with hypersegmented neutrophils Elevated serum methylmalonic acid and homocysteine levels
Folate Deficiency	Blood smear reveals megaloblastic anemia with hypersegmented neutrophils Elevated serum homocysteine level methylmalonic acid levels are normal
Intravascular hemolysis	Schistocytes
Extravascular hemolysis	Spherocytes or helmet cells
Hemolysis markers	Low Hg/Hct, haptoglobin High reticulocyte, LDH, indirect bilirubin
G6PD deficiency	Heinz bodies Bite cells
Autoimmune hemolytic anemia	Positive direct Coombs test
Hereditary Spherocytosis	Negative direct Coombs test

- To be able to manage patient with anemia.

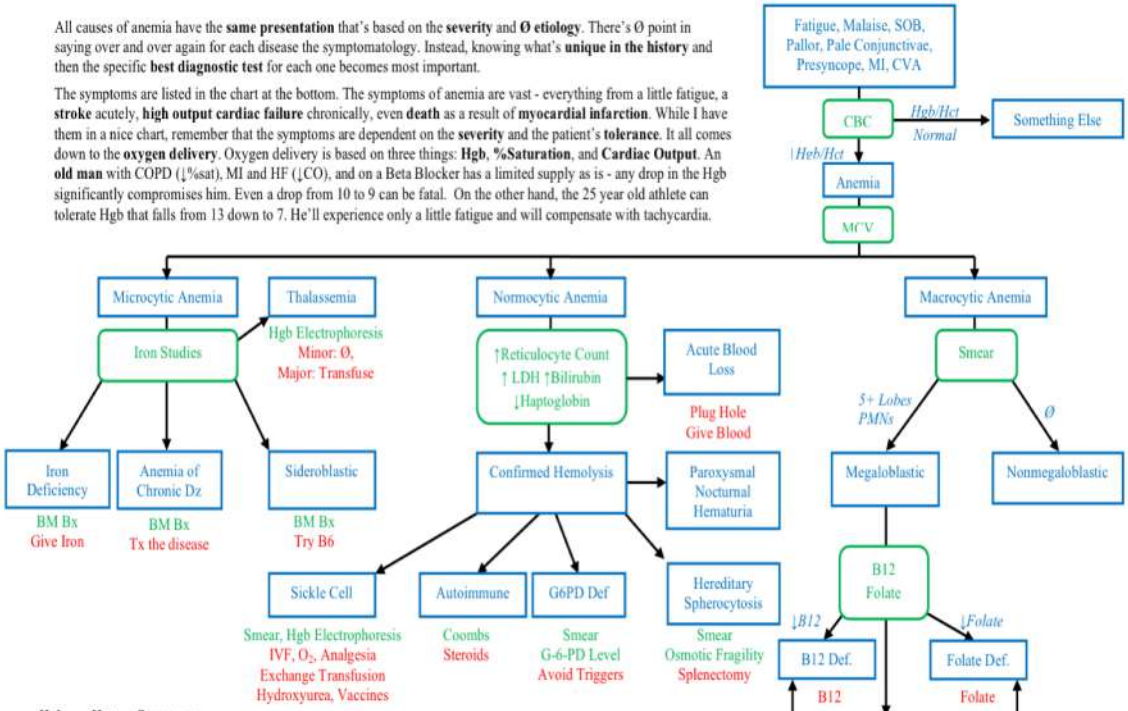






All causes of anemia have the **same presentation** that's based on the **severity** and **Ø etiology**. There's Ø point in saying over and over again for each disease the symptomatology. Instead, knowing what's **unique in the history** and then the specific **best diagnostic test** for each one becomes most important.

The symptoms are listed in the chart at the bottom. The symptoms of anemia are vast - everything from a little fatigue, a **stroke** acutely, **high output cardiac failure** chronically, even **death** as a result of **myocardial infarction**. While I have them in a nice chart, remember that the symptoms are dependent on the **severity** and the patient's **tolerance**. It all comes down to the **oxygen delivery**. Oxygen delivery is based on three things: **Hgb**, **%Saturation**, and **Cardiac Output**. An **old man** with COPD (↓%sat), MI and HF (↓CO), and on a Beta Blocker has a limited supply as is - any drop in the Hgb significantly compromises him. Even a drop from 10 to 9 can be fatal. On the other hand, the 25 year old athlete can tolerate Hgb that falls from 13 down to 7. He'll experience only a little fatigue and will compensate with tachycardia.



Hgb	*Hct*	*Symptoms*
>10	>30	Ø Symptoms
8-9	24-30	Tired, Fatigue, Malaise
6-8	18-23	Dyspnea on Exertion
4-6	12-17	Lightheaded, Presyncope, Syncope
<4	<12	Chest Pain, Stroke, High Output Failure

	Hgb X	%Sat X	CO	
DO_2=				
Old Man	↓	↓	↓↓	No Compensation
Athlete	↓			Compensates

- To understand the pathophysiology of hemoglobinopathy in sickle cell disease and thalassemia.

❖ Sickle Cell Anemia

1. It's caused by an Autosomal Recessive mutation in the B-Globin and commonly seen in African Americans.
2. When the patient undergoes an oxidant stress (hypoxia, infection,DKA, or dehydration) the hemoglobin, termed Hemoglobin S. polymerizes inducing sickling.
3. It creates a non-deforming cell that gets trapped in capillaries, which causes hemolysis and microvascular occlusion.

❖ Thalassemia

Something different is going on in thalassemia. It's not the iron stores that are the problem - it's the **hemoglobin**. There's a **genetic** disease (d,chromosome 16,frameshift and B.chromosome 11, deletion) that leads to I production of the normal hemoglobin with 2a and 2ß; HgbA1 a2P. It doesn't matter which portion is broken - the patient is going to have anemia with normal iron studies.

Anemia results from a combination of inefficient erythropoiesis and increased hemolysis. The degree to which both mechanisms contribute to the severity of the disease depends on a patient's exact genotype.

Inefficient erythropoiesis → anemia

- Beta thalassemia minor and major: faulty β-globin chain synthesis → ↓ β-chains→ ↑ γ-,δ-chains → ↑ HbF and ↑ HbA2.
    - HbF protects infants up to the age of 6 months, after which HbF production declines and symptoms of anemia appear.
- Alpha thalassemia intermedia (HbH disease) and alpha thalassemia major (Bart disease): faulty α-globin chain synthesis → ↓ α-chains → impaired pairing of α-chains with β-chains and γ-chains→ ↑ free β-, γ-chains → ↑ HbH, ↑ Hb-Bart's
- In minor and minima forms, production of the affected chain is reduced, but enough is produced to prevent severe anemia.

Increased hemolysis:

- One of the chains (either α or β) is reduced → compensatory overproduction of other chains → excess globin chains precipitate and form inclusions within RBCs → erythrocyte instability with hemolysis

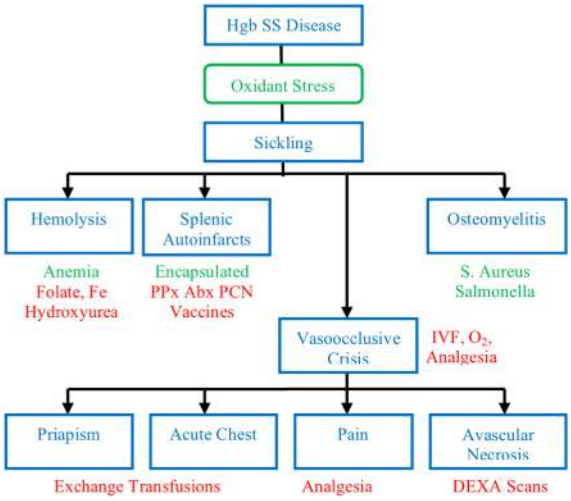
Anemia → ↑ erythropoietin → bone marrow hyperplasia and skeletal deformities

- Learn approach patients with vaso-occlusive crisis and identify acute chest syndrome.

Vaso-occlusive crises

(painful episodes, painful crisis): recurrent episodes of severe deep bone pain and dactylitis → most common symptom in children and adolescents

- Acute chest syndrome
- Priapism
- Stroke (common in children)
- Acute sickle hepatic crisis (manifests with RUQ pain, jaundice, nausea, fever, hepatomegaly, and elevated transaminase levels)
- Infarctions of virtually any organ (particularly spleen) and avascular necrosis with corresponding symptoms



- Microvascular occlusion causes infarction. Infarction hurts. These people will be on chronic pain management because their joints hurt all the time.
- Occasionally, they'll suffer an acute crisis where they need IVF, Oz, and Analgesia to ride out the attack.
- If the patient develops an acute chest (ARDS picture) or priapism, **they need an exchange transfusion** to get over the severe crisis.
- Splenic Autoinfarction increases risk for infection by encapsulated organisms, requiring annual vaccinations (PCV, Meningococcus, H. Flu, HBV).
- Aseptic Necrosis of the hip/femur requires dexa scan screening.
- **these patients are at ^Risk for salmonella osteomyelitis.**
- Decrease the amount of bad hemoglobin (HbSS) by giving **Hydroxyurea** (**induces fetal hemoglobin**, which does not sickle).
- Prevent sickling by avoiding stressors and staying hydrated
- Control the pain with analgesia chronically and reduce the anemia with Iron and Folate.
- But how do we know who has sickle cell disease? Seeing sickled cells on a blood smear is sufficient for the diagnosis.
- Definitive diagnosis of the disease or of the carrier state may be confirmed by **Hemoglobin Electrophoresis.**

Acute chest syndrome

Vaso-occlusion of the pulmonary vasculature

- **Clinical features:**

- Chest pain
- Fever
- Respiratory distress, cough, shortness of breath, wheezing
- Signs of vaso-occlusive crisis (e.g., pain in arms or legs)
- Rib or sternal pain

- **Diagnosis**:

ACS is a clinical diagnosis supported by characteristic clinical features and the presence of **new** pulmonary infiltrate on imaging

- **Management**:

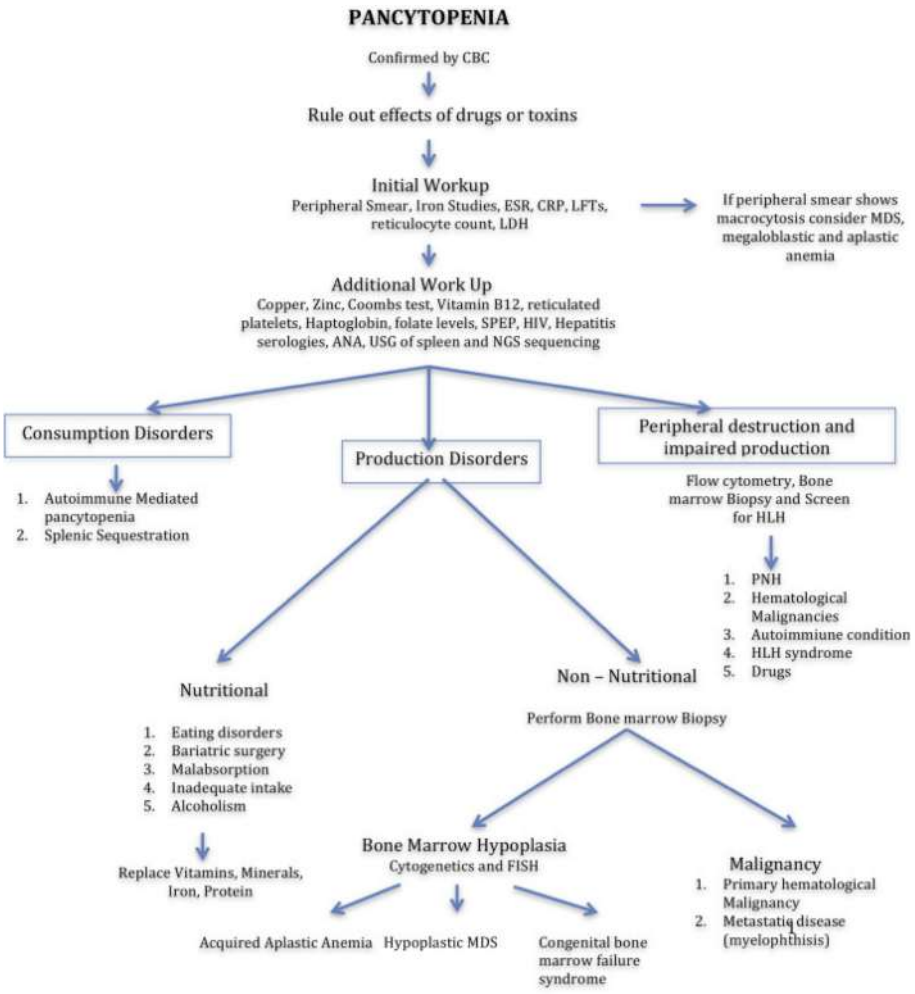
- ABC.
- Oxygenation & bronchodilators.
- Intensive care
- RBC exchange transfusion (definitive treatment)
- Pain relief.
- Hydration: D5 in NaCl 0.45%, 500 ml with 10 mEq Potassium.
- Prophylactic antibiotics: 3rd gen cephalosporin (ceftriaxone) plus macrolide (azithromycin)
- Folic acid

- **indications for exchange transfusion in ACS**

1. Severe Acute Chest Crisis
2. Rapid or significant clinical deterioration
3. Worsening chest radiography
4. P02 < 70 mmHg
5. Baseline hemoglobin >90. Why?

It precludes use of simple transfusion due to risk of hyperviscosity

- Learn approach to Bi-cytopenia and pancytopenia and recognize hematologic emergency (blasts, HUS/TTP) and basic managements



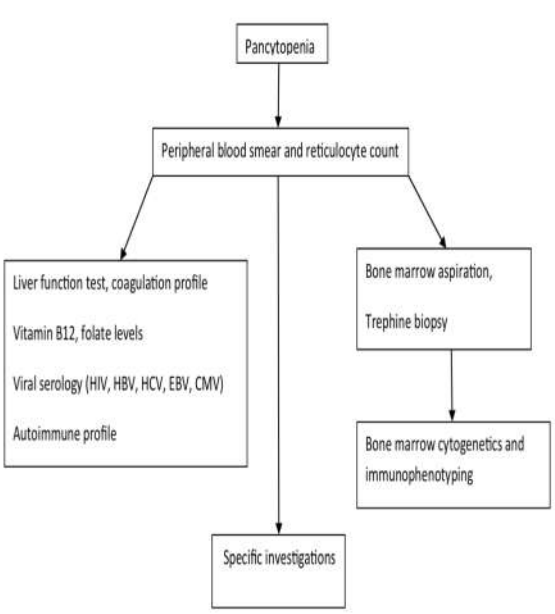


Fig. 1: Flow diagram for Evaluation of Pancytopenia

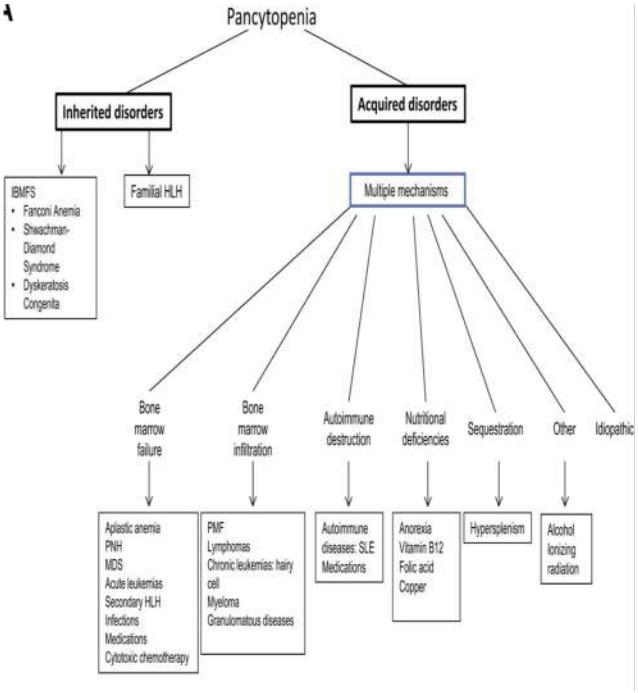


Table 1: Causes of pancytopenia with cellular bone marrow

Primary bone marrow disease	Secondary to systemic disease
Myelodysplasia	Vitamin B_{12} deficiency, folate deficiency
Paroxysmal nocturnal haemoglobinuria	Hypersplenism
Myelophthisis	Alcoholism
Myelofibrosis	Sepsis, enteric fever
Subleukaemic leukaemia	HIV infection, hepatitis B, hepatitis C, Ebstein-Barr virus, cytomegalovirus
Bone marrow lymphoma	Malaria, leishmaniasis, filariasis
Hairy cell leukaemia	Systemic lupus erythematosus, sarcoidosis

Table 2: Causes of pancytopenia with hypocellular marrow

Acquired aplastic anemia
Congenital aplastic anaemia (Fanconi's anaemia)
Some myelodysplasias
Acute myeloid leukaemia
Acute lymphoid leukaemia
Lymphoma of bone marrow

❖ Blast crisis

The blast crisis is the terminal stage of **CML**.
Symptoms resemble those of acute leukemia:

- Rapid progression of bone marrow failure → pancytopenia, bone pain
- Severe malaise

Subtypes :

- Myeloid blast crisis → AML (⅔ of cases)
- Lymphoid blast crisis → ALL (⅓ of cases)

❖ Thrombotic Thrombocytopenic Purpura

1. TTP is an autoimmune disease where clots form - just like in DIC. But these clots are **hyaline clots that don't consume factors**, fibrinogen, or platelets. Instead, **ADAMTS-13 is deficient.**
2. It fails to cleave vWF multimers, which persist and swallow platelets.
3. The thrombocytopenia has nothing to do with the clots, but with these large vWF multimers (at least we think).
4. There's a classic pentad for TTP, with the mnemonic FAT RN. There's Fever, Anemia, Thrombocytopenia, Renal Failure, and Neurologic symptoms that wax and wane.
5. Diagnosis is based on a normal DIC panel despite thrombocytopenia and anemia. **Schistocytes** may be present. The Laboratory diagnosis separates them.
6. For TTP, **NEVER give platelets** (it'll worsen the MAHA). Instead, do a **plasma exchange** (take out the antibodies and give back plasma with a lot of ADAMTS-13), or a plasma transfusion (give ADAMTS-13 only).

TTP
Normal, then FAT RN
↓ Platelet
Schistocytes
Nrml PT/PTT
Nrml D-Dimer
Nrml Fibrinogen
Exchange Transfusion
NEVER give platelets

❖ Hemolytic uremic syndrome:

- A diarrheal illness (usually bloody) for the past 5–10 days precedes the onset of HUS symptoms in many children.
- The triad of clinical findings occurring in HUS consists of: Thrombocytopenia , Petechiae, purpura , Mucosal bleeding , Prolonged bleeding after minor cuts Microangiopathic hemolytic anemia ,Fatigue, dyspnea, and pallor , Jaundice , Impaired renal function Hematuria, proteinuria , Oliguria, anuria

E. coli O157:H7 infection → Shiga-like toxin in systemic circulation → **toxin-mediated endothelial injury** → microthrombus formation → blockage of small vessels → RBC fragmentation (hemolysis) and end-organ damage

❖ **Management:**

Supportive care

- Avoid antibiotics and antimotility agents (may increase the likelihood of HUS in suspected infection with EHEC).
- Monitor and correct:
  - Fluid status abnormalities
  - Electrolyte disturbances
  - Acid-base abnormalities
  - Blood pressure
- RBC transfusions
- Antiepileptic drugs (e.g., diazepam, phenytoin) in patients with seizures
- Dialysis (as indicated for AKI): Up to 50% of HUS patients require dialysis.
- Plasma exchange therapy: only in refractory cases
- Eculizumab

Quick HIT

TTP and HUS

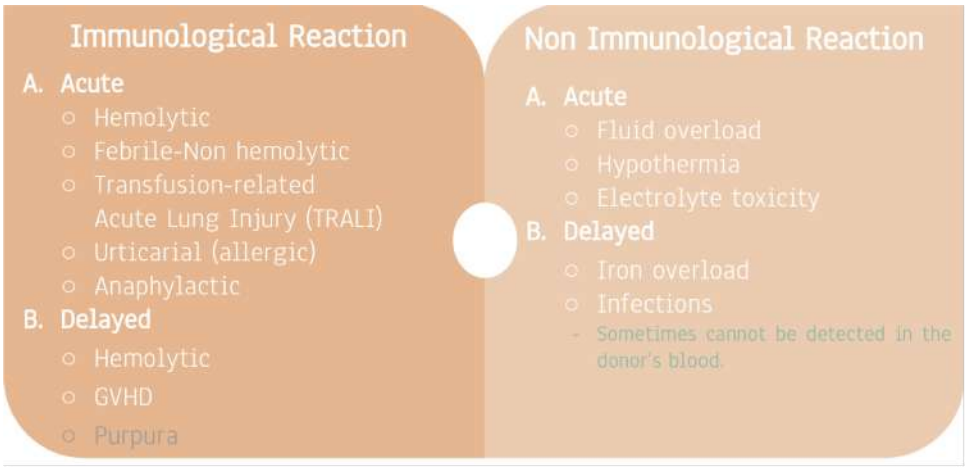
- There is no consumption of clotting factors in TTP, so PT and PTT are normal.
- TTP = HUS + fever + altered mental status
- HUS = microangiopathic hemolytic anemia + thrombocytopenia + renal failure

TTP *versus* HUS

TTP	HUS
• Adults—20-50	• Children <5 years old
Pentad	Tetrad
• Hemolytic anemia with RBC fragmentation	• Hemolytic anemia with RBC fragmentation
• Renal dysfunction	• Acute renal failure
• Thrombocytopenia (35,000)	• Thrombocytopenia (95,000)
• Severe CNS symptoms	• Mild CNS symptoms
• Fever	

Blood products & transfusion medicine

- To recognize common blood transfusion reactions.



- To be able to manage patients with anaphylaxis.

- Stabilize the patient (ABCDE approach)
- Stop transfusions
- Administer epinephrine IM

Hematological Malignancy

- To identify common presentation of patients with lymphomas, leukemia & multiple myeloma

Clinical Features of:

❖ **hodgkin lymphoma**

1. Painless lymphadenopathy—most common symptom
    a. May involve supraclavicular, cervical, axillary, or mediastinal lymph nodes
    b. Spreads by continuity from one lymph node to adjacent nodes
2. B symptoms (e.g., fever, night sweats, weight loss)
3. Pruritus
4. Cough—secondary to mediastinal lymph node involvement

❖ **non hodgkin lymphoma**

1. Painless lymphadenopathy—sometimes the only manifestation of disease
    a. Lymph nodes are usually firm and mobile
    b. Most often involves supraclavicular, cervical, and axillary nodes
2. B symptoms—less common than in Hodgkin lymphoma
3. Hepatosplenomegaly
4. Anemia, leukopenia, or thrombocytopenia—due to bone marrow involvement

Hodgkin	non-Hodgkin lymphoma
Localized, single group of nodes; contiguous spread (stage is strongest predictor of prognosis). Many patients have a relatively good prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread.
Characterized by Reed-Sternberg cells.	Majority involve B cells; a few are of T-cell lineage.
Bimodal distribution—young adulthood and > 55 years; more common in men except for nodular sclerosing type.	Can occur in children and adults.
Associated with EBV.	May be associated with HIV and autoimmune diseases.
Constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.	May present with constitutional signs/symptoms.

In dealing with Leukemias we must consider whether they're acute (undifferentiated, aggressive) or chronic (differentiated, indolent). The acute leukemia patients are going to be SICK (fever, night sweats, bleeding, and infection). It's a product of useless, immature cells crowding out effective cell lines, creating a pancytopenia. Conversely, Chronic leukemia will be asymptomatic and found on a routine screen for something else (unless very late stage). Patients present with an enormous number of leukocytes. Which line gets elevated is dependent on the type of cancer. Myelogenous is Neutrophils, while Lymphocytic is Lymphocytes. In all cases the first test will be a smear to rule out acute disease (the presence of blasts). Then, a differential is done to rule out chronic disease. Definitive diagnosis is made with a bone marrow biopsy.

- **Acute Myelogenous leukemia**

This is a disease of immature (acute) neutrophils (myelogenous) cancer in the blood (leukemia). It can arise de novo after exposure to radiation, benzene, or chemo, or be a transformation (so-called "blast crisis") from other marrow cancers (CML, MDS). The symptoms of bleeding, bruising, petechiae, pallor and fever set in rapidly. CBC is of no use as all values could be ↑ or ↓. What gives the diagnosis away is seeing blasts on a peripheral smear. To confirm the diagnosis a Bone Marrow Biopsy showing ›20%Blasts is required, as well as cytogenetic analysis showing neutrophils (myeloperoxidase). A special form of AML, the M3 type (Promyelocytic), is diagnosed by the presence of Auer Rods. Treatment with chemotherapy (idarubicin + Ara-C) can push AML into remission. M3 is treated with Vitamin A, which induces development out of the blast phase by all-trans retinoic acid. ›20% blasts on peripheral blood also makes the diagnosis.

- **Acute Lymphocytic leukemia**

This is a disease of immature (acute) lymphocytes (lymphoid) cancer in the blood (Leukemia). It's often found in the pediatric patient who presents with bleeding and bone pain. As in AML, look at the smear for blasts then get a Bone Marrow Biopsy to confirm ›20% blasts and cytogenics. Like AML, it's treated with chemo (cyclophosphamide, doxorubicin, vincristine, and methotrexate) with a fairly decent sustained remission (90%) and poor cure rate (50%). Consider doing intrathecal ppx chemo-radiation with Ara-C or Methotrexate, because the CNS is a sheltered region for ALL to hide while undergoing therapy for systemic blood and marrow cancer. ›20% blasts on peripheral blood also makes the diagnosis.

❖ Chronic Lymphocytic leukemia

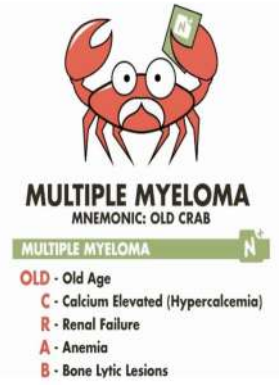
This is a disease of mature (chronic) lymphocytes (lymphoid) cancer in the blood (leukemia). It occurs in old men most commonly presenting as an asymptomatic ↑ in WBC. A diff will show an absolute lymphocyte count >50. You might see smudge cells (artificial rupture of fragile cells during smear preparation) on smear, but it's the diff and subsequent bone marrow biopsy that defines the disease. The average survival is about ten years. If they're old do nothing; they're more likely to die with it than from it. If they become symptomatic, treat with chemotherapy: fludarabine or rituximab-based. If the patient is young (<65) and there's a donor go ahead and perform a stem cell transplant.

❖ Chronic Myeloid Leukemia

This is a disease of matured (chronic) neutrophils (Myelogenous) cancer in the blood (leukemia). It's associated with the Philadelphia chromosome – a t(9,22) translocation with overactive activity of a tyrosine kinase BCR-ABL. It presents as an elevated white count with an abnormal percentage of neutrophils (>60 WBC, >90% PMNs). Once the diagnosis is made confirm with a Bone Marrow Biopsy. Revolutionary therapy with the tyrosine-kinase inhibitor Imatinib has prolonged survival and delayed the blast crisis. Newer tyrosine- kinase inhibitors have been used in imatinib-refractory cancers. However, inevitably this cancer becomes resistant, progresses to AML, and the patient ultimately succumbs.

❖ Multiple Myeloma

1. Lytic bone lesions—result in significant bone pain (especially in the low back, chest, and jaw), pathologic fractures, and loss of height secondary to collapse of vertebrae
2. Anemia—present in most patients due to bone marrow infiltration and renal failure
3. Renal failure—due to **myeloma nephrosis** (immunoglobulin precipitation in renal tubules) and hypercalcemia
4. Recurrent infections (especially of the lung or urinary tract)—most common cause of death, due to lack of normal immunoglobulins
5. Cord compression—may occur secondary to a plasmacytoma or fractured bone fragment



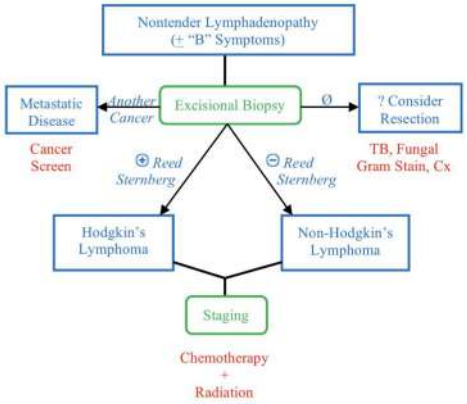
- To be able to list a work-up plan to establish the diagnosis of lymphoma, leukemia and multiple myeloma

❖ lymphoma

To differentiate between Hodgkin and non-Hodgkin lymphoma:

1. History and the presence of B symptoms (fever, night sweats, weight loss)
    a. Pel Ebstein fevers or the painful lymphadenopathy with EtOH is clues to Hodgkin lymphoma
    b. B symptoms is used for staging
    c. B symptoms is more common in Hodgkin lymphoma
2. Blood test:
    a. CBC:
        i. Hodgkin: Elevated or decreased WBC count, Anemia, Eosinophilia (commonly Leukocytosis with eosinophilia)
        ii. Non-Hodgkin: anemia, thrombocytopenia; WBC count may be high or low (commonly leukopenia, lymphocytosis)
    b. LDH: high
    c. Hypercalcemia: most commonly due to paraneoplastic production of 1,25-dihydroxyvitamin D (Hodgkin)
    d. Elevated alkaline phosphatase (if bone or liver involvement)
    e. Elevated liver function tests or bilirubin (if liver involvement)
3. Excisional biopsy:
    a. any lymph node >1 cm present for more than 4 weeks that cannot be attributed to infection should be biopsied
    b. Reed-Stemberg cells "Owls eyes" is diagnostic of Hodgkin lymphoma
    c. inflammatory cell infiltrates distinguishes Hodgkin lymphoma from NHL (These include plasma cells, eosinophils, fibroblasts, and T and B lymphocytes)
4. CXR and CT CAP (may reveal lymph node involvement)
5. Bone marrow biopsy (may reveal bone marrow involvement)

Staging is based on physical examination, CT scan (chest, abdomen, pelvis), and bone marrow biopsy.



Stage	
I	One Group of lymph nodes
II	> One Group of lymph nodes on same side of diaphragm
III	> One Group of lymph nodes on opposite side of diaphragm
IV	Diffuse Disease in (blood or bone marrow)

"A" = No B Symptoms "B" = Positive B Symptoms

❖ **Acute leukemia:**

1. CBC:
    a. Leukopenia or leukocytosis-WBC count is variable (from 1,000/mm3 to 100,000/mm3)
    b. Anemia
    c. Thrombocytopenia
2. peripheral blood Smear:
    a. significant numbers of blast cells >20 (immature cells)
3. Electrolyte disturbances
    a. (e.g., hyperuricemia, hyperkalemia, hyperphosphatemia) TLS
4. Bone marrow biopsy (required for diagnosis)
    a. In ALL, reveals proliferation of blasts of the lymphoid lineage (>20%)
    b. AML, reveals proliferation of blasts of the myeloid lineage (>20%) and Auer rods, especially if it is the APL phenotype

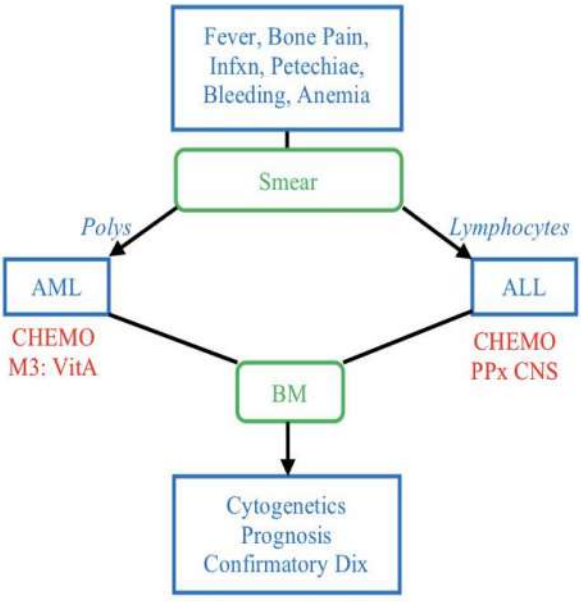
❖ **Chronic leukemia:**

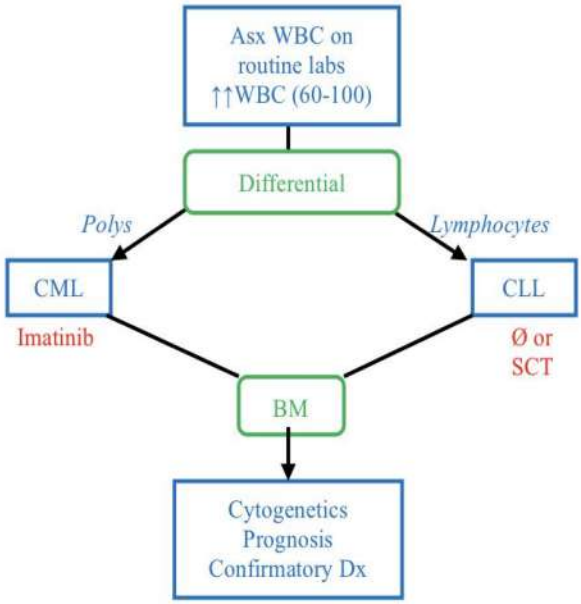
CLL

1. CBC
    a. Persistent lymphocytosis with a high percentage of small mature lymphocytes
    b. Anemia (due to autoimmune hemolysis)
    c. Neutropenia
    d. Thrombocytopenia
2. Blood smear
    a. Reveals absolute lymphocytosis- almost entirely mature, small lymphocytes
    b. Reveals smudge cells ("fragile" leukemic cells that rupture when placed on glass slide)
3. Flow cytometry
    a. detection of B-CLL immunophenotype (CD5, CD19, CD20, CD23), light chain restriction (kappa or lambda)
4. Serum antibody electrophoresis
    a. antibody deficiency (decreased γ globulin fraction)
5. Bone marrow aspiration
    a. High percentage (> 30%) of small, mature lymphocytes
    b. Decreased number of myeloid progenitor cells
6. Additional diagnostic procedures
    a. Genetics: FISH analysis to detect mutations associated with CLL (e.g., del(17p13))
    b. Ultrasound: splenomegaly and/or hepatomegaly
    c. Liver histology: periportal lymphocyte infiltration and centrilobular necrosis
    d. Lymph node biopsy: A biopsy may be performed if the peripheral blood smear does not yield diagnostic clues, to confirm the diagnosis, or to differentiate CLL from other diseases (e.g., Hodgkin disease).

CML

1. Initial diagnostic workup should include:
    a. CBC:
        i. Leukocytosis WBCs from 50,000 to 200,000 with Basophilia and eosinophilia
        ii. Thrombocytosis
        iii. Anemia
    b. Peripheral blood smear
        i. Blast cells in peripheral blood can indicate the transition to AP-CML.
    c. Bone marrow aspiration and biopsy
        i. hyperplastic myelopoiesis (predominantly granulocytosis) with elevated granulocytic precursor cells, especially myelocytes and promyelocytes
2. Diagnostic confirmation:
    a. identification of the Philadelphia chromosome and/or the BCR-ABL1 fusion gene.





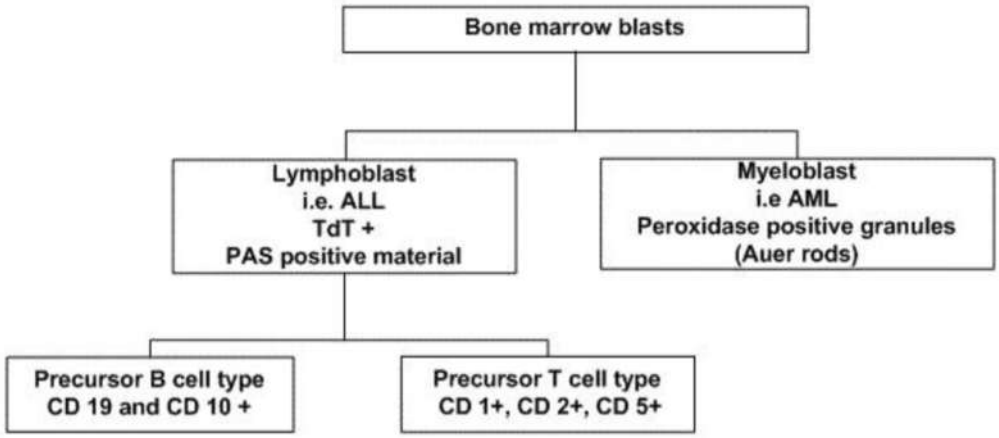
Disease	*Patient*	*Age*	*Cell*	*1st Test*	*Best Test*	*Treatment*	*Special*
Acute	Fever, Bleeding, Petechiae, Infection, Pallor Bruising Bone Pain	7	Lymphoid	Smear	BM Bx >20% Blasts	Ara-C MTX Cyclophosphamide Doxyrubicin	CNS PPx
		67	Myelogenous (Neutrophils)	Smear	BM Bx >20% Blasts	Auer Rods/M3 = Vit A Idarubicin + Ara-C	Auer Rods
Chronic	↑White Count, Found on routine screen	47	Myelogenous (Neutrophils)	Diff	BM Bx Philadelphia Chromosome t(9,22) BCR-ABL	Imatinib	Blast Crisis
		87	Lymphoid	Diff	BM Bx	If old or Ø Donor = Ø If old and symptomatic = Chemo If young and donor = BM Transplant	

❖ **multiple myeloma**

1. Serum and urine protein electrophoresis
    a. reveals monoclonal protein spike (**M-spike**) (due to a malignant clone of plasma cells synthesizing a single Ig (usually IgG, although specific subtype can be determined via immunofixation))
2. Low-dose CT, PET/CT, or MRI
    a. reveal lytic bone lesions
3. Bone marrow biopsy (required for diagnosis)
    a. reveals >10% abnormal plasma cells
4. Hypercalcemia (due to bone destruction)
5. Elevated serum total protein (due to paraproteins in blood (hyperglobulinemia))
6. Elevated creatinine (due to renal damage)
7. CBC:
    a. Anemia, leukopenia, or thrombocytopenia (especially in advanced disease due to bone marrow invasion)
8. Peripheral blood smear
    a. reveals normocytic anemia with RBCs in rouleaux formation (RBCs resemble a stack of poker chips as a result of clumping caused by hyperglobulinemia)
9. Urinalysis
    a. reveals large amounts of free light chains called **Bence Jones protein**

Recognize patients presenting with leukemias and be able to differentiate between the types

- In dealing with Leukemias we must consider whether they're acute (undifferentiated, aggressive) or chronic (differentiated, indolent).
- **Acute leukemia**
    - patients are going to be SICK (fever, night sweats, bleeding, and infection).
    - It's a product of useless, immature cells crowding out effective cell lines, creating a pancytopenia.
- **Chronic leukemia**
    - will be asymptomatic and found on a routine screen for something else (unless very late stage).
    - Patients present with an enormous number of leukocytes. Which line gets elevated is dependent on the type of cancer.
    - Myelogenous is Neutrophils, while Lymphocytic is Lymphocytes.
- In all cases the first test will be a smear to rule out acute disease (the presence of blasts).
- Then, a differential is done to rule out chronic disease.
- Definitive diagnosis is made with a bone marrow biopsy.



Acute Lymphoblastic Leukemia	
Epidemiology	• Most common childhood cancer • Peak age: 2-5 years • Male > female • **Associated with Down syndrome**
Clinical features	• Nonspecific systemic symptoms • Bone pain • Lymphadenopathy • Hepatosplenomegaly • Pallor (from anemia) • Petechiae (from thrombocytopenia) • **T-cell ALL can present as mediastinal mass (SVC-like syndrome)**
Diagnosis	• Bone marrow biopsy with >25% lymphoblasts
Treatment	• Multi-drug chemotherapy

Acute myeloid leukemia	
Background	• Most common adult acute leukemia • Median age 65
Manifestations	• **Fatigue** is common (other B symptoms unusual) • Often presents with **symptoms from cytopenias**: o Fatigue, weakness (anemia) o Bleeding, bruising (thrombocytopenia) o Infection (granulocytopenia) • Hepatosplenomegaly/lymphadenopathy rare • Disseminated intravascular coagulation (if APML)
Laboratory	• Cytopenias (leukocytes may be ↑, normal or ↓) • Elevated lactate dehydrogenase • Peripheral smear - usually **myeloblasts** with **Auer rods**
Diagnosis	• **Bone marrow biopsy** - usually hypercellular with myeloid blasts

APML = acute promyelocytic leukemia.

Examination may show pallor and ecchymosis, but lymphadenopathy and hepatosplenomegaly are rare. Leukocyte count may be elevated (sometimes >100,000/mm^3), normal, or low.

One unique type of AML is APML, which is characterized by life-threatening coagulopathy due to **disseminated intravascular coagulation** (prolonged PT/active PTT, hypofibrinogenemia). In APML, bone marrow biopsy would reveal **atypical promyelocytes**.

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:
	  ○ Multiple chain lymphadenopathy
	  ○ Hepatosplenomegaly
	  ○ Anemia & thrombocytopenia

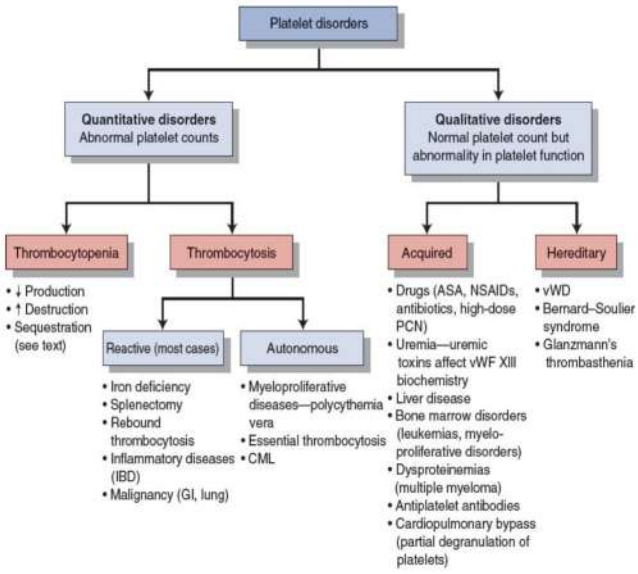
Complications	• **Infection** • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter transformation)

Chronic myeloproliferative disorders		
Disorder	**Diagnostic features**	**Mutation**
Chronic myelogenous leukemia	Constitutional symptoms (eg, fatigue, weight loss, excessive sweating), splenomegaly & **leukocytosis with marked left shift** (eg, myelocytes, metamyelocytes, band forms)	Philadelphia chromosome t(9:22) BCR-ABL fusion protein
Essential thrombocytosis	Hemorrhagic & thrombotic symptoms (eg, easy bruising, microangiopathic occlusion), **thrombocytosis** & megakaryocytic hyperplasia	JAK2
Polycythemia vera	Pruritus, erythromelalgia, splenomegaly, thrombotic complications, **erythrocytosis** & thrombocytosis	
Primary myelofibrosis	Severe fatigue, splenomegaly (often causing early satiety/abdominal discomfort), hepatomegaly, anemia & **bone marrow fibrosis**	

	ALL	AML	CLL	CML
Epidemiology	most common malignancy in children under age 15	mostly in adults	Most patients with CLL are >60 years of age	Patients are usually >40 years of age
cause/ risk factors	- No identifiable cause or risk factors in most cases - Down syndrome - Prior bone marrow damage due to alkylating chemotherapy or ionizing radiation	- exposure to radiation - myeloproliferative syndromes - Down syndrome - prior chemotherapy (e.g., alkylating agents)	- Advanced age - Environmental factors: organic solvents - Family history	
Clinical feature	- Dyspnea and pallor (due to Anemia) - Increased risk of bacterial infections (due to neutropenia) - epistaxis, bleeding at puncture sites, petechiae/purpura, ecchymoses (due to Thrombocytopenia) - Hepatosplenomegaly - lymphadenopathy painless - Bone and joint pain (due to invasion of periosteum) - Diffuse or focal neurologic dysfunction (e.g., meningitis, seizures) due to CNS involvement - Testicular involvement (ALL) - Anterior mediastinal mass (T-cell ALL) - Skin nodules (AML)		- Usually asymptomatic at time of diagnosis - Painless lymphadenopathy - Hepatosplenomegaly - Recurrent infections - In more advanced disease: fatigue, weight loss, pallor, skin rashes, easy bruising, bone tenderness, and/or abdominal pain (CLL) - Patients may also present in more advanced stages (i.e., the accelerated phase or blast crisis) (CML) Constitutional symptoms (CML)	
Findings	- reveals a predominance of lymphoblasts	- Neoplasm of myelogenous progenitor cells - Auer rods	- monoclonal proliferation of lymphocytes that are morphologically mature but functionally defective - smudge cells	- Neoplastic, clonal proliferation of myeloid stem cells
Other	- Poor prognostic indicators include age <2 or >9, WBC >105/mm3, and/or CNS involvement -Presence of any of the following is associated with an increased risk for CNS involvement: B-cell phenotype, increased LDH, rapid leukemic cell proliferation	- Poor prognostic indicators include older age, presence of other medical comorbidities, and history of exposure to cytotoxic agents and/or radiation therapy - acute promyelocytic leukemia (APL) Is a variant of AML characterized by t(15;17) may cause DIC treatment of APL is by all-trans retinoic acid	- least aggressive type of leukemia	- The end-stage of the disease course is usually an acute phase (also known as a blast crisis) - associated with (t9,22) fusion of the BCR gene on chromosome 22 with the ABL1 gene on chromosome 9 is known as the **Philadelphia chromosome.** - patients without the Philadelphia chromosome have shorter survival times and respond more poorly to treatment.

Bleeding disorder

- To learn different between platelets disorders V. Coagulation disorders and How to differentiate between them clinically and laboratory.



Bleeding disorders

Type	Symptoms	Examples	Laboratory results
Clotting defect	• Hemarthrosis • Deep tissue hematomas	• Hemophilia A • Hemophilia B	↑Activated partial thromboplastin time
Platelet aggregation defect	• Easy or prolonged mucosal bleeding • Ecchymoses • Petechiae	• von Willebrand disease • Bernard-Soulier syndrome	Abnormal platelet function testing
Thrombocytopenia		• Idiopathic thrombocytopenic purpura • Leukemia	↓Platelet count

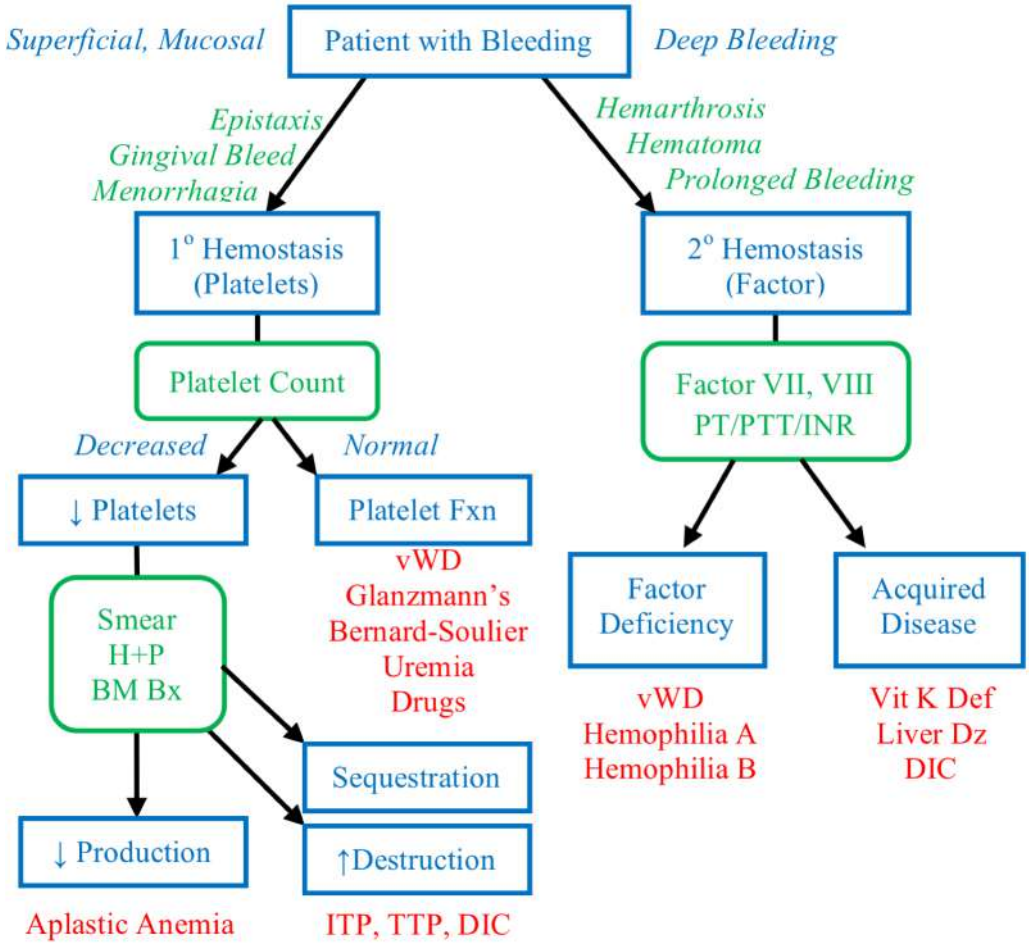
©UWorld

Laboratory characteristics of coagulopathies

	PT	aPTT	Platelet count	Bleeding time
Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; **PT** = prothrombin time.

- Understand approach to patient with bleeding



- Enlist differential diagnosis for an isolated or combined coagulation profile prolongation

Causes of Abnormal Coagulation Profile
Isolated Prolonged PT/INR
Warfarin (low dose)
Mild vitamin K deficiency
Factor VII deficiency
Isolated Prolonged APTT
Unfractionated heparin - therapeutic or contamination
Overcoagulation with low molecular weight heparin
Factor deficiency - VIII, IX, VI, XII
Factor inhibitors
Von Willebrand disease
Lupus anticoagulant (antiphospholipid antibody)
Prolonged PT/INR and APTT
Artefactual - high haematocrit
Liver disease
Disseminated intravascular coagulation (DIC)
Common pathway deficiency - X, V, II, fibrinogen
Severe vitamin K deficiency
Excess heparin (line contamination)
Warfarin
Factor IIa inhibitors (dabigatran)
Factor Xa inhibitors (rivaroxaban, apixaban)

Venous thrombosis

- Identify patients at risk of hypercoagulable state.

❖ **The etiology of thrombophilia can be classified into two categories:**

1. **Hereditary**

- Factor V Leiden (autosomal dominant inheritance): most common genetic cause of hypercoagulability in white populations
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Autosomal dominant inheritance
- Occasionally acquired
- Renal failure
- Liver failure
- Nephrotic syndrome (urinary loss of antithrombin)
- Prothrombin G20210A mutation
- Hyperhomocysteinemia
- Plasminogen deficiency
- Sickle cell anemia
- MTHFR gene mutation

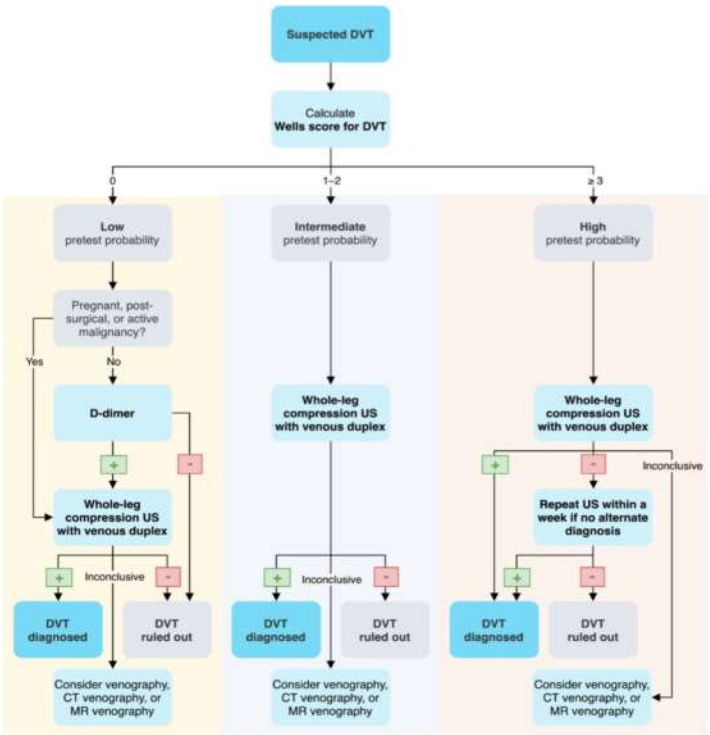
2. **Acquired**

- Pregnancy
- Advanced age
- Smoking
- Obesity
- Surgery
- Immobilization
- Trauma
- Malignancy (especially adenocarcinoma)
- Antiphospholipid syndrome
- Nephrotic syndrome
- Oral contraceptive pills (OCPs)/hormone replacement therapy (HRT)
- Systemic lupus erythematosus (SLE)
- Heparin-induced thrombocytopenia

- Identify patients presenting with acute deep vein thrombosis and initiate work-up plan and basic management plan

❖ **Clinical features:**

- May be asymptomatic
- Localized unilateral symptoms
- Typically affects deep veins of the legs, thighs, or pelvis
- More common in the left lower extremity
- May-Thurner syndrome: compression of the left iliac vein between the right iliac artery and a lumbar vertebral spur (occurs in > 20% of adults)
- Swelling, feeling of tightness or heaviness
- Warmth, erythema, and possibly livid discoloration
- Progressive tenderness, dull pain
- Homans sign: calf pain on dorsal flexion of the foot
- Meyer sign: Compression of the calf causes pain.
- Payr sign: pain when pressure is applied over the medial part of the sole of the foot
- Distention of superficial veins
- Distal pulses are normal.
- General symptoms: fever
- Possible signs of pulmonary embolism: dyspnea, chest pain, dizziness, weakness
- In patients with a low pretest probability of DVT, a negative D-dimer (< 500 ng/mL) rules out DVT.
- A positive D-dimer alone does not confirm DVT



❖ **Treatment:**

1. Anticoagulation
    a. Prevents further propagation of the thrombus
    b. Multiple options: Injectable LMWH (e.g., enoxaparin, dalteparin) (best choice for DVT/PE associated with malignancy), DOACs (e.g., apixaban, rivaroxaban, edoxaban, dabigatran), and warfarin (requires IV heparin bridge as below). LMWH was the preferred choice for DVT/PE treatment in patients with malignancy, however a recent study showed that edoxaban was non-inferior to dalteparin, and also significantly reduced VTE recurrence compared to dalteparin (though with a higher bleeding risk).
    c. If warfarin chosen: Heparin bolus followed by a constant infusion and titrated to maintain the PTT at 1.5 to 2 times aPTT
    d. Start warfarin once the aPTT is therapeutic and continue for 3 to 6 months.
    e. Anticoagulate to INR at 2 to 3
    f. Continue heparin until the INR has been therapeutic for 48 hours
    g. All patients (especially high risk) should be on anticoagulation while completing
    h. diagnostic evaluations, so start heparin before sending that patient off to the radiology department for the CT or the V/Q scan

1. Thrombolytic therapy
    a. (streptokinase, urokinase, tissue plasminogen activator [tPA])
    b. Speeds up the resolution of clots
    c. Indicated mainly for patients with massive PE who are hemodynamically unstable (hypotension with SBP <90 mm Hg), and with no contraindications for thrombolytics
    d. High risk of intracranial hemorrhage with tPA (1% to 2%)

1. Inferior vena cava filter placement (Greenfield filter)
    a. Indications for treatment of VTE If absolute contraindication to anticoagulation (bleeding) If failure of appropriate anticoagulation
    b. Effective only in preventing PE, not DVT

- To be able to identify patients with PE and establish the management

❖ **Clinical Features of:**

PE

- Acute onset of symptoms, often triggered by a specific event (e.g., on rising in the morning, sudden physical strain/exercise)
- Dyspnea and tachypnea (> 50% of cases)
- Sudden pleuritic chest pain (~ 50% of cases), worse with inspiration
- Cough and hemoptysis
- Possibly decreased breath sounds, dullness on percussion, split second heart sound audible in some cases
- Tachycardia (~ 25% of cases), hypotension
- Jugular venous distension and Kussmaul sign (in the event of a massive pulmonary embolism)
- Low-grade fever

Features of DVT:
unilaterally painful leg swelling

Features of massive PE:
syncope and obstructive shock with circulatory collapse (e.g., due to a saddle thrombus)

❖ **Treatment**:

1. Give oxygen and start heparin immediately before the diagnosis is confirmed and while the diagnostic workup is being completed
2. Once the diagnosis is confirmed:
    a. Heparin—LMWH or unfractionated for 5–7 days (or until INR is therapeutic) In most institutions, LMWH has supplanted the use of unfractionated heparin as the primary heparinoid in the treatment of PE and DVT.
    b. Warfarin (Coumadin®)—should be started with heparin and continued for 3 months for both pulmonary emboli and DVT.

Reassessment of need for anticoagulation
After 3 months of anticoagulation, then annually

- Indications for extended anticoagulation

1- Unprovoked PE with a low to moderate risk of bleeding
2- Patients with cancer with any level of bleeding risk

Myeloproliferative disorders

- To identify common presentation of patients with Myelofibrosis, Primary thrombocythemia, Polycythemia Rubra Vera and chronic Myelogenous Leukemia

According to the WHO classification, the following disorders belong to the group of myeloproliferative neoplasms:

- Chronic myeloid leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- With the exception of CML, all of these disorders show varying degrees of JAK2 mutations, which can be used as a diagnostic marker

Chronic myeloproliferative disorders		
Disorder	**Diagnostic features**	**Mutation**
Chronic myelogenous leukemia	Constitutional symptoms (eg, fatigue, weight loss, excessive sweating), splenomegaly & **leukocytosis with marked left shift** (eg, myelocytes, metamyelocytes, band forms)	Philadelphia chromosome t(9:22) BCR-ABL fusion protein
Essential thrombocytosis	Hemorrhagic & thrombotic symptoms (eg, easy bruising, microangiopathic occlusion), **thrombocytosis** & megakaryocytic hyperplasia	JAK2
Polycythemia vera	Pruritus, erythromelalgia, splenomegaly, thrombotic complications, **erythrocytosis** & thrombocytosis	
Primary myelofibrosis	Severe fatigue, splenomegaly (often causing early satiety/abdominal discomfort), hepatomegaly, anemia & **bone marrow fibrosis**	

- To be able to list a work-up plan to establish the diagnosis of Myelofibrosis, Primary thrombocythemia, Polycythemia Rubra Vera and chronic Myelogenous Leukemia

❖ **Diagnosis of:**

myelofibrosis

- Laboratory studies: ↑ leukocyte alkaline phosphatase, LDH, and uric acid
- Peripheral blood smear: dacrocytes (teardrop cells)
- Bone marrow aspiration: punctio sicca

thrombocythemia

- ET is a diagnosis of exclusion; all other causes of thrombocytosis must be ruled out before the diagnosis can be made.
- Thrombocytosis (› 600,000/µL)
- ↑ LDH and uric acid
- Bone marrow aspiration: hyperplasia of megakaryocytes

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) • Ruxolitinib (JAK1/2 inhibitor)

	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
Treatment	treat underlying cause	Bcr-abl tyrosine kinase inhibitors (eg,imatinib)

LAP = leukocyte alkaline phosphatase.

Pulmonary Disorders

Pulmonary disorders	
1	Airway diseases (e.g., COPD and asthma, Cystic fibrosis and bronchiectasis) - To be able to identify the severity of asthma and to understand the basics of management. - To understand the basics of management of COPD. - To apply the modalities of treatment in bronchiectasis and the prevention of exacerbations. - Identify symptoms that raise suspension of cystic fibrosis and the role of testing. - To Identify obstructive V. restrictive lung diseases in PFT and differentiate between common airway diseases.
2	Diffuse Parenchymal Lung disease - To be able to identify the risk factors for ILD. - Recognize the common findings in HRCT. - Analyze the serologic testing and link it to the causes of ILD. - To Identify obstructive V. restrictive pattern lung diseases in PFT and differentiate between common airway diseases.
3	Obstructive Sleep Apnea - To be able to identify patients at risk of obstructive sleep apnea - Recognize common symptoms of obstructive sleep apnea - Implementation of a sleep study in patients suspected to have obstructive sleep apnea and modalities of management.
4	Respiratory failure - To differentiate between type 1 and type 2 respiratory failure. - To recognize the common causes of respiratory failure. - To apply invasive and non-invasive modalities of management in respiratory failure.
5	Pneumonia, Tuberculosis and approach to Pleural effusion - Recognize common presentation of different types of pneumonia and typical findings in chest x-ray - Apply medical therapy for community-acquired pneumonia. - Implement isolation and precautions for patients with suspected/confirm tuberculosis. - Apply modalities of diagnostics for latent and active tuberculosis. - Recognize and list treatment of active/latent tuberculosis. - To apply light's criteria to differentiate between exudative and transudative pleural effusion.
6	Pulmonary Hypertension - Recognize clinical features, classification and common causes of pulmonary hypertension. - Apply modalities of diagnostics for pulmonary hypertension - Understand the basics of management of pulmonary hypertension
7	Interpretation of Chest Radiographs - To be able to differentiate between different views. - To recognize what is normal and abnormal. - Adapt a systematic approach to a chest x-ray interpretation. - To be able to recognize common and important diseases based on chest x-rays.

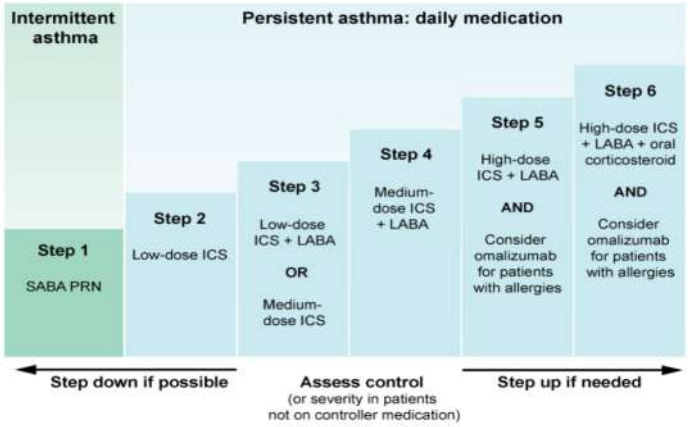
Airway diseases (COPD and asthma, Cystic fibrosis and bronchiectasis)

- To be able to identify the severity of asthma and to understand the basics of management.

Asthma severity for patients not on controller medication			
Asthma severity	**Symptom frequency/ SABA use**	**Nighttime awakenings**	**Indicated therapy initiation**
Intermittent	**≤2 d**/week	**≤2**/month	Step 1
Mild persistent	**>2 d**/week but not daily	**3-4**/month	Step 2
Moderate persistent	**Daily**	**>1**/week but not nightly	Step 3
Severe persistent	**Throughout** the day	**4-7**/week	Step 4 or 5

SABA = short-acting beta-2 agonist.

The need to initiate **controller medication therapy** (and the level of controller therapy) is evaluated by categorizing symptoms into 1 of 4 levels of asthma severity: intermittent, mild persistent, moderate persistent, and severe persistent. A patient has been requiring his albuterol inhaler 2 days per week, which suggests good control. However, he has been having 3-4 nighttime awakenings per month, which indicates he is undertreated with an as-needed SABA alone. Based on his current level of symptoms, he now meets the criteria for **mild persistent asthma** and warrants a step up in therapy with the addition of a low-dose **inhaled corticosteroid (ICS)** (Step 2).



ICS = inhaled corticosteroid; **LABA** = long-acting beta-agonist; **SABA** = short-acting beta-agonist; **PRN** = as needed.

Once patients begin asthma controller therapy (eg, ICS), they are evaluated based on a symptomatic assessment of asthma control (similar to the assessment of asthma severity). Patients whose condition remains **well controlled on the same therapy for 3 months** should be considered for a **step down** in medication management. In patients with **very poorly controlled** symptoms, medication therapy should be **increased by 1 or 2 steps**, and a **short course of *oral* prednisone** should be considered.

https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf
2021 GINA guidelines for asthma

- To understand the basics of management of COPD.

❖ **Management of Stable Phase COPD:**

The goal in treatment is to treat airway inflammation and bronchospasm, reduce airway resistance and work of breathing, and improve gas exchange and ventilation-perfusion (V/Q) mismatching.

- **Anticholinergic agents** (ipratropium bromide and tiotropium) are the first-line drugs in COPD. These agents are given via MDI (metered dose inhaler) and control airway caliber and tone. Anticholinergic agents can be used synergistically with β2-adrenergic agonists in patients with COPD.
- **β2-adrenergic agonists** (albuterol) are used after anticholinergic agents. The inhaled route is the preferred administration. Beta agonists are not first-line agents in the management of COPD because many of the patients have underlying heart disease and the tachycardia commonly associated with these agents may precipitate heart failure.
- **Chronic inhaled corticosteroids** are reserved for severe cases of COPD.
- **Theophylline**, role is controversial, may be added to the regimen if beta-2 agonists and anticholinergics are not effective in managing the symptoms of chronic obstructive lung disease. Remember that theophylline has significant toxicity. Symptoms include nausea and vomiting, palpitations, and tremulousness. Death can occur from theophylline toxicity from cardiac arrhythmias.

Despite the above treatments, the only interventions which have been shown to **decrease mortality in patients with COPD are home oxygen and smoking cessation.**
Home oxygen therapy is given to patients with hypoxemia (Pao2 <55 mm Hg or saturation <88%), and the goal is to try to keep the O2 saturation >90% as much as possible

Prevention:
All patients with COPD must have the **pneumococcal vaccine** (Pneumovax®) every 5 years and the **influenza vaccine** yearly. They should also receive the H.influenzae vaccine if they were not previously immunized.

Quick HIT

Criteria for continuous or intermittent long-term oxygen therapy in COPD:
- PaO_2 **55 mm Hg** *OR*
- **O_2 saturation ≤88%** (pulse oximetry), either at rest or during exercise *OR*
- PaO_2 55 to 59 mm Hg plus polycythemia or evidence of cor pulmonale
- Note that the above must be consistent findings despite optimal medical therapy

Treatment guidelines—stepwise therapy based on severity of symptoms and prior number of exacerbations or COPD-related hospitalizations

a. Low risk of exacerbation (0 to 1 exacerbations in past year)

- Begin with a short-acting bronchodilator (anticholinergic and/or β-agonist) as needed in a metered-dose inhaler (MDI) formulation (with spacer to improve delivery).
- Add daily long-acting bronchodilator, if more symptomatic.
- Inhaled glucocorticoids may be used as well. Use the lowest dose possible.

b. High risk of exacerbation (2 or more exacerbations per year)

- Regular use of long-acting bronchodilator (anticholinergic and/or β-agonist).
- Add inhaled corticosteroid, if more symptomatic.
- Consider additional agents (roflumilast or theophylline).
- Continuous oxygen therapy (if patient is hypoxemic).
- Pulmonary rehabilitation.

Acute COPD exacerbation: Definition: Increased dyspnea, sputum production, and/or cough. Acute COPD exacerbation can lead to acute respiratory failure requiring hospitalization, and possibly mechanical ventilation; potentially fatal.

a. Bronchodilators (β2 -agonist) alone or in combination with anticholinergics are first-line therapy.
b. Systemic corticosteroids are used for patients requiring hospitalization. A short course of oral prednisone is common practice. Do not use inhaled corticosteroids in acute exacerbations.
c. Antibiotics (azithromycin, doxycycline, or fluoroquinolones): Reserved for those with moderate or severe exacerbations requiring hospitalization.
d. Supplemental oxygen is used to keep O2 saturation 88% to 92%. Start with a nasal cannula; a face mask may need to be used.
If SaO2 is >92%, the patient is at risk of CO2 retention from worsening V/Q mismatch, loss of hypoxemic respiratory drive, and the Haldane effect.
e. Noninvasive positive pressure ventilation (NPPV) (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP]): Studies have shown a benefit in acute exacerbations. It may decrease the likelihood of respiratory failure requiring invasive mechanical ventilation.
f. Intubation and mechanical ventilation may be required if the above do not stabilize the patient. Intubate, if increasing RR, increasing PaCO2 , and worsening acidosis.

- To apply the modalities of treatment in bronchiectasis and the prevention of exacerbations.

Bronchiectasis	
Signs & symptoms	• Cough with daily mucopurulent sputum production • Rhinosinusitis • Dyspnea, hemoptysis • Wheezing, crackles
Pathophysiology	• Infection PLUS • Impaired bacterial clearance (eg, obstruction of airway, impairment of drainage, defect in immune response)
Etiologies	• Airway obstruction (eg, cancer) • Congenital (eg, cystic fibrosis, alpha-1-antitrypsin deficiency) • Chronic infection (eg, aspergillosis, non-TB mycobacteria) • Immunodeficiency (eg, hypogammaglobulinemia) • Postinfection (eg, TB, necrotizing pneumonia) • Rheumatic disease (eg, RA, Sjögren syndrome) • Toxic inhalation/aspiration
Evaluation	• CXR>> linear atelectasis/consolidation • HRCT scan of the chest (needed for initial diagnosis) • Immunoglobulin quantification • Sweat chloride &/or genetic testing for CF • Sputum culture for bacteria, fungi & mycobacteria • Pulmonary function testing

Management:

- Bronchodilators, chest physical therapy, and postural drainage are used to control and improve drainage of bronchial secretions.
- Give an antibiotic such as trimethoprim sulfamethoxazole, amoxicillin, or amoxicillin/clavulanic acid when sputum production increases or there are mild symptoms. ("Rotating antibiotics" describes choosing a different antibiotic each time to diminish resistance of microorganisms.) Chronic prophylaxis with antibiotics is not recommended.
- All patients with bronchiectasis require yearly **vaccination for influenza** and **vaccination for pneumococcal** infection with a single booster at 5 years.

- Identify symptoms that raise suspension of cystic fibrosis & the role of testing.

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

©UWorld

Cystic fibrosis	
Pathogenesis	• Mutation (ΔF508) *CFTR* gene • Autosomal recessive
Clinical features	• Recurrent sinopulmonary infections • Intestinal obstruction (eg, meconium ileus) • Pancreatic insufficiency & diabetes • Male infertility
Diagnosis	• Elevated sweat chloride levels • CFTR mutation on genetic testing • Abnormal nasal potential difference
Management	• Nutritional support • Airway clearance • Antibiotic coverage (*S aureus, P aeruginosa*)

CFTR = cystic fibrosis transmembrane conductance regulator.

Chronic respiratory symptoms (cough, wheezing), steatorrhea (bulky, oily stools), and failure to thrive (FTT) are features of **cystic fibrosis** (CF). CF is due to an autosomal recessive mutation in the CF transmembrane conductance regulator gene. This defect results in tenacious secretions accumulating in ducts throughout the body, such as the **lungs**, **pancreas**, and **vas** deferens.

Cystic fibrosis (CF) is the MC autosomal recessive disorder in patients of Northern European descent, affecting approximately 1 in 2,500 such births in the United States. The majority of cases are identified by newborn screening; however, a small number are not identified until the patient is symptomatic.

The accumulation of **inspissated mucus** in the fetal genital tract obstructs the developing vas deferens. As a result, almost all men with CF are infertile due to **congenital absence of bilateral vas deferens**. Although spermatogenesis is typically normal, sperm cannot be ejaculated (**obstructive azoospermia**).

In contrast, women with CF usually have normal reproductive tract

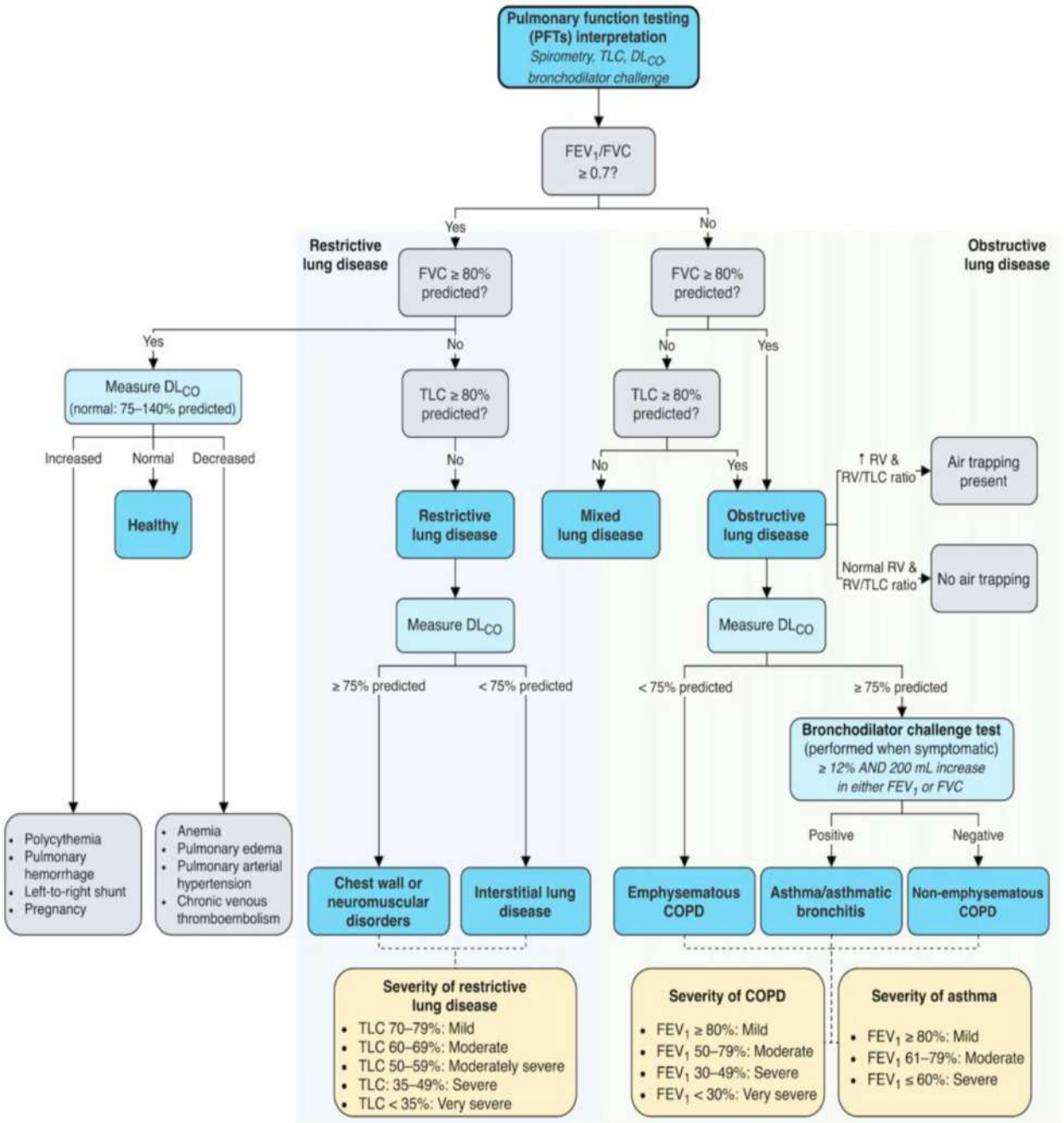
Primary ciliary dyskinesia versus cystic fibrosis		
	Primary ciliary dyskinesia	**Cystic fibrosis**
Respiratory tract features	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing
Extrapulmonary features	• Situs inversus (50% of cases) • Infertility due to immotile spermatozoa • Normal growth	• Pancreatic insufficiency • Infertility due to absent vas deferens (azoospermia) • Failure to thrive

©UWorld

anatomy. However, many are **malnourished** from pulmonary and pancreatic insufficiency. In turn, poor nutrition and low weight can result in **pubertal delay and amenorrhea**. In addition, viscous cervical mucus can obstruct sperm entry.

Up to 40% of patients have nasal polyps, which are benign outgrowths of chronically inflamed mucosa that further obstruct the nasal passages and exacerbate sinusitis. Symptomatic relief of polyps includes intranasal glucocorticoids and, in some cases, surgical resection.

- To Identify obstructive V. restrictive lung diseases in PFT & differentiate between common airway diseases



Differential diagnosis based on carbon monoxide diffusing capacity of the lung			
	Obstructive pattern (FEV_1/FVC <70% predicted)	**Restrictive pattern (FEV_1/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, also known as the TLCO, is a measurement of the conductance or ease of transfer for CO molecules from alveolar gas to the hemoglobin of the red blood cells in the pulmonary circulation.

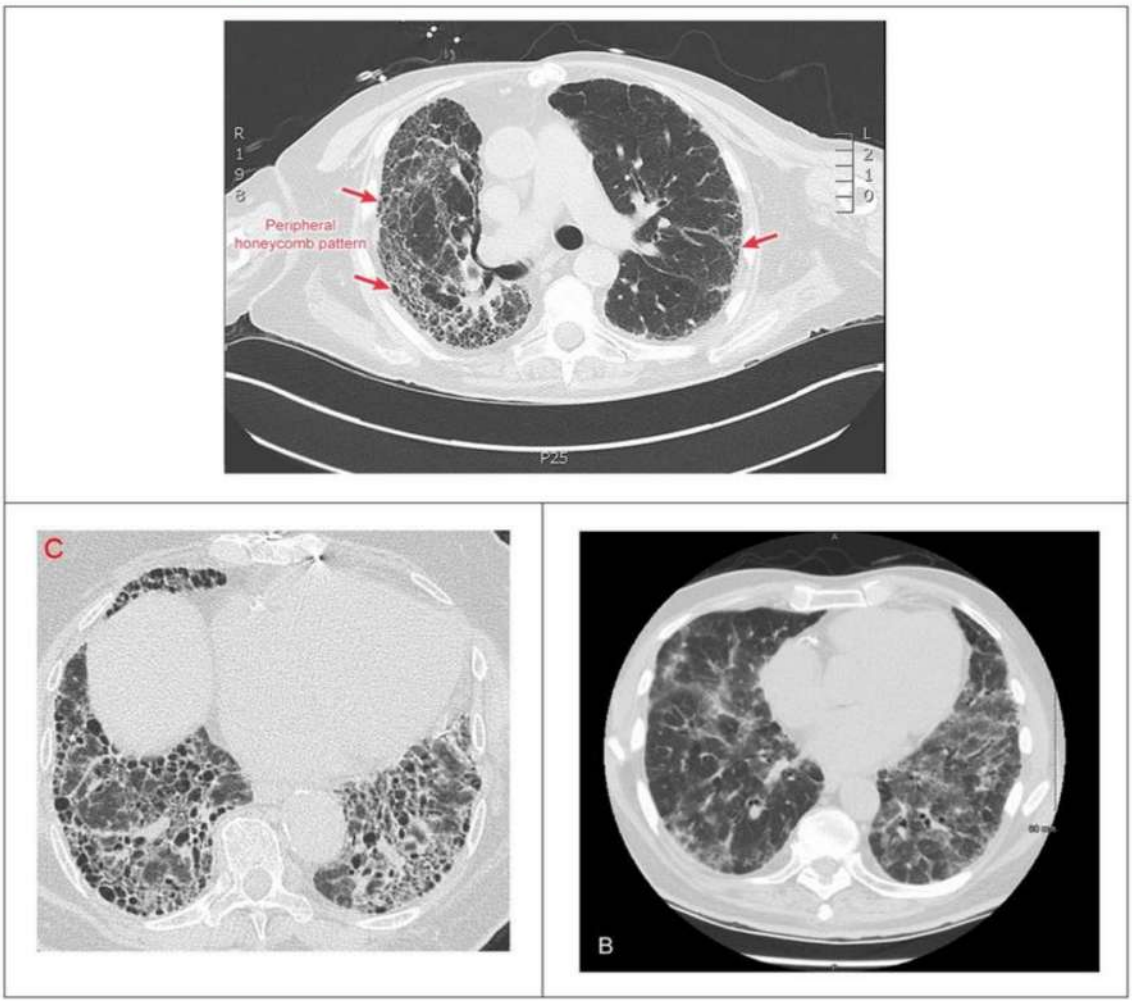
Diffuse Parenchymal Lung Disease

- To be able to identify the risk factors for ILD.

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.**	

- Recognize the common findings in HRCT.

Interstitial lung diseases>>



❖ **Findings seen on high-resolution chest CT scanning are as follows:**

- Linear reticular opacities are the most common findings.
- A ground-glass pattern is less common. It is an opacification that does not obscure underlying lung markings and is thought to be a favorable prognostic finding.
- Airspace consolidation may be present in eosinophilic pneumonia and COP.
- The presence of nodules suggests Henoch-Schönlein purpura (HSP), granulomatous disease (eg, sarcoidosis), Pulmonary Langerhans cell histiocytosis (PLCH), and Respiratory bronchiolitis–associated interstitial lung disease (RBILD).
- Large cystic spaces may be seen in PLCH and Lymphangioleiomyomatosis (LAM).
- Honeycombing is indicative of end-stage disease and carries a poor prognosis.

- Analyze the serologic testing and link it to the causes of ILD.

A full serologic workup to detect antibodies associated with specific connective tissue diseases is recommended in all patients with ILD.[4] The particular tests are determined in part by clinical presentation and context, but may include the autoantibodies listed in the table below. Use of a panel test that detects a variety of autoantibodies may be the most efficient testing approach.

Autoantibody Testing to Consider in Patients with Suspected ILD[a]	
ANCAs (ANCA-associated vasculitis)	c-ANCA, p-ANCA, anti-MPO, anti-PR3
Rheumatoid arthritis-associated antibodies	anti-CCP, RF
Systemic sclerosis-associated antibodies	anti-Scl-70, anticentromere, anti-RNA polymerase III
SLE-associated, mixed connective tissue disease-associated, or Sjögren syndrome-associated antibodies	ANAs, anti-dsDNA, anti-SSA-52 (Ro52), SSA-60 (Ro60), anti-SS-B, anti-Smith, Sm/RNP
Myositis-specific and myositis-associated antibodies	anti-Jo1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP, anti-MDA5, NXP-2, anti-Ku, PM/Scl-100, Sm/RNP, SSA-52

[a]Refer to ARUP Laboratories' Interstitial Lung Disease Autoantibody Panel 3001784.
ANAs, antinuclear antibodies; ANCAs, antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; MPO, myeloperoxidase; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3; RF, rheumatoid factor; RNP, ribonucleoprotein; SS-A, Sjögren's syndrome-related antigen A; SS-B, Sjögren's syndrome-related antigen B; SRP, signal recognition particle; SLE, systemic lupus

- To Identify obstructive V. restrictive pattern lung diseases in PFT and differentiate between common airway diseases

Slide no. 96 , 97

Obstructive Sleep Apnea

- To be able to identify patients at risk of obstructive sleep apnea
- Recognize common symptoms of obstructive sleep apnea

Obstructive sleep apnea	
Pathophysiology	• Relaxation of pharyngeal muscles, leading to closure of airway • Loud snoring with periods of apnea
Symptoms	• Daytime somnolence • Nonrestorative sleep with frequent awakenings • Morning headaches • Affective & cognitive symptoms
Sequelae	• Systemic HTN • PHTN & RHF

This patient with obesity who has daytime sleepiness and appears to choke at night likely has **obstructive sleep apnea** (OSA). OSA results from laxity of the pharyngeal musculature, leading to transient upper airway obstruction and **nocturnal hypoventilation** in the reduced-consciousness setting of sleep.

Typical manifestations include **excessive daytime sleepiness**, morning headaches, impotence, **poor judgment,** and **depression**. A history of snoring and/or periods of apnea or gagging witnessed by bed partners is often reported. Physical examination often demonstrates **obesity** and **increased neck girth,** which **correlate with OSA severity**.

1. Nocturnal Symptoms
    - Snoring
    - 40% of men, 20% of women report habitual snoring
    - Associated with considerable social and marital hazard

2. Daytime Sleepiness
    Differential diagnosis includes:
    - Insufficient Sleep (Commonest cause)
    - Medical and psychological disorders (Hypothyroidism, DM, Parkinsonism)
    - Medications (Anti-depressant, Antipsychotic, Anti-epileptic)

3. Nocturnal Choking / Gasping

Bed partners may recognize this more commonly than the patient.

❖ **Physical examination findings may include the following:**

- Obesity – Body mass index (BMI) greater than 30 kg/m2
- Large neck circumference – Greater than 43 cm (17 in) in men and 37 cm (15 in) in women
- Abnormal (increased) Mallampati score
- Narrowing of the lateral airway walls, which is an independent predictor of the presence of OSA in men but not women
- Enlarged (ie, "kissing") tonsils (3+ to 4+)
- Retrognathia or micrognathia
- Large degree of overjet
- High-arched hard palate
- Systemic arterial hypertension, present in approximately 50% of patients with OSA
- Congestive heart failure (CHF)
- Pulmonary hypertension
- Stroke
- Metabolic syndrome
- Type 2 diabetes mellitus

Implementation of a sleep study in patients suspected to have obstructive sleep apnea and modalities of management

Sleep studies

- Indicated in all patients with excessive daytime sleepiness and at least two of the following:

1. Loud snoring
2. Witnessed choking, gasping, or apnea during sleep
3. Diagnosis of hypertension

- Consider in patients with comorbidities (including complications of OSA) and risk factors for OSA.

In-laboratory polysomnography (PSG)

Description: Physiologic variables are recorded during sleep to diagnose sleep-related disorders. Variables include oxygen saturation, respiratory pauses and flow, sleep stages, and arousal events.
Recordings include EEG, EMG, EOG, and ECG.

Indications

- Patients with significant cardiovascular or respiratory disease
- Suspicion of other types of sleep-related disorders
- Circumstances precluding a home assessment
- Home sleep apnea testing is inconclusive or negative.

Findings

- Apnea and hypopnea events
- Oxygen desaturation
- Respiratory effort-related arousal events, possibly causing sleep fragmentation
- In some cases, signs of associated comorbidities (e.g., hypertension, cardiac arrhythmias)

Home sleep apnea testing (HSAT)

Description: an ambulatory screening method for sleep-related breathing disorders that assesses ventilation and oxygenation parameters but not sleep stages or arousal events

Indications

- Patients with a high pretest probability for OSA and no significant comorbidities
- In-laboratory testing is not feasible.

Findings: cardiorespiratory findings similar to those in PSG

- **Treatment:**

1. General Measures:
    a. These measures should be tried in all patients with OSDB:
    b. Weight loss
    c. Avoidance of alcohol & sedatives
    d. Sleep position (sleep on the side for mild cases)
    e. Driving and operation of heavy machinery
2. Specific Measures:
    a. Continuous Positive Airway Pressure (CPAP) Treatment of choice.
    b. Intra – Oral Appliances
    c. Surgical Treatment
    d. Hypoglossal Nerve Stimulation

Benefits of CPAP:

- Improves quality of life even in mild OSA
- Improves bed partner sleep
- Improves daytime sleepiness
- Decreases motor vehicle accident
- Improves hypertension
- Increases ejection fraction in systolic CHF
- Improves insulin resistance
- Decreases inflammatory markers: CRP (C-reactive protein)

Respiratory Failure

- To differentiate between type 1 and type 2 respiratory failure.

Respiratory failure is the acute or chronic inability of the respiratory system to maintain gas exchange. This leads to:
-Failure to oxygenate the body: defined as a PaO2 of ‹ 60 mmHg (8 kPa)
-Failure to eliminate carbon dioxide: defined as a PaCO2 of › 50 mmHg (6.5 kPa)

Types of respiratory failure [1]		
	Type 1 (hypoxemic respiratory failure)	Type 2 (hypercapnic respiratory failure)
Definition	• Respiratory failure characterized by hypoxemia and normocapnia or hypocapnia on arterial blood gas analysis	• Respiratory failure characterized hypercapnia and normoxemia or hypoxemia on arterial blood gas analysis
PaO_2	• ↓ (< 60 mmHg)	• Normal or ↓ (< 80 mm Hg)
$PaCO_2$	• Normal or ↓ (< 33 mm Hg)	• ↑ (> 50 mmHg)

❖ **Hypoxia respiratory failure (type I):**

Causes include:

- disease processes that involve the lung itself (e.g., ARDS, severe pneumonia, pulmonary edema).
- Ventilation/perfusion (V/Q) mismatch and intrapulmonary shunting are the major pathophysiologic mechanisms.

❖ **Hypercapnic (hypercarbic) respiratory failure (type II):**

- failure of alveolar ventilation.
- Either a decrease in minute ventilation or an increase in physiologic dead space leads to CO2 retention and eventually results in hypoxemia.
- May be caused by an underlying lung disease (COPD, asthma, CF, severe bronchitis)
- May also occur in patients with no underlying lung disease who have impaired ventilation due to neuromuscular diseases, CNS depression, mechanical restriction of lung inflation, or any cause of respiratory fatigue (e.g., prolonged hyperventilation in diabetic ketoacidosis [DKA])

9.5 Respiratory failure: underlying causes and blood gas abnormalities

	Type I		Type II	
	Hypoxia (PaO_2 <8.0 kPa (60 mmHg))		Hypoxia (PaO_2 <8.0 kPa (60 mmHg))	
	Normal or low $PaCO_2$ (<6.6 kPa (50 mmHg))		Raised $PaCO_2$ (>6.6 kPa (50 mmHg))	
	Acute	Chronic	Acute	Chronic
H^+	→ or ↑	→	↑	→ or ↑
Bicarbonate	→	→	→	↑
Causes	Acute asthma Pulmonary oedema Pneumonia Lobar collapse Pneumothorax Pulmonary embolus ARDS	Emphysema Lung fibrosis Lymphangitis carcinomatosa Right-to-left shunts	Acute severe asthma Acute exacerbation of COPD Upper airway obstruction Acute neuropathies/paralysis Narcotic drugs Primary alveolar hypoventilation Flail chest injury	COPD Sleep apnoea Kyphoscoliosis Myopathies/muscular dystrophy Ankylosing spondylitis

- To recognize the common causes of respiratory failure.

❖ **Causes:**

Pulmonary causes

- Airway obstruction (hypoventilation) and/or increased physiologic dead space (e.g., due to exacerbation of COPD, acute severe bronchial asthma, bronchiolitis)
- Impaired alveolar diffusion (e.g., due to pulmonary edema, severe pneumonia, pulmonary hemorrhage , idiopathic pulmonary fibrosis)
- Right-to-left shunt
  - Pulmonary right-to-left shunt (e.g., due to ARDS, pulmonary contusions/hemorrhage, lung collapse)
  - Intracardiac right-to-left shunt (e.g., due to atrial septal defect, VSD, PDA)
- V/Q mismatch (e.g., due to severe pneumonia, pulmonary edema, pulmonary embolism, atelectasis)
- Decreased FiO2 (e.g., due to asphyxiant gas exposure, high altitude)

Extrapulmonary causes

- CNS depression (e.g., due to narcotic or sedative overdose, brain trauma/herniation, stroke)
- Respiratory muscle weakness (e.g., due to myasthenia gravis, Guillain-Barre syndrome, myopathies, ALS, high cervical spinal cord injury, poliomyelitis)
- Decreased chest wall compliance (e.g., due to rib fractures, tension pneumothorax, tetanus, seizures, fibrothorax)
- Increased O2 consumption and/or CO2 production (e.g., due to severe sepsis, toxic shock syndrome, cardiogenic shock, multiorgan dysfunction)
- Electrolyte disturbances (e.g., anorexia nervosa)

- To apply invasive and non-invasive modalities of management in respiratory failure

- **Non-invasive Ventilation**

Noninvasive ventilation (NIV) is a modality that supports breathing without the need for intubation. NIV avoids the adverse effects of invasive ventilation and has become an important mechanism of ventilator support both inside and outside the ICU. Forms of NIV include bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP).

- Bi-level positive airway pressure (BiPAP or BPAP) applies 2 different levels of PAP i.e., it delivers positive pressure at alternating levels—higher for inspiration and lower for expiration—optimizing lung efficiency and at the same time diminishing the work of breathing. BPAP has been shown to be an effective management tool for COPD and acute (pneumonia, status asthmaticus, etc.) and chronic respiratory failure.
- Continuous positive airway pressure (CPAP) applies air pressure on a continuous basis, allowing the airways to continuously be open (splinted). It is typically used in the treatment of obstructive sleep apnea, preterm infants with underdeveloped lungs, CHF with pulmonary edema, near drowning, and other severe causes of respiratory distress. Portable CPAP machines used at home deliver a constant flow of pressure and are thus effective at preventing the airway from collapsing.

- **Invasive Ventilation**

Invasive ventilation, or mechanical ventilation, follows endotracheal intubation, and is used to improve oxygen exchange during acute hypoxemic or hypercapnic respiratory failure with respiratory acidosis. While hypoxemia and respiratory failure is one of the common reasons for endotracheal intubation, it is also introduced in order to protect the airways.

- Positive end-expiratory pressure (PEEP) is the alveolar pressure above atmospheric pressure that exists at the end of expiration.
- Applied (extrinsic) PEEP is one of the first ventilator settings chosen when mechanical ventilation is initiated, and it is set directly on the ventilator.

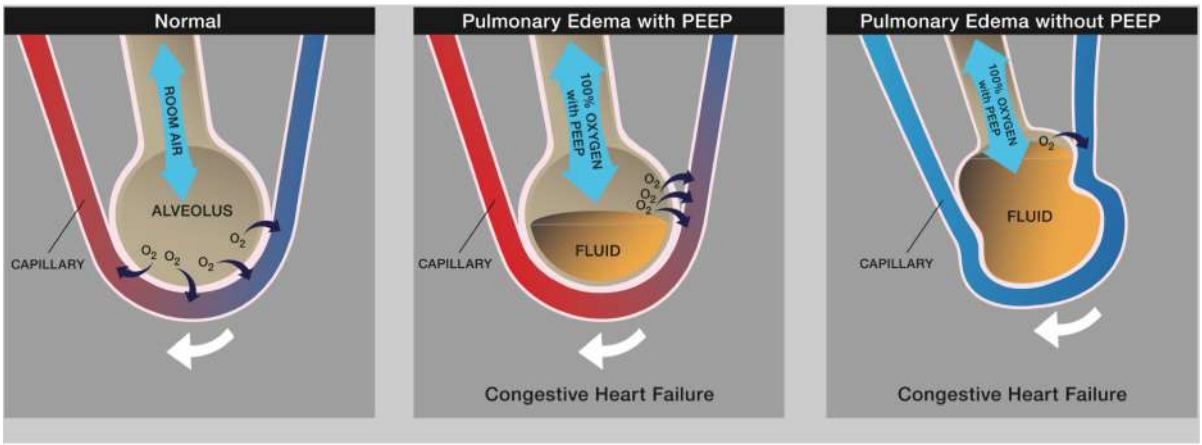


Figure 9-8. Effect of PEEP (Positive End-Expiratory Pressure)

Pneumonia, Tuberculosis and approach to Pleural effusion

- Recognize common presentation of different types of pneumonia and typical findings in chest x-ray.

	Typical Pneumonia	Atypical Pneumonia
Common Agents	a. S. pneumoniae (60%) b. Haemophilus influenzae (15%) c. Aerobic gram-negative rods (6% to 10%)—Klebsiella (and other Enterobacteriaceae) d. S. aureus (2% to 10%)	a. Mycoplasma pneumoniae (most common) b. Chlamydia pneumoniae c. Chlamydia psittaci d. Coxiella burnetii (Q fever) e. Legionella spp. f. Viruses: influenza virus (A and B), adenoviruses, parainfluenza virus, RSV
Clinical features	**Symptoms** Acute onset of fever and shaking chills Cough productive of thick, purulent sputum Pleuritic chest pain (suggests pleural effusion) Dyspnea **Signs** Tachycardia, tachypnea Late inspiratory crackles, bronchial breath sounds, increased tactile and vocal fremitus, dullness on percussion Pleural friction rub (associated with pleural effusion)	**Symptoms** Insidious onset—headache, sore throat, fatigue, myalgias Dry cough (no sputum production) Fevers (chills are uncommon) **Signs** Pulse-temperature dissociation—normal pulse in the setting of high fever is suggestive of atypical CAP Wheezing, rhonchi, crackles
CXR	- Lobar consolidation - Multilobar consolidation indicates very serious illness	- Diffuse reticulonodular infiltrates - Absent or minimal consolidation

Quick HIT

- "Classic" CAP presents with a sudden chill followed by fever, pleuritic pain, and productive cough.
- The "atypical pneumonia" syndrome, associated with *Mycoplasma* or *Chlamydia* infection, often begins with a sore throat and headache followed by a nonproductive cough and dyspnea.

Indications of CXR: all patients suspected of having pneumonia.

Findings:

- Lobar pneumonia

Opacity of one or more pulmonary lobes
Presence of air bronchograms: appearance of translucent bronchi inside opaque areas of alveolar consolidation

- Bronchopneumonia

Poorly defined patchy infiltrates scattered throughout the lungs
Presence of air bronchograms

- Atypical or interstitial pneumonia

Diffuse reticular opacity
Absent (or minimal) consolidation

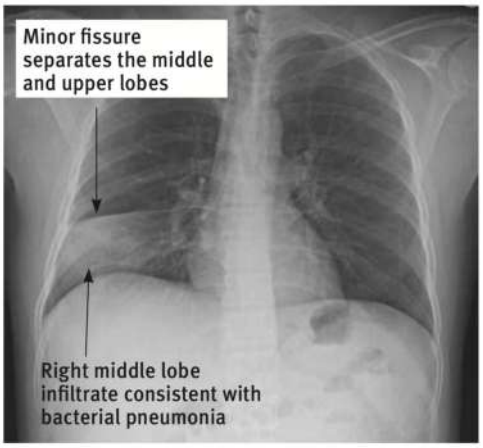


Figure 5.2: Right middle lobe infiltrate characteristic of bacterial pneumonia. *Source: Nirav Thakar, MD.*

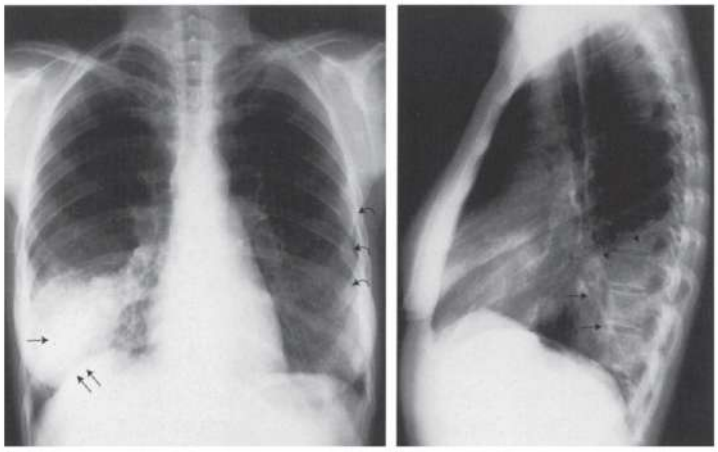


FIGURE 10.1 **Chest PA (A) and lateral (B) radiographs: Right lower lobe pneumonia (*straight arrows*). On the PA radiograph, the right cardiac border is clearly visible, and the right hemidiaphragm is partially silhouetted (*double straight arrows*). These findings indicate that the infiltrate is posterior or in the right lower lobe as confirmed on the lateral radiograph (*straight arrows*).**

(From Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging.*

- Apply medical therapy for community-acquired pneumonia.

Duration of treatment
5 days of therapy is usually sufficient for CAP that is treated in the outpatient setting.

Empiric antibiotic therapy for community-acquired pneumonia in an outpatient setting	
Patient profile	**Recommended empiric antibiotic regimen [10]**
Previously healthy patients without comorbidities or risk factors for resistant pathogens	• **Monotherapy** with one of the following: ◦ Amoxicillin ◦ Doxycycline ◦ A macrolide (only in areas with a pneumococcal macrolide resistance < 25%) ▪ Azithromycin ▪ Clarithromycin
Patients with comorbidities or risk factors for resistant pathogens	• **Combination therapy** ◦ An antipneumococcal β-lactam: ▪ Amoxicillin-clavulanate ▪ Cefuroxime ▪ Cefpodoxime ◦ PLUS one of the following: ▪ A macrolide ▪ Azithromycin ▪ Clarithromycin ▪ Doxycycline • **Monotherapy**: with a respiratory fluoroquinolone ◦ Gemifloxacin ◦ Moxifloxacin ◦ Levofloxacin

Empiric antibiotic therapy for community-acquired pneumonia in an inpatient setting	
Patient profile	**Recommended empiric antibiotic regimen [10]**
Nonsevere CAP/non-ICU treatment	• **Combination therapy** ◦ An antipneumococcal β-lactam: ▪ Ampicillin-sulbactam ▪ Ceftaroline ▪ Ceftriaxone ▪ Cefotaxime ◦ PLUS one of the following: ▪ A macrolide ▪ Azithromycin ▪ Clarithromycin ▪ Doxycycline • **Monotherapy**: with a respiratory fluoroquinolone ◦ Gemifloxacin ◦ Moxifloxacin ◦ Levofloxacin
Severe CAP/ICU treatment	• **Combination therapy** ◦ An antipneumococcal β-lactam: ▪ Ampicillin-sulbactam ▪ Ceftaroline ▪ Ceftriaxone ▪ Cefotaxime ◦ PLUS one of the following: ▪ A macrolide ▪ Azithromycin ▪ Clarithromycin ▪ Doxycycline ▪ A respiratory fluoroquinolone ▪ Moxifloxacin ▪ Levofloxacin

- **Outpatient Treatment:**

1- Previously healthy or no antibiotics in the past 3 months and mild symptoms → macrolide (azithromycin or clarithromycin) **or** doxycycline

2- Comorbidities or antibiotics in the past 3 months
→ respiratory fluoroquinolone (levofloxacin or moxifloxacin)

- **Inpatient Treatment:**

Respiratory fluoroquinolone: levofloxacin or moxifloxacin **or** Ceftriaxone and azithromycin

- Implement isolation and precautions for patients with suspected/confirm tuberculosis.

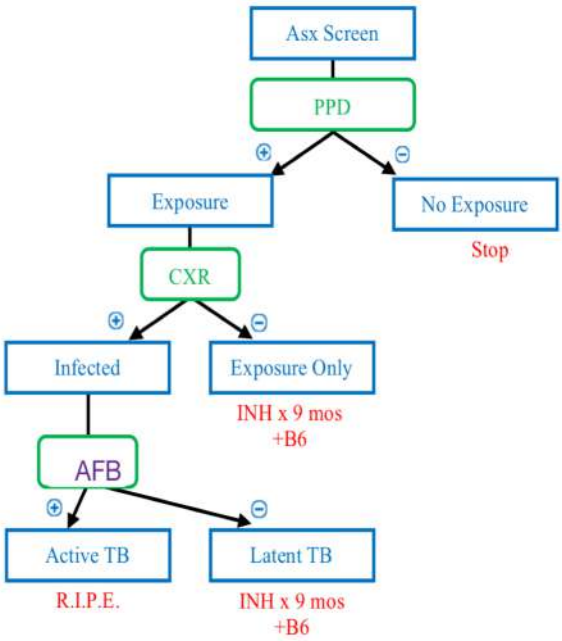
Airborne precautions

- Used for the care of patients with suspected or confirmed infection capable of spreading via the dissemination of smaller droplets (i.e., particulates and aerosols < 5 µm in size), such as tuberculosis, measles, varicella, smallpox, and severe acute respiratory syndrome (SARS) infections
- Patients should be kept in airborne infection isolation rooms (AIIRs) with constant negative air pressure and frequent air changes (6–12 air cycles/hour) to prevent the contaminated air from escaping.
- Individuals must wear PPE, including an N95 respirator (or a higher-level respirator), when entering the room.
- Minimize transport of patients and mask them if it is mandatory.
- Implement hand hygiene after contact with respiratory secretions.

Criteria for Patients to Be Considered Noninfectious

Criteria
Patients can be considered noninfectious when they meet all of the following three criteria:
1. They have three consecutive negative AFB sputum smears collected in 8- to 24-hour intervals (at least one being an early morning specimen);
2. Their symptoms have improved clinically (for example, they are coughing less and they **no longer** have a fever); **and**
3. They are compliant with an adequate treatment regimen for 2 weeks or longer.

- Apply modalities of diagnostics for latent and active TB.



patient is symptomatic, has a positive PPD, or a positive Gamma-Interferon Assay, a chest x-ray is required to assess for active disease. In these patients, the chest x-ray will also serve as their annual screen (once the PPD is positive, it'll always be positive). If the CXR and they've never been treated, they require Isoniazid + B6 x 9 months.

If CXR an active infection must be ruled out with AFB smears. This is a good time to isolate the individual. If the AFB Smear positive , there's an active infection; treat with RIPE. If the AFB Smear negative , the patient has latent TB; treat with Isoniazid + B6 x 9 months.

For the acutely ill patient there's no need (or time) to wait the 48-72 hrs of the PPD. First do a CXR looking for apical lesions. However, if there's a CXR it's insufficient to rule out active disease; an AFB Smear and Culture must also be done. If the disease is suspected a positive confirmation is desired.

Diagnosis of active TB			
Test	**Characteristics**	**Advantages**	**Disadvantages**
Bacteriological confirmation			
Acid-fast bacilli smear microscopy	●Ziehl Neelsen stain and auramine rhodamine stain are used	●Rapid detection ●Inexpensive	●Low sensitivity ●Cannot differentiate M. tuberculosis from other nontuberculous mycobacteria ●Both viable and nonviable mycobacteria will stain.
PCR	●Used as an adjunct along with acid-fast staining and culture	●High sensitivity ●Rapid diagnosis ●Rapid detection of drug-resistant strains ●Species identification	●Expensive ●Cannot be used in resource-limited settings.
Culture	●Gold standard diagnostic test ●Used for drug susceptibility testing	●High sensitivity ●Species identification ●Identification of drug resistance	●Long time for positive cultures to develop ●Delays the initiation of treatment, especially drug-resistant TB
Radiological confirmation			
Chest x-ray [58]	●Primary TB (middle/lower lobes) ○Hilar lymphadenopathy (can be unilateral or bilateral) ○Ghon complex ○Consolidation ○Pleural effusion ○Cavitation (primary progressive TB) ●Reactivation TB: fibrocaseous cavitary lesions in upper lobes	●Inexpensive	●Low specificity ●Variability in interpretation

Diagnosis of latent TB		
	Tuberculin skin test (purified protein derivative test, Mantoux test)	**Interferon-γ release assay (IGRA)**
Mechanism	• Tests cell-mediated immunity against *M. tuberculosis* through delayed hypersensitivity reaction (type IV HSR) mounted by T cells	• Tests cell-mediated immunity against *M. tuberculosis*-specific antigens by measuring the amount of IFN-γ released by T cells
Procedure	• Step 1: 0.1 mL (or 5 units) of PPD injected intradermally on the volar surface of forearm resulting in wheal formation • Step 2: transverse diameter of palpable induration checked 48–72 hours later	• Blood is drawn into tubes coated with *M. tuberculosis*-specific antigens • ELISA test measures the amount of IFN-γ released by T cells after antigen exposure.

Interpretation	• Positive TST indicates active TB or latent TB
	• ≥ 5 mm is considered positive in:
	  ◦ Close contacts of patients with TB
	  ◦ HIV infection
	  ◦ Individuals with clinical or radiographic evidence of active or prior TB
	  ◦ Individuals with organ transplants or receiving immunosuppressive therapy
	• ≥ 10 mm is considered positive in:
	  ◦ Individuals who have moved within the last 5 years from a high TB burden country (> 20 cases per 100,000 population) [57]
	  ◦ Individuals living or working in high-risk settings (e.g., homeless shelters, prisons)
	  ◦ Intravenous drug users
	  ◦ Mycobacteriology laboratory workers
	  ◦ Individuals with illnesses such as diabetes and CKD
	  ◦ Children < 5 years of age
	  ◦ Children who have had contact with adults in high-risk categories
	• ≥ 15 mm is considered positive in all other individuals.
		• Positive test indicates active TB or latent TB
		• Negative
		• Indeterminate, and commonly seen in:
		  ◦ Immunosuppressed states
		  ◦ Children < 5 years of age

Benefits	• Inexpensive • Preferred test in children < 5 years of age	• Only requires a single office visit • Preferred test in individuals with prior BCG vaccination • Results are available within 24 hours. [60]

Limitations	• No differentiation between active and latent TB
	• Variability in test interpretation
	• Requires two office visits
	• False positives resulting from either of the following:
	  ◦ Prior BCG vaccination
	  ◦ Exposure to nontuberculous mycobacteria
	• False negatives in any of the following:
	  ◦ Sarcoidosis
	  ◦ Immunosuppressed state (anergy)
	  ◦ Young children
	  ◦ Recent TB infection (within 6–8 weeks)
	  ◦ Recent live-virus vaccine
	  ◦ Disseminated TB
		• No differentiation between active and latent TB
		• Expensive
		• Requires phlebotomy
		• Errors in collecting and transporting blood can decrease accuracy.

- Recognize and list treatment of active/latent tuberculosis.

❖ **Active TB:**

First-line drugs for tuberculosis		
	Duration of treatment	Common side effects
Rifampin	• 6 months	• Hepatotoxicity • Orange discoloration of body fluids (e.g., urine, tears) • Cytochrome P450 inducer (rifabutin is preferred in patients with HIV who are on HAART) • Thrombocytopenia • False positive result on urine opiate screening [66]

Isoniazid	• 6 months	• Hepatotoxicity
		• Cytochrome P450 inhibitor
		• Drug-induced lupus
		• Vitamin B6 deficiency (prevented with pyridoxine use)
		  ◦ Peripheral neuropathy
		  ◦ Sideroblastic anemia
		• CNS toxicity
		  ◦ High doses of INH can precipitate benzodiazepine-refractory seizures.
		  ◦ Psychosis
		  ◦ Ataxia
		• Anion gap metabolic acidosis
		• Pellagra
		• Optic neuritis

Pyrazinamide	• 2 months	• Hepatotoxicity • Hyperuricemia • Arthralgia • Photosensitivity
Ethambutol	• 2 months	• Optic neuritis (reversible red-green color blindness) • Hyperuricemia [67]

❖ **Latent TB:**

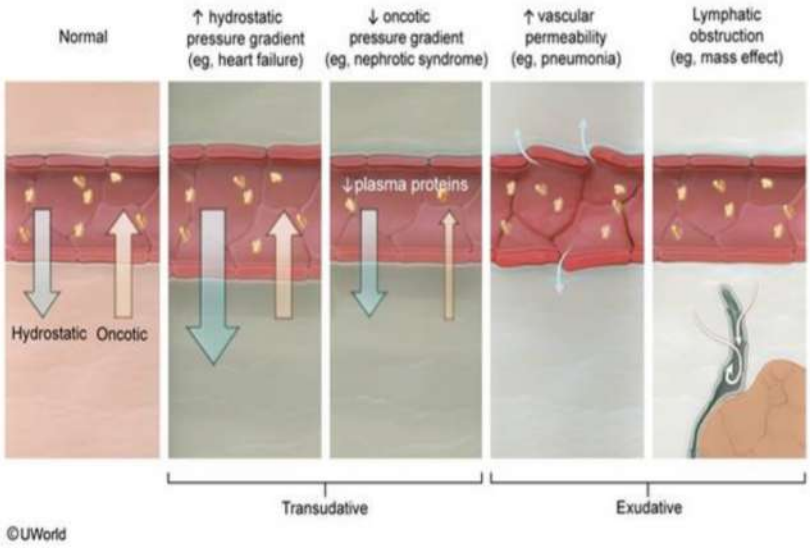
Indication: positive IGRA or TST

Treatment of latent TB		
Drug(s)	Frequency	Duration of therapy
Preferred regimens		
Isoniazid PLUS rifapentine	• Once weekly	• 3 months
Rifampin (OR rifabutin)	• Daily	• 4 months
Isoniazid PLUS rifampin	• Daily	• 3 months
Alternative regimen		
Isoniazid	• Daily or twice weekly	• 6 months
		• 9 months

- To apply light's criteria to differentiate between exudative and transudative pleural effusion

Exudative & transudative pleural effusions		
	Exudate	**Transudate**
Light criteria	• Pleural fluid protein/serum protein ratio >0.5 OR • Pleural fluid LDH/serum LDH ratio >0.6 OR • Pleural fluid LDH >two-thirds upper limit of normal of serum LDH	• Exudate criteria not met
Pathophysiology	• Inflammation	• Hydrostatic or oncotic pressure
Common causes	• Infection (eg, pneumonia) • Malignancy • Rheumatologic disease	• Heart failure • Cirrhosis (hepatic hydrothorax) • Nephrotic syndrome
LDH = lactate dehydrogenase.		

Causes of pleural effusion



Pulmonary Hypertension

- Recognize clinical features, classification & common causes of pulmonary hypertension.

Group 1: Pulmonary arterial hypertension (PAH) Idiopathic, familial, veno-occlusive disease, and PAH with associated conditions (connective tissue disorders, congenital shunting, HIV, drugs and toxins) An abnormal increase in pulmonary arteriolar resistance leads to thickening of pulmonary arteriolar walls. This worsens the pulmonary HTN, which in turn causes further wall thickening, thus leading to a vicious cycle. The cause is unknown; it usually affects young or middle-aged women. The prognosis is poor. Mean survival is 2 to 3 years from the time of diagnosis.

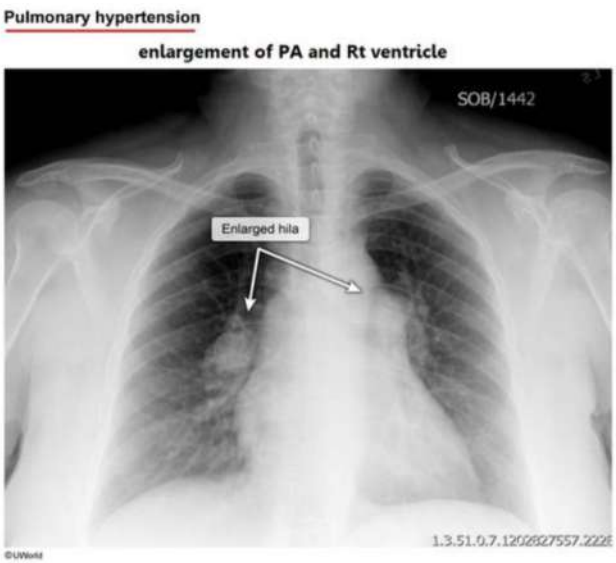
Group 2: Left heart disease Secondary to any cause of left heart failure, including mitral stenosis and mitral regurgitation

Group 3: Lung disease and/or chronic hypoxemia Causes include ILD, COPD, OSA, and any other cause of chronic hypoxemia

Group 4: Chronic thromboembolic disease Recurrent PE (many patients do not have symptoms of PE), including nonthrombotic etiologies (e.g., tumor emboli)

Group 5: Miscellaneous Pulmonary vascular compression (e.g., tumors or lymphadenopathy), sarcoidosis, Langerhans cell histiocytosis, etc.

Pulmonary hypertension	
WHO classification	
Pulmonary arterial hypertension (Group 1)	• Primary change in pulmonary arteries ○ Hereditary (eg, *BMPR2* mutation) ○ Connective tissue disease (eg, RA, SS) ○ HIV infection • Treatment targeted at endothelial dysfunction
Pulmonary hypertension (Groups 2-5)	• Secondary to another disease process ○ Left-sided heart failure ○ Chronic lung disease/hypoxia ○ Chronic pulmonary thromboembolism • Treatment aimed at underlying disease
Symptoms	• Dyspnea, fatigue/weakness • Exertional angina • Syncope • Abdominal distention/pain
Signs	• 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



Apply modalities of diagnostics for pulmonary hypertension

1. ECG: Often suggests right ventricular hypertrophy—specifically, right-axis deviation and right atrial abnormality are frequently present
2. CXR: Enlarged pulmonary arteries with or without clear lung fields based on the cause of pulmonary hypertension
3. Echocardiogram
    a. Dilated pulmonary artery
    b. Dilatation/hypertrophy of RA and RV
    c. Abnormal movement of IV septum (due to increased right ventricular volume)
4. Right heart catheterization: required for confirmatory diagnosis of pulmonary HTN. Reveals increased mean pulmonary artery pressure >25 mm Hg

Understand the basics of management of pulmonary hypertension

1. One specific treatment plan cannot be recommended due to the variety of causes of pulmonary HTN. If the pulmonary HTN is secondary to another disease process (e.g., recurrent PE), then the underlying disease should be treated and optimized.
2. Vasoactive agents are typically used in PAH (Group 1), since trials have been done in this group.
    a. Right heart catheterization with a trial of vasodilators should precede the use of these agents.
    b. Vasoactive agents may lower pulmonary vascular resistance in some patients.
        i. Available options include inhaled nitric oxide, phosphodiesterase inhibitors (e.g., sildenafil), oral CCBs, prostacyclins (e.g., epoprostenol), and endothelin receptor antagonists (e.g., bosentan).
3. Many patients require home oxygen, diuretics, and occasionally inotropes (e.g., digoxin).
4. Lung transplantation in qualified patients.

Interpretation of Chest Radiographs

- To be able to differentiate between different views.
- To recognize what is normal and abnormal.
- Adapt a systematic approach to a chest x-ray interpretation.
- To be able to recognize common & important diseases based on chest x-rays.

Go back to the lecture + you can check the link below https://geekymedics.com/chest-x-ray-interpretation-a-methodical-approach/

Cardiovascular Disorders

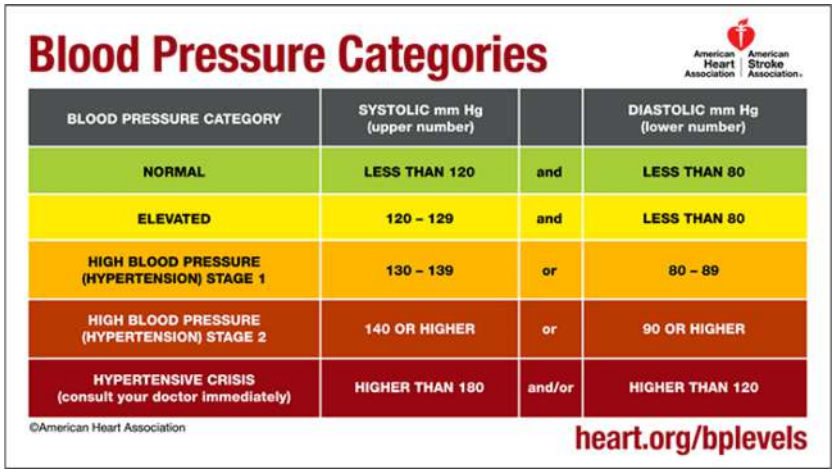
Lectures List

Cardiovascular disorders	
1	Hypertension - Understand the definition of hypertension. - Differentiate between essential and secondary hypertension. - To be able to recall the consequences of sustained hypertension. - List the initial testing for patients diagnosed with hypertension. - To be able to formulate a general plan for the management of hypertension
2	Coronary artery disease - Differentiate between stable and unstable angina and develop an approach plan. - Recognize ST-Elevation myocardial infarction (STEMI) and know the management guidelines for STEMI - Recall the general guidelines in the management of non-ST-Elevation myocardial infarction. - Understand the importance of modification of risk factors in the prevention and management of coronary artery disease..
3	Valvular disease (including endocarditis) - To be able to identify patients with the valvular disease based on symptoms and clinical findings. - Implement diagnostics to identify the valvular heart disease and to establish the severity - Recall general key points in the management of valvular heart disease. - Identify the risk factors and the presentation for infective endocarditis. - Initiate investigation plan and enlist key points in the management for infective endocarditis - List indications for infective endocarditis prophylaxis.
4	Diseases of Myocardium and pericardium - To be able to identify clinically patient with suspected pericardial disease (acute pericarditis, pericardial effusion/tamponade, constrictive pericarditis) - Initiate investigation plan and enlist key points in the management for patient with pericardial disease - To be able to identify clinically patient with suspected myocardium disease (HCM, RCM) - Initiate investigation plan and enlist key points in the management for patient with myocardium diseases
5	Arrhythmia and ECG abnormality - To be able to approach patients with symptomatic bradycardia. - To be able to approach patients with sinus tachycardia. - Define the atrial fibrillation and its complications and be able to initiate therapy. - Identify ventricular arrhythmias based on ECG and initiate a management plan. - Identify atrial fibrillation and heart blocks on ECG.
6	Heart failure - Understand the pathophysiology of heart failure. - Identify the symptoms and signs suggestive of heart failure - List the initial diagnostic testing for patients presenting with heart failure. - To able to describe the treatment strategies used in heart failure.

Hypertension

- Understand the definition of hypertension

Definition of hypertension in adults: persistent systolic blood pressure of ≥ 130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg



Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

heart.org/bplevels

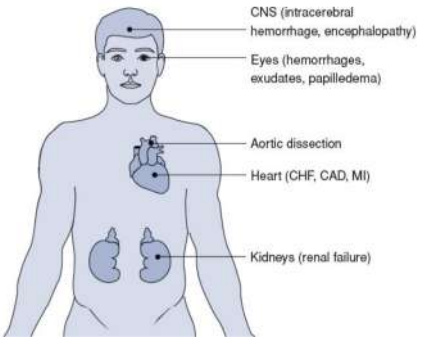
- Differentiate between essential and secondary hypertension

- Essential hypertension (HTN)
  - There is no identifiable cause
- Secondary HTN has many identifiable causes.
  - Renal/renovascular disease, renal artery stenosis (most common cause of secondary HTN), chronic renal failure, polycystic kidneys.
  - Endocrine causes-hyperaldosteronism, thyroid or parathyroid disease, Cushing syndrome, pheochromocytoma, acromegaly.
  - Medications- oral contraceptives, decongestants, estrogen, appetite suppressants, chronic steroids, tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Coarctation of the aorta.
  - Cocaine, other stimulants.
  - Obstructive sleep apnea (OSA).

RECENT: **R**enal (e.g., renal artery stenosis, glomerulonephritis), **E**ndocrine (e.g., Cushing syndrome, hyperthyroidism, Conn syndrome), **C**oarctation of the aorta, **E**strogen (oral contraceptives), **N**eurologic (raised intracranial pressure, psychostimulants use), **T**reatment (e.g., glucocorticoids, NSAIDs) are the causes of secondary hypertension.

- To be able to recall the consequences of sustained hypertension.

  - Cardiovascular system
    - Left ventricular hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy
    - Congestive heart failure
    - Coronary artery disease and myocardial infarction
    - Atrial fibrillation
    - Aortic aneurysm
    - Aortic dissection
    - Carotid artery stenosis
    - Peripheral artery disease
    - Atherosclerosis
  - Brain
    - Stroke , TIA
    - Subcortical leukoencephalopathy
    - Cognitive changes such as memory loss
  - Kidneys
    - Hypertensive nephrosclerosis
    - Chronic kidney disease
  - Eyes



Classification system according to Keith-Wagener-Barker [11]		
	Findings	Symptoms
Grade I	Vessel diameter variation: arteriolar constriction and tortuosity	Usually asymptomatic
Grade II	Gunn sign and marked constriction of vessels and sclerosis of arterioles	
Grade III	Cotton-wool exudates, hard exudates, retinal hemorrhage, retinal edema, macular star formation	Decreased and/or blurred vision, headaches
Grade IV	Papilledema, optic atrophy	

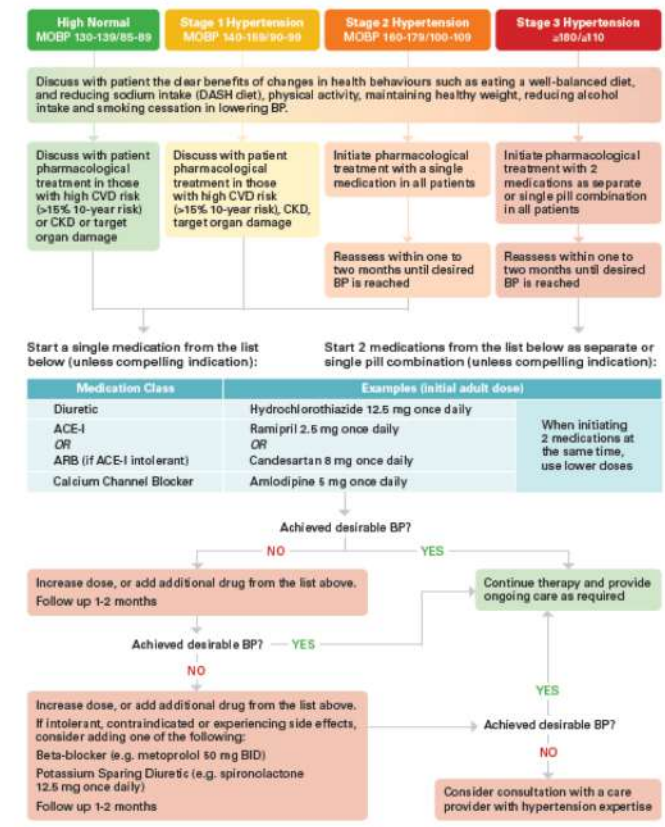
- List the initial testing for patients diagnosed with hypertension.

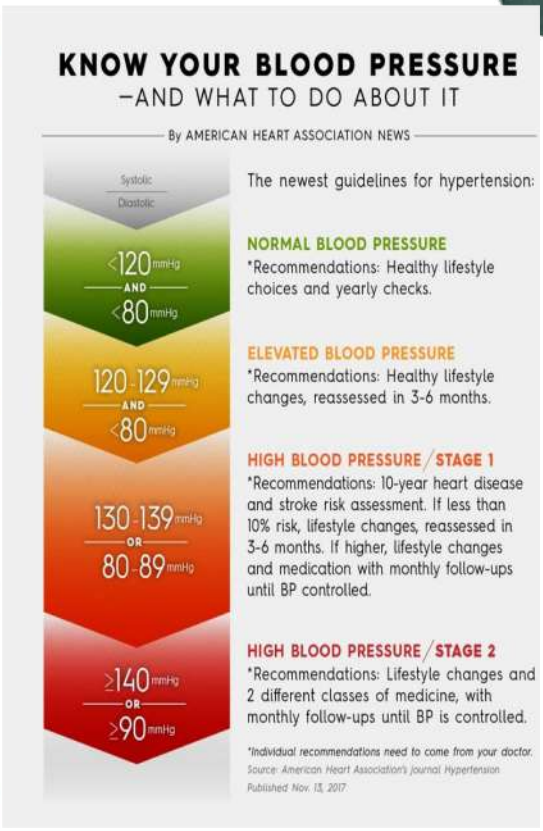
❖ **Basic investigations:**

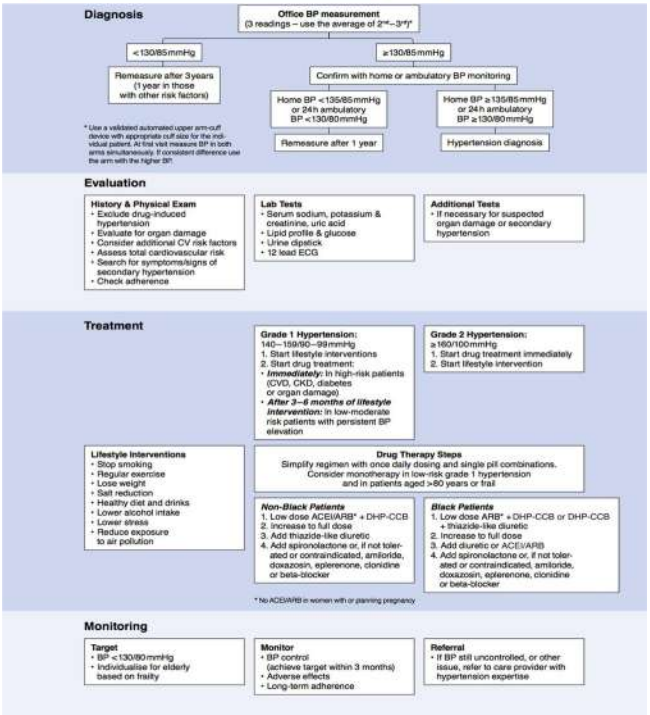
1. Urinalysis (protein, glucose, blood, casts)
2. Blood chemistry: potassium, sodium, creatinine with e-GFR, fasting blood glucose,
3. and serum uric acid
4. Complete fasting lipid profile
5. Hemoglobin and hematocrit
6. Electrocardiography (ECG)
7. Additional optional investigations, if needed:
   a. TSH, free T4
   b. CXR
   c. Abdominal Sonography
   d. Echocardiography

- To be able to formulate a general plan for the management of hypertension

Figure 4: Management of Hypertension







- For adults with confirmed hypertension and known CVD, or 10-year ASCVD event risk of 10% or higher, a BP goal of less than 130/80 mm Hg is recommended. For adults without additional markers of increased CVD risk, a BP goal of less than 130/80 mm Hg may also be reasonable.
- old people (>75) and African Americans (AA) don't get an Ace-I / Arb to start.
- CKD (even if you are old or AA) patients get an Ace-I / Arb as the first medication.

Coronary artery disease

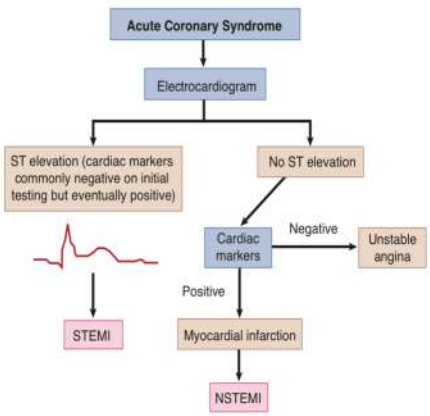
- Differentiate between stable and unstable angina and develop an approach plan.

Overview of acute coronary syndrome (ACS) [1][2]

	NSTE-ACS		STE-ACS
	Unstable angina (UA)	**Non-ST-segment elevation myocardial infarction (NSTEMI)**	**ST-segment elevation myocardial infarction (STEMI)**
Description	• Acute myocardial ischemia that is not severe enough to cause detectable quantities of myocardial injury biomarkers or ST-segment elevations on ECG	• Acute myocardial ischemia that is severe enough to cause detectable quantities of myocardial injury biomarkers but without ST-segment elevations on ECG	• Acute myocardial ischemia that is severe enough to cause ST-segment elevations on ECG
Clinical presentation	• Symptoms are not reproducible/predictable. • **Angina** at rest/with minimal exertion and is usually not relieved by rest or nitroglycerin [3] • New-onset angina • Severe, persistent, and/or worsening angina (**crescendo angina**) • **Autonomic symptoms** may be present: diaphoresis, syncope, palpitations, nausea, and/or vomiting		
Pathophysiology	• **Partial occlusion** of coronary vessel → decreased blood supply → ischemic symptoms (also at rest)	• Classically due to partial occlusion of a coronary artery • Affects the inner layer of the heart (**subendocardial infarction**)	• Classically due to complete occlusion of a coronary artery • Affects the full thickness of the myocardium (**transmural infarction**)
Cardiac troponin	• **Not elevated**	• **Elevated**	• Usually elevated
ECG findings	• **No ST elevations**	• **No ST elevations** • Normal or nonspecific (e.g., ST depression, loss of R wave, or T-wave inversion)	• **ST elevations** (in two contiguous leads) or new **left bundle branch block** with strong clinical suspicion of myocardial ischemia [1]
Treatment	• Invasive management depends on risk stratification (e.g., TIMI score) • Anticoagulants, antiplatelet therapy (e.g., aspirin, ADP receptor inhibitors) • Statins • Antihypertensive therapy (beta blockers, ACEIs) • Pain management (opioids, nitrates) • See "Acute management checklist for NSTE-ACS."		• **Immediate revascularization** • Adjunctive medical therapy similar to NSTE-ACS • See "Acute management checklist for STEMI."

❖ Diagnosis

1. Rule out the most severe disease (STEMI) first with a 12-Lead ECG looking for ST-segment elevations or a new LBBB. STEMI goes to **emergent cath.**
2. If negative rule out NSTEMI with biomarkers (Troponin-I). NSTEMI goes to **urgent cath.**
3. If both the troponins and the ECG are negative, you're left considering if this pain is coronary in nature at all. This can be determined using the stress test. If the stress test is positive, go to **elective cath.**



- Recognize ST-Elevation myocardial infarction (STEMI) and know the management guidelines for STEMI

"A **46 y/o man** known to have **DM** and **HTN** comes to the ER with **central crushing** chest pain"
this is a typical scenario for an ACS pt. and to differentiate between the types we need to do the following investigations

1- **ECG:** to monitor the ST elevation.
2- **CK-MB:** released in MI pt.(4-6 h) after the onset and then falls within (48-72h)
3- **Troponin:** released in MI pt. (4-6 h) and can last up to 2 weeks.

Pharmacological Therapy

1. Increase O2 supply

Vasodilators: Nitroglycerine	Antiplatelet: Aspirin + P2Y12 inhibitor: clopidogrel, ticagrelor and prasugrel.	Antithrombotic: Unfractionated Heparin or Low Molecular Heparin.

2. Reduce O2 demand

Beta blockers: acebutolol, atenolol, propranolol ... etc.	Analgesics for the pain

3. Other medications

ACE inhibitors: captopril, benazepril ... etc.	Statin therapy

Reperfusion Therapy

1. Fibrinolytic

For STEMI only!!

Used within the first 12 hours after the onset of the symptoms

2 types: Non-fibrin specific: streptokinase
Fibrin specific: tenecteplase (TNK) – alteplase reteplase

Absolute contraindication (never use fibrinolytics):

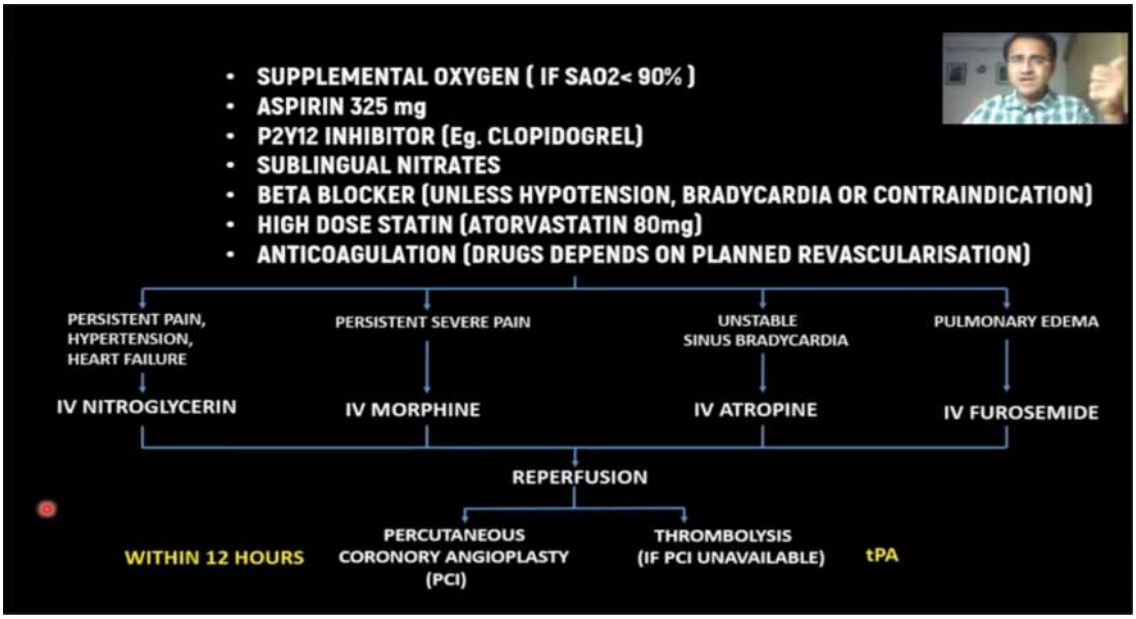
Prior intracranial hemorrhage
cerebral vascular lesions
intracranial neoplasm
suspected aortic dissection
ischemic stroke within the past 3 months
active bleeding or known bleeding disorder
recent close-head trauma / surgery within 3 months

Relative contraindication where it depends on the doctor's decision:

Oral anticoagulant, pregnancy\ 1 week postpartum, internal bleeding (peptic ulcer)… etc.

2. Primary PCI

- Preferred treatment for STEMI
- Best time time to open the artery is within 60 minutes



- Recall the general guidelines in the management of non-ST-Elevation myocardial infarction.

- Same as STEMI but **without** the fibrinolytics
- Patients with NSTEMI who have:
  - unstable hemodynamics
  - intractable angina
  - suspected posterior infarction
  - and/or left main-vessel occlusion

  require **urgent PCI (< 2 hours)**, even if no ST elevations are present.
- Fibrinolytic therapy is not indicated in patients with unstable angina or NSTEMI.

- Understand the importance of modification of risk factors in the prevention and management of coronary artery disease

Chronic Therapy

1. Adjust risk factors:
   a. HDL – High potency statin. Old LDL goal < 100. Now, start **statin**.
   b. DM – tight glucose control to near normal values (80-120 or HbA1C < 7%) with **oral medications** or **insulin**.
   c. HTN – regular control of blood pressure to <140 / <90 with **Beta-Blockers** (reduce arrhythmias) and **ACE-inhibitors**.
   d. Titrate heart rate to between 50-65 bpm and 75% of the heart rate that produced symptoms on stress test.
2. Reduce Risk of Thrombosis
   a. Aspirin (Cox-Inhibitor) is the standard therapy.
   b. Clopidogrel (ADP-inhibitor) can be used, but is indicated for stents only.
3. Surgical Management
   a. Surgical management choices are Stent or CABG.
   b. The decision is made based on the severity of occlusive disease.
      i. If it's really bad (i.e. requires multiple stents) do a CABG.
      ii. If the atherosclerosis is global, distal, or microvascular then medical management only may suffice.

Mnemonic (discharge medications after ACS) : ABCDE
A: Aspirin and anti-anginals
B : Beta blockers and blood pressure
C : Cholesterol and cigarettes
D : Diet and diabetes
E : Education and exercise

Valvular disease
(including endocarditis)

- To be able to identify patients with the valvular disease based on symptoms and clinical findings.

Symptoms:

- Dyspnea Commonest (present for all valves)
- paroxysmal nocturnal dyspnea
- orthopnea
- Palpitation
- Fatigue due to low cardiac output
- Chest pain is typical of **Aortic stenosis**
- Dizziness , pre-fainting , syncope present in **Aortic stenosis.**
- Oedema , Ascites typical of **tricuspid regurgitation**
- Cough. due to the increase in pulmonary artery pressure from **mitral stenosis**
- Hemoptysis due to **mitral stenosis** (precisely from the high pulmonary artery pressure)
- Symptoms of thromboembolic complication (clot formation due to atrial fibrillation)

Signs of Valvular heart disease

- Abnormal look (mitral facies)
- Abnormal pulse (Atrial fibrillation = irregularly irregular pulse)
- Abnormal JVP due to right sided heart failure
- Apex beat abnormality if shifted from 5th intercostal space it means the heart is enlarged (but you should also check the trachea because the whole hilum or mediastinum may be shifted)
- Sternal or parasternal heave in pulmonary hypertension and right ventricular hypertrophy
- Thrill murmur at the apex, base of the heart and aortic area
- Abnormal heart sound
- Murmurs (systolic or diastolic)

Auscultation in valvular defects			
	Maximum point	Murmur	Characteristics
Aortic stenosis	• Aortic valve (parasternal 2nd right intercostal space) • Erb point	• **Harsh crescendo-decrescendo systolic ejection murmur**	• Radiation to the carotids • Soft S_2 • Possibly ejection click
Aortic regurgitation	• Aortic valve (parasternal 2nd right ICS) • Erb's point	• **Diastolic murmur** with a **decrescendo** • Possible additional quiet systolic murmur	• Immediately following the 2nd heart sound ("immediate diastolic murmur") • Austin Flint Murmur
Mitral stenosis	• Heart apex (midclavicular 5th left ICS)	• Delayed **diastolic murmur** with a **decrescendo**	• "Tympanic" 1st heart sound • Mitral opening murmur/opening snap (OS)
Mitral valve prolapse	• Heart apex (midclavicular 5th left ICS)	• **Late-systolic crescendo**	• Midsystolic high-frequency click (due to the tensing of the chordae tendinae) • Loudest before S_2
Mitral regurgitation	• Heart apex (midclavicular 5th left ICS) • Left axilla	• Holosystolic murmur • 3rd heart sound audible • Quiet 1st heart sound	• Blowing • Radiation into the axilla
Pulmonary stenosis	• Pulmonary valve (parasternal 2nd left ICS)	• Crescendo-decrescendo ejection systolic murmur	• Possible radiation into the back • Possible early systolic pulmonary ejection click and/or widely split 2nd heart sound
Pulmonary regurgitation	• Pulmonary valve (parasternal 2nd left ICS)	• Diastolic murmur with a decrescendo	• Graham Steel murmur: high-frequency decrescendo diastolic murmur
Tricuspid stenosis (extremely rare)	• Tricuspid valve (parasternal 4th left ICS)	• Delayed diastolic murmur with a decrescendo • Possible pre-systolic crescendo	
Tricuspid regurgitation (extremely rare)	• Tricuspid valve (parasternal 4th left ICS)	• Holosystolic murmur	• Augmentation of the murmur's intensity with inspiration (**Carvallo sign**)

Systolic murmurs: aortic/pulmonary stenosis, mitral/tricuspid regurgitation
Diastolic murmurs: aortic/pulmonary regurgitation, mitral/tricuspid stenosis

Heart sounds:
S1: closure of AV valves
S2: closure of semilunar valves
S3: filling of ventricles "passive"
S4: (atrial kick) atrial contraction to force blood into the left ventricle "active"

- Implement diagnostics to identify the valvular heart disease and to establish the severity

Dx & workup

- ECG
- CXR
- Echocardiography
- Holter monitor
- MRI
- Cardiac catheterization
- Exercise test

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000923

Table 3. Stages of Progression of VHD

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD:
		C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated
		C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

VHD indicates valvular heart disease.

❖ **Mitral regurgitation:**

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	At risk of MR	• Mild mitral valve prolapse with normal coaptation • Mild valve thickening and leaflet restriction	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.3 cm	• None	• None
B	Progressive MR	• Severe mitral valve prolapse with normal coaptation • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE	• Central jet MR 20%–40% LA or late systolic eccentric jet MR • Vena contracta <0.7 cm • Regurgitant volume <60 mL • Regurgitant fraction <50% • ERO <0.40 cm^2 • Angiographic grade 1–2+	• Mild LA enlargement • No LV enlargement • Normal pulmonary pressure	• None
C	Asymptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension may be present at rest or with exercise • **C1:** LVEF >60% and LVESD <40 mm • **C2:** LVEF ≤60% and LVESD ≥40 mm	• None
D	Symptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension present	• Decreased exercise tolerance • Exertional dyspnea

❖ Mitral stenosis:

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	• Mild valve doming during diastole	• Normal transmitral flow velocity	• None	• None
B	Progressive MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA >1.5 cm^2	• Increased transmitral flow velocities • MVA >1.5 cm^2 • Diastolic pressure half-time <150 ms	• Mild-to-moderate LA enlargement • Normal pulmonary pressure at rest	• None
C	Asymptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS)	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• None
D	Symptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• Decreased exercise tolerance • Exertional dyspnea

❖ Aortic stenosis:

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis	• Aortic V_{max} <2 m/s	• None	• None
B	Progressive AS	• Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or • Rheumatic valve changes with commissural fusion	• Mild AS: Aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mm Hg • Moderate AS: Aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	• Early LV diastolic dysfunction may be present • Normal LVEF	• None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) • Very severe AS is an aortic V_{max} ≥5 m/s or mean ΔP ≥60 mm Hg	• LV diastolic dysfunction • Mild LV hypertrophy • Normal LVEF	• None: Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2)	• LVEF <50%	• None

Grades of AS

what you have to know
(Severe AS)

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Peak Velocity (m/s)	≤ 2.5 m/s	2.6 - 2.9	3.0 - 4.0	≥ 4.0
Mean gradient (mmHg)	-	< 20	20 - 40	≥ 40
AVA (cm2)	-	>1.5	1.0 - 1.5	< 1
Indexed AVA (cm2/m2)	-	> 0.85	0.60 - 0.85	< 0.6

- Recall general key points in the management of valvular heart disease.

1. **Symptomatic:**

- Treatment of heart failure
- Endocarditis prophylaxis
- Prevention of thromboembolism (if necessary)

1. **Surgery:**

The choice of procedure is based on the patient's individual risk profile and an evaluation of benefits.

- **Valve reconstruction (annuloplasty)**
  - Procedure: ring-shaped device attached to the outside of the valve opening to re-establish shape and function of valve
  - Reduced thromboembolic risk compared to mechanical prosthetic valve; but high risk of recurrent stenosis
  - Lower mortality rate than valve replacements, though replacements are more durable
- **Prosthetic valve replacement**
  - Immunosuppression not necessary

Prea load reduction for stenosis
After load reduction for regurgitation

❖ **Treatment of MS**

- **Medical therapy:**
  - diuretics and salt-restricted diet
  - digitalis to control the ventricular rate in patients with AF
  - anticoagulants in patients with AF
  - balloon valvotomy (standard of care for MS).

- **Surgical management:**
  - is indicated when patient remains symptomatic (functional class III) despite medical therapy.
  - Mitral commissurotomy or valve replacement is done if balloon dilation fails.
  - Pulmonary hypertension is not a contraindication for surgery.

❖ **Treatment of MR**

- **Medical therapy:**
  - the goal is to relieve symptoms by increasing forward cardiac output and reducing pulmonary venous hypertension.
  - ARBs/hydralazine, arteriolar vasodilators (ACE inhibitors), digitalis, and diuretics are used.
- **Surgical therapy**.
  - Mitral valve replacement is indicated when symptoms persist despite optimal medical management.
  - Indicated with significantly limiting symptoms and severe mitral regurgitation
  - the risk of surgery rises in chronic heart failure.
  - Repair is preferable to replacement.
  - Patients with regurgitation but few symptoms should defer surgery, as their condition may remain stable for years.

❖ **Treatment of AS**

- Surgery (valve replacement) is advised when symptoms develop usually when the valve area is reduced <0.8 cm2 (normal aortic orifice, 2.5–3 cm2)
- Generally, if patient has symptoms, surgery is the treatment of choice
- Balloon valvuloplasty may be useful in those too ill to tolerate surgery.

❖ **Treatment of AR**

- **Medical therapy:**
  - Salt restriction, diuretics, after load reduction (e.g., ACE inhibitors)
  - Vasodilators such as an ACE, ARB, or nifedipine are the standard of care.
- **Surgical management:**
  - Aortic valve replacement when symptoms worsen or ejection fraction decreases.
  - Perform aortic valve replacement when the ejection fraction is <50% with HF symptoms (NYHA level II-IV) or left ventricular systolic diameter is >55 mm.

- Identify the risk factors and the presentation for infective endocarditis.

❖ **Risk factors:**

- **Demographics**
  - Male sex
  - Age > 60 years
- **Cardiac conditions**
  - Acquired valvular disease (e.g., rheumatic heart disease, aortic stenosis, degenerative valvular disease)
  - Prosthetic heart valves
  - Congenital heart defects (e.g., VSD, bicuspid aortic valve)
  - Previous IE
- **Noncardiac risk factors**
  - Poor dental status
  - Dental procedures
  - Non Sterile venous injections (e.g., in IV drug use)
  - Intravascular devices
  - Surgery
  - Chronic hemodialysis
  - Immunocompromised (e.g., HIV infection, diabetes)
  - Other bacterial infections (e.g., UTIs, spondylodiscitis, periodontal infection)

❖ **Clinical manifestations:**

Table 7-6. Incidence of Clinical Findings in Infective Endocarditis

Symptoms, %	Signs, %
Chills, 41	Heart murmur or changing murmur, 80–90
Weakness, 38	Fever, 90
Dyspnea, 36	Embolic events, 50
Sweats, 24	Skin manifestations, 50
Anorexia, weight loss, 24	Splenomegaly, 28
Malaise, 24	Septic complications, 19
Cough, 24	Mycotic aneurysms, 18
Skin lesions, 21	Glomerulonephritis, 10
Stroke, 18	Digital clubbing, 12
Nausea, vomiting, 17	Retinal lesions, 5
Chest pain, 16	

Table 7-7. Peripheral Manifestations of Infective Endocarditis

Physical Findings (Frequency)	Pathogenesis	Most Common Organisms
Petechiae (20–30%): red, nonblanching lesions in crops on conjunctivae, buccal mucosa, palate, extremities	Vasculitis or emboli	*Streptococcus, Staphylococcus*
Splinter hemorrhages (15%): linear, red-brown streaks most suggestive of IE when proximal in nailbeds	Vasculitis or emboli	*Staphylococcus, Streptococcus*
Osler's nodes (5–10%): 2–5 mm painful nodules on pads of fingers or toes	Vasculitis	*Streptococcus*
Janeway lesions (10–15%): macular, red, or hemorrhagic, painless patches on palms or soles	Emboli	*Staphylococcus*
Roth's spots (<5%): oval, pale, retinal lesions surrounded by hemorrhage	Vasculitis	*Streptococcus*

- Initiate investigation plan and enlist key points in the management for infective endocarditis

❖ **Diagnosis:**

To diagnose endocarditis use **Duke clinical criteria**: Two Major Criteria, one major and three minor criteria, or five minor criteria are required to diagnose infective endocarditis.

- major criteria are: positive blood cultures and abnormal echocardiogram.
  - The sensitivity of transthoracic echo is <60%, but its specificity is excellent.
  - Transesophageal echo is >90% sensitive and >95% specific.
- The minor criteria are:
  - Fever
  - Predisposing cardiac lesion
  - IV drug use
  - Vascular phenomena (arterial embolic, septic pulmonary infarcts, Janeway lesions),immunologic phenomena (such as Osler nodes, Roth spots, glomerulonephritis, or a positive rheumatoid factor)
  - Microbiologic evidence (positive blood cultures not meeting major criteria or evidence of active infection with an organism consistent with infective endocarditis)

TABLE 1-3 Duke Criteria

Major	Minor
• **Sustained bacteremia** by an organism known to cause endocarditis • **Endocardial involvement** documented by either echocardiogram (vegetation, abscess, valve perforation, prosthetic dehiscence) or clearly established **new valvular regurgitation**	• **Predisposing condition** (abnormal valve or abnormal risk of bacteremia) • **Fever** • **Vascular phenomena:** Septic arterial or pulmonary emboli, mycotic aneurysms, intracranial hemorrhage, Janeway lesions[a] • **Immune phenomena:** Glomerulonephritis, Osler nodes,[b] Roth spots,[c] rheumatoid factor • **Positive blood cultures** not meeting major criteria • **Positive echocardiogram** not meeting major criteria

Note: Definitive (i.e., highly probable) diagnosis if two major, or one major plus three minor, or five minor criteria are present.

Quick HIT

TEE is better than transthoracic echocardiography (TTE) in the diagnosis of endocarditis for especially mitral valve pathology and small aortic vegetations. Most patients should get TTE as an initial screening test.

❖ Management

Antibiotics will be required for a minimum of 6 weeks. Which antibiotic is chosen will be dependent on the culture and sensitivity of the organism. But when treatment is begun we must use empiric coverage.

Therapeutic approach to infective endocarditis [15][6][32][33]

Management	Recommendations
Consults	• Consult infectious diseases (ID) early to plan treatment and evaluate the need for empiric therapy. • Identify patients requiring surgery consult (e.g., prosthetic valve endocarditis).

Empiric antibiotics	• Indicated for **hemodynamically unstable** patients
	• Consider for hemodynamically stable patients with acute symptoms and/or complications. [6][33]
	• Take the following into account when choosing an agent:
	  ◦ Patient-related factors: See "Risk factors for IE".
	  ◦ Disease-related factors: See "Classification".
	  ◦ Local and individual flora and resistance patterns
	• Common regimens: See "Empiric antibiotics for IE".
	  ◦ Native valve endocarditis: vancomycin PLUS beta-lactam (e.g., ceftriaxone, cefepime)
	  ◦ Prosthetic valve endocarditis: **Add** gentamicin PLUS rifampin to vancomycin PLUS beta-lactam (if ≤ 1 year after placement).

Targeted antibiotics	• Recommended for all patients [6][33]
	• Duration of therapy: variable; can be ≥ 2–6 weeks after the first sterile blood culture
	• Common regimens: See "Targeted antibiotics for IE".
	  ◦ Staphylococci
	  ▪ Methicillin-susceptible staphylococci (e.g., MSSA): antistaphylococcal beta-lactams (e.g., nafcillin, oxacillin)
	  ▪ Methicillin-resistant staphylococci (e.g. MRSA: vancomycin
	  ▪ Prosthetic valve endocarditis (≤ 1 year after placement): **add** gentamicin PLUS rifampin to regimen.
	  ◦ Viridans group streptococci: beta-lactams (e.g., penicillin G, ampicillin)
	  ◦ Enterococci: combination therapy (e.g., ampicillin PLUS gentamicin)
	  ◦ HACEK: ceftriaxone (first-line)
	• Blood culture-negative endocarditis: empirical therapy until additional investigations (e.g., serology) yield results

Antithrombotic therapy	• Native valve endocarditis: not routinely recommended • Prosthetic valve endocarditis: anticoagulation commonly stopped for ≥ 2 weeks in the case of CNS emboli [15]

Surgery

Go to surgery if
>15mm even without embolization
>10 mm + embolization
Abscess
Valve destruction or CHF
Fungus

List indications for infective endocarditis prophylaxis

- **Dental procedures**:
  - Amoxicillin
  - for penicillin-allergic patients, use clindamycin, azithromycin, clarithromycin, or cephalexin
- **Urinary or GI procedures**: no longer require prophylaxis
- **Cardiac Conditions Which Do Require Prophylactic Therapy**
  - Prosthetic cardiac valves, including bioprosthetic and homograft valves
  - Previous bacterial endocarditis, even in the absence of heart disease
  - Most congenital cardiac malformations, especially cyanotic lesions (negligible risk with isolated ASD) if not repaired
- **Anatomic Defects or Conditions Which Require Prophylaxis**
  - Prosthetic valves
  - Unrepaired cyanotic heart disease
  - Previous endocarditis
  - Transplant status
- **Dental or Surgical Procedures Which Predispose to Endocarditis**
  - Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning
  - Tonsillectomy and/or adenoidectomy

Bad Valve	Mouth and Throat
Congenital Heart Disease	Dental Procedures
Prosthetic Valve	Biopsy of the Airway
History of Endocarditis	

↓

Antibiotics
Amoxicillin (1st line)
Ceftaz (back up)
Clinda (last line)

Diseases of Myocardium & pericardium

- To be able to identify clinically patient with suspected pericardial disease (acute pericarditis, pericardial effusion/tamponade, constrictive pericarditis)
- Initiate investigation plan & enlist key points in the management for patient with pericardial disease

1. Acute Pericarditis:

Acute pericarditis is inflammation of the pericardial lining around the heart.

❖ Etiology:

- Idiopathic
- Infections (viral)
- Uremia
- Vasculitis (connective tissue diseases)
- Lupus (and other rheumatoid disorders)
- Disorders of metabolism
- Neoplasms
- Trauma

❖ Clinical Manifestations:

- Chest pain, often localized substernally or to the let of the sternum, is usually worsened by lying down, coughing, and deep inspiration (which helps in the differential diagnosis with MI) and is relieved by sitting up and leaning forward.
- Pericardial friction rub (diagnostic of pericarditis) is a scratchy, high-pitched sound that has 1 to 3 components corresponding to atrial systole, ventricular systole, & early diastolic ventricular filling.

❖ Diagnosis:

- ECG may be diagnostic and reveals a diffuse ST-segment elevation with upright T waves at the onset of chest pain. PR segment depression is very specific. The diffuseness of the ST-segment elevation, absence of reciprocal leads, and absence of the development of Q waves distinguish the characteristic pattern of acute pericarditis from the pattern seen in acute MI.

❖ **Treatment:**

- Treatment of acute pericarditis involves treating its etiology.
- In idiopathic pericarditis, treat with anti-inflammatory medications (NSAIDs, aspirin, corticosteroids).
- Adding colchicine to an NSAID decreases recurrence.

2. Pericardial Effusion:

- an accumulation of fluid in the pericardial space between the parietal and visceral pericardium. May be acute or chronic.
- The fluid may be a transudate, as in the serous cavity effusions that develop in patients with CHF, overhydration, or hypoproteinemia. More often, however, the pericardial effusion is an exudate, reflecting the presence of pericardial injury.

❖ **Etiology:**

- Hemopericardium
  - Cardiac wall rupture (e.g., complication of myocardial infarction)
  - Chest trauma (traumatic cardiac tamponade)
  - Aortic dissection
  - Cardiac surgery (e.g., heart valve surgery, coronary bypass surgery)

- Serous or serosanguinous pericardial effusion
  - Idiopathic
  - Acute pericarditis (especially viral, but also fungal, tuberculous or bacterial)
  - Malignancy
  - Postpericardiotomy syndrome
  - Uremia
  - Autoimmune disorders
  - Hypothyroidism
  - Right heart failure

❖ **Clinical manifestations:**

- Initially asymptomatic in most cases
- Shortness of breath, especially when lying down (orthopnea)
- Retrosternal chest pain
- Can cause compressive symptoms (e.g. Hoarseness, Nausea, Dysphagia, Hiccups)a
- Apical impulse is difficult to locate or nonpalpable.
- Ewart sign (dullness to percussion at the base of the left lung with increased vocal fremitus and bronchial breathing due the compression of lung parenchyma by the pericardial effusion)

❖ **Diagnosis:**

- Echocardiography
  - TTE (gold standard)
  - The presence of echo-free space between the posterior pericardium and the posterior left ventricular epicardium in patients with small effusions.
  - In patients with large effusions, the heart may swing freely within the pericardial sac, and this motion may be associated with electrical alternans.
- ECG
  - Used to rule out an ischemic cause
- Chest x-ray
  - may show a **"water-bottle"** configuration of the cardiac silhouette.
- Pericardiocentesis with pericardial fluid analysis

❖ **Treatment:**

- Treatment includes fluid aspiration and management of the etiology.

3. Cardiac tamponade:

pathophysiological process whereby elevated intrapericardial pressure from a pericardial effusion causes compression of the heart (especially the right ventricle)

❖ **Etiology:**

- Neoplasia
- Idiopathic (usually viral) pericarditis
- Non Viral infection: tuberculous; suppurative
- Intrapericardial hemorrhage with or without pericarditis
- Wounds, including surgery of chest; heart; pericardium
- Postpericardiotomy syndrome
- Uremia
- Mediastinal and juxtamediastinal radiation therapy
- Vasculitis–connective tissue disease group

❖ **Clinical Manifestations**:

- dyspnea, fatigue, and orthopnea.
- Pulsus paradoxus (very common)
    - The paradoxical pulse often can be noted by marked weakening or disappearance of a peripheral pulse during inspiration.
    - Paradoxical pulse is not diagnostic of cardiac tamponade; it can occur in chronic lung disease, acute asthma, severe CHF, and even hypovolemic shock.
- Neck vein distension with clear lung
- Shock (hypotension)
- Decreased heart sounds
- **Beck's triad** is associated with acute tamponade
    - Low blood pressure
    - Distended neck veins
    - Decreased heart sounds

❖ **Diagnosis:**

- Clinical manifestations followed by echocardiography “TTE (gold standard)“
- A surgical pericardial window may be needed for chronic effusions.
- Cardiac catheterization will confirm that left and right atrial pressures are equal.

❖ **Treatment:**

- Treat with pericardiocentesis and subxiphoid surgical drainage.

4. Constrictive Pericarditis:

- Constrictive pericarditis is the diffuse thickening of the pericardium in response to prior inflammation, resulting in reduced distensibility of the cardiac chambers.
- Cardiac output is limited and filling pressures are increased to match the external constrictive force placed on the heart by the pericardium.
- The fundamental hemodynamic abnormality is abnormal diastolic filling.

❖ **Etiology:**

- Idiopathic
- Following open-heart surgery
- Following thoracic radiation
- Post Viral infection

❖ **Clinical Manifestations:**

- Most patients complain of dyspnea on exertion due to limited cardiac output
- Orthopnea occurs in about 50% of patients.
- Symptoms and signs related to systemic venous hypertension are often reported: ascites, edema, jaundice, hepatic tenderness, and hepatomegaly (manifestations of right-side failure)
- Kussmaul sign (Jugular venous distension increases with inspiration)
- Heart sounds are distant, and an early diastolic apical sound, or "pericardial knock" is often present and can be confused with an S3 gallop.

❖ **Diagnosis:**

- Chest CT or MRI (best test):
  - thickened pericardium; pericardial calcifications may be seen in tuberculous constriction
- EKG
  - low-voltage and nonspecific T-wave changes
- Chest x-ray
  - heart is usually normal in size
- Cardiac catheterization
  - Marked "y" descent is present in right atrial pressure tracing
  - Characteristic "dip and plateau" or "square root" sign is present in left and right ventricular pressure tracing
  - Equalization of end-diastolic pressures in all 4 chambers and pulmonary artery
  - It is sometimes difficult to distinguish constrictive pericarditis from restrictive cardiomyopathy
  - Left ventricular ejection fraction is more likely to be decreased in the latter.

❖ **Treatment:**

- Treated conservatively at rest with mild sodium restriction and diuretics.
- Pericardiectomy may be needed.

- To be able to identify clinically patient with suspected myocardial disease (HCM, RCM)

	Dilated	Hypertrophic	Restrictive
	Biventricular dilatation	Marked hypertrophy of left ventricle and occasionally of right ventricle; can have disproportionate hypertrophy of septum	Reduced ventricular compliance; usually caused by infiltration of myocardium (e.g., by amyloid, hemosiderin, or glycogen deposits)
Cardiac output	↓	Normal or ↓	Normal to ↓
Stroke volume	↓	Normal or ↑	Normal or ↓
Ventricular filling pressure	↑	Normal or ↑	↑
Chamber size	↑	Normal or ↓	Normal or ↑
Ejection fraction	↓	↑	Normal to ↓
Diastolic compliance	Normal	↓	↓
Other findings	May have associated functional mitral or tricuspid regurgitation.	Obstruction may develop between interventricular septum and septal leaflet of mitral valve.	Characteristic ventricular pressure tracing that resembles those recorded in constrictive pericarditis, with early diastolic dip-and-plateau configuration

	Dilated cardiomyopathy	Hypertrophic cardiomyopathy	Restrictive cardiomyopathy
Distinctive clinical features	• Signs of left heart failure and right heart failure • S3 gallop • Systolic murmur	• Frequently asymptomatic • Signs of left heart failure (dyspnea, **syncope**, dizziness) • Arrhythmias • S4 gallop • Possible holosystolic murmur from mitral regurgitation • **Sudden death**	• Signs of left heart failure and right heart failure

- Initiate investigation plan and enlist key points in the management for patient with myocardial diseases

1. Dilated (Congestive) Cardiomyopathy

- Characterized by diminished myocardial contractility, usually involving both ventricles; most common cause for heart transplants.

❖ Diagnosis:

Diagnostic approach to DCM aims to:

1. Investigate the underlying cause with confirming either the secondary cause or idiopathic disease
2. Assess cardiac function
3. Assess structural remodeling
4. Specific investigations are guided by suspected underlying cause or complications

- Laboratory
  - ↑ BNP: in concomitant heart failure
  - Troponin and CK-MB: to rule out myocardial infarction
- X-ray:
  - cardiomegaly with pulmonary congestion
- EKG:
  - sinus tachycardia, arrhythmias, conduction disturbances
- Echo (key diagnostic study):
  - dilated left ventricle, generalized decreased wall motion, mitral valve regurgitation
  - transesophageal echo is more sensitive and specific than transthoracic
- Catheterization:
  - dilated hypercontractile ventricle, mitral regurgitation

❖ Treatment:

- Patients are treated as those with systolic heart failure.
- ACE, beta blockers, and spironolactone lower mortality.
- Diuretics and digoxin decrease symptoms.
- Implantable defibrillator may decrease risk of sudden death when the ejection fraction is <35%.

2. Hypertrophic Cardiomyopathy

❖ Diagnosis

- EKG:
  - Left ventricular hypertrophy
  - Pseudo Q waves (often seen V1–V3)
  - Ventricular arrhythmias
- Echocardiogram
  - Is the mainstay of diagnosis
  - It typically shows hypertrophy
  - Systolic anterior motion of mitral valve
  - Mid systolic closure of aortic valve

❖ Treatment:

- Beta-blockers
- Calcium channel blockers that reduce heart rate: diltiazem, verapamil
- Disopyramide, occasionally
- Use implantable defibrillator if there is syncope
- Surgery in severe cases—septoplasty

avoid the following with HOCM:
- Digitalis
- Diuretics
- Vasodilators
- Exercise

3. Restrictive Cardiomyopathy

❖ Diagnosis:

- X-ray
  - mild cardiomegaly, pulmonary congestion
- EKG
  - low voltage, conduction disturbances, Q waves
- Echo
  - characteristic myocardial texture in amyloidosis with thickening of all cardiac Structures
- Catheterization
  - square root sign; elevated left- and right-sided filling pressures
- Endo/myocardial biopsy
  - Histology classically shows fibrosis.
  - Diagnosis of underlying cause if other tests are inconclusive (e.g., amyloid or iron depositions, eosinophilic infiltrates in Löffler endocarditis)

❖ **Treatment:**

- Here is no good therapy; death ultimately results from CHF or arrhythmias.
- Treatment is generally limited and often palliative.
- Treatment of underlying condition (e.g., phlebotomy for hemochromatosis)
- Symptomatic treatment
    - Maintenance of sinus rhythm: beta blockers
    - ↑ Ventricular filling time, ↓ sympathetic activity: cardioselective calcium channel blockers
    - ↓ Preload: ACE inhibitors, except in amyloidosis (ACEIs are poorly tolerated in amyloidosis)
    - For fluid overload: diuretics
- Anticoagulation (e.g., warfarin) to prevent embolism in patients with a history of atrial fibrillation
- Heart transplant (in patients with refractory symptoms)

Arrhythmia and ECG abnormality

- approach patients with arrhythmia

Step 1: General Principles

In order to identify the rhythm, follow these simple principles.

1. Determine the rate: tachycardia is > 100, bradycardia < 60.
2. Determine the QRS complex: wide is > .12 msec and means it's a ventricular rhythm while narrow is < .12 msec and means it's an atrial rhythm.
3. The third and final decision is if the rhythm is regular or irregular.

Of course, to determine any of this an ECG, preferably a 12-lead, is needed.

With the ECG ask if there's an arrhythmia or not. Note that there are two, maybe three, rhythms that aren't arrhythmias.

- Normal Sinus Rhythm is what everyone should be in.
- Sinus tachycardia is typically a normal, physiologic response to an underlying stressor.
- Sinus bradycardia may be a normal rhythm in a competitive athlete, though they usually do not appear in a vignette or in the hospital as an "arrhythmia."

Step 2: Symptoms or No Symptoms

Ask, "are there symptoms?" An arrhythmia without any symptoms does not warrant attention. Simply: if there are no symptoms then do nothing. "Nothing" means routine care: IV, O2, and Monitor. Likely, this will be a question about rhythm identification.

Step 3: Stable vs Unstable

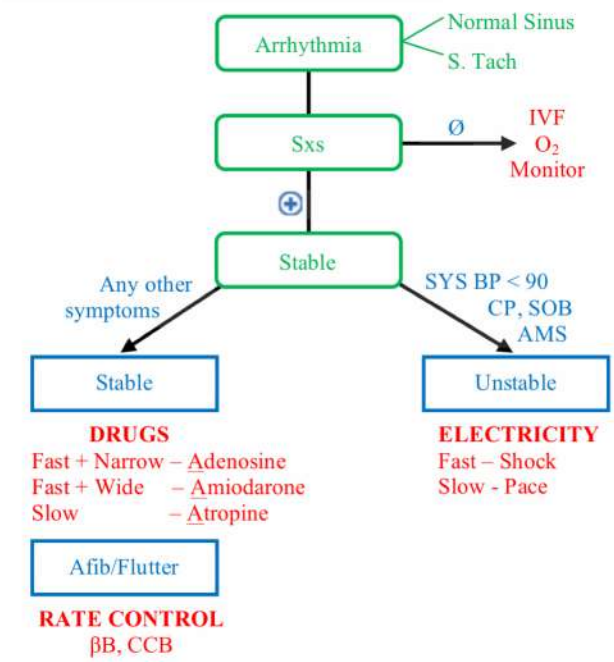
If the patient has symptoms decide whether there's time to stay and play or if definitive therapy is needed right now. Stability is a product of your own comfort. But for a test, if there's chest pain, shortness of breath, altered mental status, or a systolic BP < 90, then the patient is considered unstable.

- If they're unstable use electricity.
- If instead the patient has symptoms, but not any one of those listed above, the patient is stable. A patient who is stable has time to fix the rhythm. They're not going to die at this moment; pharmacotherapy can be used.

Step 4: Choose an intervention

If you've chosen unstable/electricity only one question needs to be asked - fast of slow.

- If the rhythm is fast + unstable then shock.
- If the rhythm is slow + unstable then pace.



Tachy Rhythms
- Sinus Tachycardia
- Supraventricular Tachycardia
- Multifocal Atrial Tachycardia
- Afib
- Aflutter
- Vtach
- Vfib
- Torsades

Atrial Narrow

Ventricular Wide

Brady Rhythms
- Sinus Bradycardia
- 1° Block
- 2° Block
- 3° Block
- Junctional
- Idioventricular

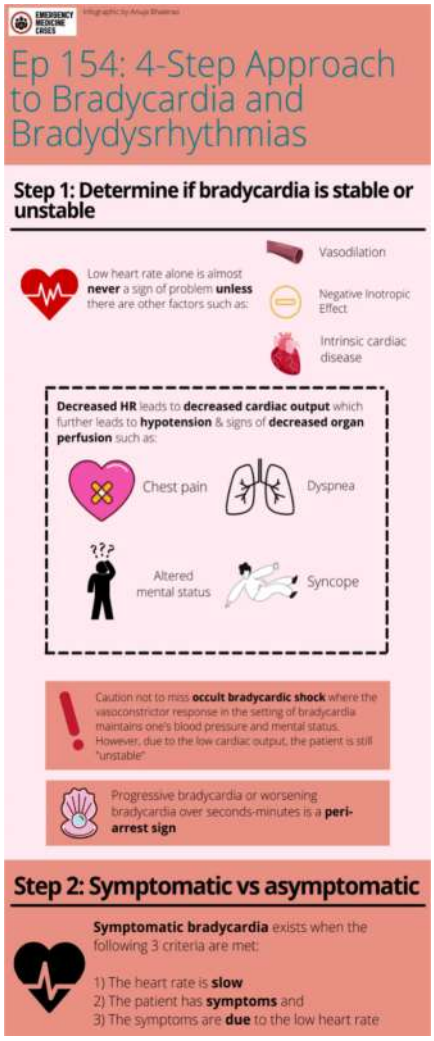
Varying degree of PR intervals

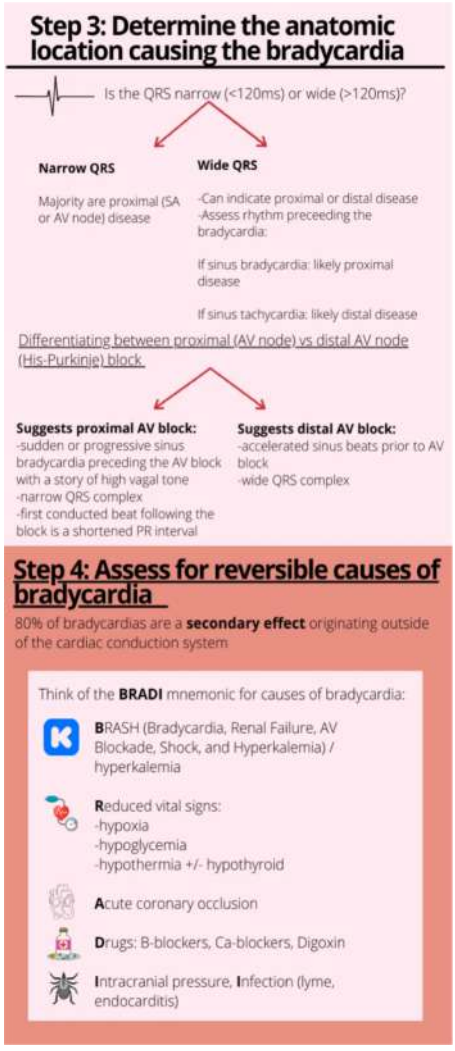
Intervention	*Heart Rate*	*QRS Complex*	*Stability*
Pacer	Brady	Any	Unstable
Cardioversion	Tachy	Any	Unstable
Atropine	Brady	Any	Stable
Adenosine	Tachy	Narrow	Stable
Amiodarone	Tachy	Wide	Stable
Rate Control	Tachy	Afib/Flutter	Stable

"Rate Control" = Verapamil / Diltiazem, Metoprolol

- To be able to approach patients with symptomatic bradycardia

https://emergencymedicinecases.com/approach-bradycardia-bradydysrhythmias/





Sinus bradycardia:

Ventricular complexes are normal width, evenly spaced, rate <60min.

❖ **Etiology:**

- Excessive vagal tone causes: acute MI (particularly diaphragmatic); carotid sinus
- pressure; vomiting; Valsalva maneuver; phenothiazines; digitalis glycosides
- Depression of sinus node automaticity: beta-adrenergic blocking agents; calcium-blocking drugs
- Marathon running and swimming
- Hypothyroidism
- Normal variant

❖ **Treatment:**

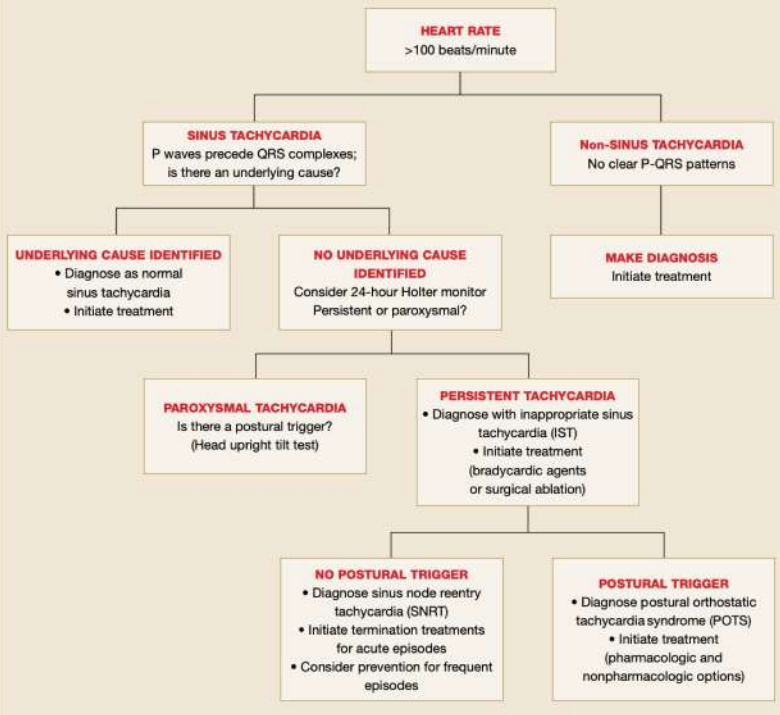
1. In the absence of symptoms, no treatment is needed.
2. If symptoms are present, administer atropine acutely.
3. If symptoms and bradycardia still continue, consider a pacemaker.

- To be able to approach patients with sinus tachycardia

- https://cdn.mdedge.com/files/s3fs-public/Document/September-2017/5601JFP_ClinicalInquiries4.pdf
- https://emergencymedicinecases.com/ecg-cases-tachycardias-wider-mnemonic-svt-vt/

FIGURE

Diagnostic algorithm for evaluating tachycardias[4]



TABLE

Potential secondary causes of resting sinus tachycardia[5–7]

Hyperthyroidism
Fever
Sepsis
Anxiety
Pheochromocytoma
Anemia
Hypotension and shock
Pulmonary embolism
Acute coronary ischemia and myocardial infarction
Heart failure
Chronic pulmonary disease
Hypoxia
Exposure to medications, stimulants, or illicit drugs
Malignancy
Pregnancy

- Define the atrial fibrillation and its complications and be able to initiate therapy.

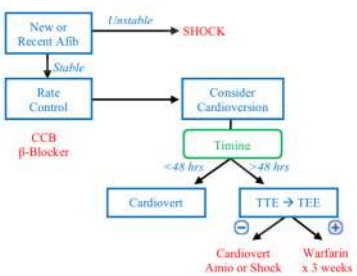
❖ Definition:

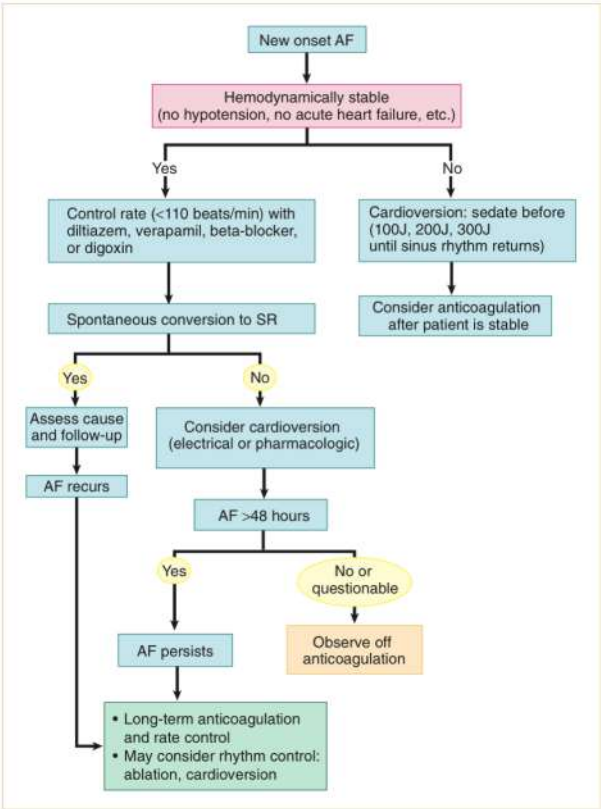
- AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with subsequent decline of atrial function.
- On ECG, there is replacement of consistent P waves by fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response (irregularly, irregular).

❖ Complications:

- Acute left heart failure → pulmonary edema
- Thromboembolic events: stroke/TIA, renal infarct, splenic infarct , intestinal ischemia , acute limb ischemia (The brain, kidney, and spleen are the three organs most likely to be damaged by emboli)
- Life-threatening ventricular tachycardia
- Sudden cardiac arrest

Atrial Fibrillation can be identified by a **narrow complex** tachycardia with a **chaotic background, absent p-waves,** and an **irregularly irregular** R-R interval. It has a special treatment algorithm. In the acute setting (ACLS in a nutshell) simply decide between shock and rate control. **Rate control** is just as good as **rhythm control** (cardioversion). But, you have to weigh risks and benefits in each patient. If the goal is **rhythm control** (cardioversion) it's necessary to determine **how long** the Afib's been present. Simply cardioverting an Afib that's lasted > 48 hrs runs the risk of throwing an **embolism** (and a stroke). If < 48hours cardioversion is ok. But if it's been present **> 48 hours** the patient needs to go on **warfarin** for four weeks. At the end of four weeks, the **TEE** is done. If no clot is found, cardioversion is done and the patient remains on warfarin for another 4 weeks. If you decide to do **rate control** (beta blockers and calcium channel blockers) **anticoagulation** may still be needed. Decide this using the **CHADS2 score**. The higher the score the higher the risk of embolism and the more likely the patient is to benefit from **warfarin** (2+ CHADS2). Now, the Xa- or Thrombin-inhibitors can be used instead (1+ CHADS2). Examples include **apixiban** or **dabigatran**.



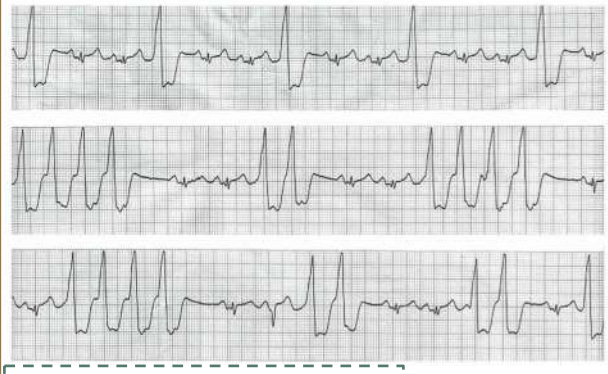


- Identify ventricular arrhythmias based on ECG and initiate a management plan.

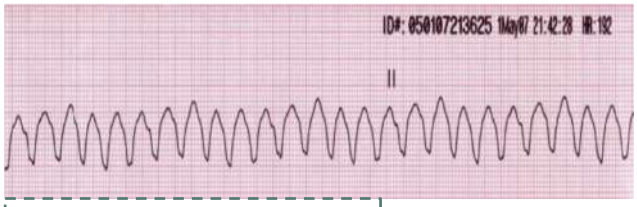
Type of arrhythmia	Causes and mechanisms	ECG findings
Premature ventricular beats	• Ectopic beat that originates from a ventricular focus • Due to hypoxia, hyperthyroidism, electrolyte abnormalities	• Premature, wide QRS complex that is not preceded by a P wave • Compensatory pause after the premature beat

Ventricular tachycardia	• Coronary artery disease
	• Myocardial infarction
	• Structural heart diseases
		• Regular, rapid rhythm
		• Wide QRS complexes (≥ 3 consecutive premature ventricular beats)
		  ◦ Monomorphic VT (most common): single QRS morphology
		  ◦ Polymorphic VT: multiple QRS morphologies
		• AV dissociation (P waves may or may not be discernible)

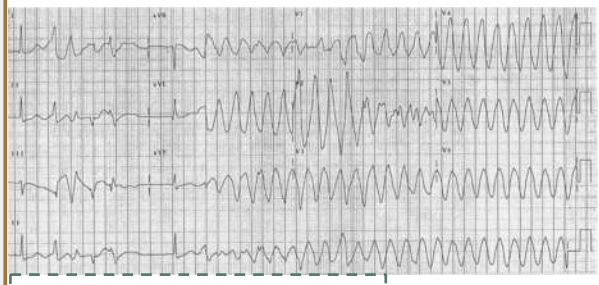
Torsade de pointes tachycardia	• Associated with Long QT syndrome • Proarrhythmic drugs • Electrolyte abnormalities (hypokalemia)	• Polymorphic ventricular tachycardia with QRS complexes that appear to twist around the isoelectric line
Ventricular fibrillation	• Myocardial infarction • Structural heart diseases	• Arrhythmic, fibrillatory baseline, usually > 300 bpm • Erratic undulations with indiscernible QRS complexes



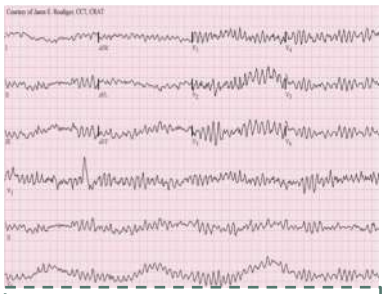
Premature ventricular beat



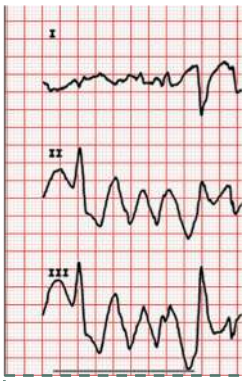
Monomorphic ventricular tachycardia



Torsade de pointes



ventricular fibrillation



Polymorphic ventricular tachycardia

❖ **Management:**

1. **premature ventricular beat:**

- Most patients do not require any treatment
- Treat any underlying disease (e.g., CAD, myocarditis)
- Only treat frequent and significantly symptomatic PVCs
- Antiarrhythmic therapy
- Catheter ablation if antiarrhythmic therapy fails

2. **Ventricular tachycardia:**

- **Treat underlying cause**
- **Ongoing or sustained VT:**
    - Hemodynamically stable patients with mild symptoms and systolic BP ›90- pharmacologic therapy "IV amiodarone"
    - Hemodynamically unstable patients or patients with severe symptoms => Immediate synchronous DC cardioversion, Follow with IV amiodarone to maintain sinus rhythm
    - ICD placement
- **Nonsustained VT or resolved sustained VT:**
    - If no underlying heart disease and asymptomatic, do not treat. (These patients are not at increased risk of sudden death)
    - If the patient has underlying heart disease, a recent MI, evidence of left ventricular dysfunction, or is symptomatic, order an electrophysiologic study: If it shows inducible, sustained VT, ICD placement is appropriate.
    - Pharmacologic therapy is second-line treatment.
- **Long-term management of patients with VT**
  (Pharmacological therapy (antiarrhythmics) is often used alongside device therapy (e.g., ICD) to minimize symptoms, risk of recurrence, and risk of sudden cardiac death. Ablation of the arrhythmogenic foci is potentially curative)
    - Pharmacological therapy
        - β-blockers are typically used as first-line therapy because they reduce the risk of sudden cardiac death.
        - Other medications (e.g., class Ic antiarrhythmics or class III antiarrhythmics) may be combined with β-blockers if symptoms persist.
    - Implantable cardioverter-defibrillator (ICD)
        - Indications for a permanent ICD: Expected survival › 1 year, Recurrent VT despite treatment of reversible causes
    - Ablation
        - Indications: Recurrent VT despite optimal therapy, Antiarrhythmics are not tolerated, Patient preference
        - Options: Radiofrequency catheter ablation, Surgical ablation

3. **Torsades de pointes:**

- Administer IV magnesium
- Avoid amiodarone, procainamide, and sotalol
- Identify and treat the underlying cause

4. **Ventricular fibrillation:**

- Resuscitation for V-fib
    a. Advanced Cardiac Life Support (ACLS)
    b. refractory V-fib consider administration of lidocaine, procainamide, or magnesium
- Post-resuscitation care
    a. Intensive care monitoring
    b. Maintain application of antiarrhythmics that were used during successful resuscitation (usually IV amiodarone or IV lidocaine)
    c. Consider administration of beta blockers
    d. Treat underlying causes (e.g., treatment of CAD)
    e. ICD (implantable cardioverter-defibrillator) in patients without a readily reversible or treatable cause and/or with a high risk of recurrent, hemodynamically significant V-fib

Identify atrial fibrillation and heart blocks on ECG

https://ksumsc.com/download_center/Archive/4th/437/437%20TeamWork/PHC/9.%20ECG%20Interpretation%20.pdf

Characteristic ECG findings in atrial fibrillation [18]	
	Appearance
Rhythm	• **Irregularly irregular RR intervals** • Rarely may be regular if there is complete AV dissociation
Rate	• Variable; **Tachycardia** is common. • Atrial rate > ventricular rate

P waves	• **P waves are indiscernible.**
	• Fibrillatory waves (f waves) are seen instead at a frequency of 300–600/minute
	  ◦ Recent-onset Afib: prominent, coarse f waves with higher amplitude in leads V_1, II, III, and aVF
	  ◦ Long-standing Afib: f waves have low amplitudes and may appear as an undulating baseline.
	• PR intervals: not distinguishable

QRS complex	• Typically **narrow QRS complex (< 0.12 seconds)**
	• Broad complexes may be seen in some situations:
	  ◦ Aberrant conduction, e.g., bundle branch block or preexcitation (as seen in Afib with WPW)
	  ◦ Complete AV block with a ventricular escape rhythm
	  ◦ **Ashman phenomenon**: intermittent aberrant ventricular conduction results in isolated or short runs of wide QRS complexes

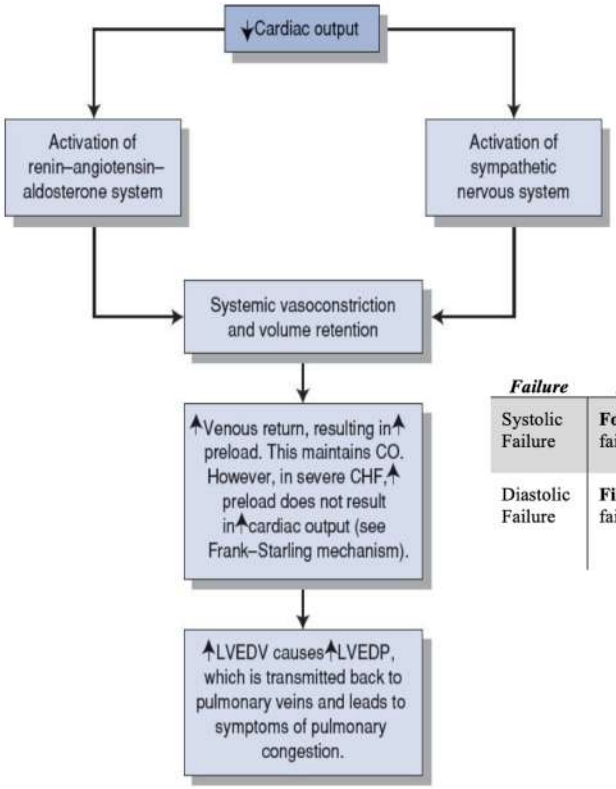
Overview of atrioventricular blocks [1][2][3]			
Type of AV block		ECG findings	Typical management
First-degree AV block		• Fixed PR interval > 200 ms • Regular rhythm • Every P wave is followed by a normal QRS complex.	• Low risk of progression to a higher degree heart block or sudden cardiac arrest • Asymptomatic patients require no treatment and can be followed-up as outpatients. • Consider an elective pacemaker for select patients.
Second-degree AV block	Mobitz type I	• Progressive lengthening of the PR interval until a beat is dropped, i.e., a normal P wave is not followed by a QRS complex • Regularly irregular rhythm • Narrow QRS complexes (< 0.12 s)	
	2:1 AV block	• Every second impulse from the atria is not conducted to the ventricles. • Regular rhythm • Narrow QRS complexes (< 0.12 s)	• Infranodal block absent: Treat as low-risk AV block. • Infranodal block present: Treat as high-risk AV block.
	Mobitz type II	• Single or intermittently dropped beats (nonconducted P waves), often at a regular conduction interval (e.g., 3:2, 4:3, 5:4) • The PR interval in conducted beats is constant. • Regularly irregular rhythm • Wide QRS complexes (> 0.12 s)	• High risk of progression to a higher degree heart block or sudden cardiac arrest • Hospital admission for temporary pacing • Management of reversible underlying conditions (e.g., inferior MI, cardiotoxic drug overdose, thyrotoxicosis) • Permanent pacemaker placement for most patients
	High-grade AV block	• ≥ 2 consecutive impulses from the atria are not conducted to the ventricles. • Typically regular rhythm • Wide QRS complexes (> 0.12 s)	
Third-degree AV block		• AV dissociation: no relationship between P waves and QRS complexes • Usually a regular escape rhythm • The morphology of QRS complexes depends on the level of the block and the type of escape rhythm.	

Heart failure

- Understand the pathophysiology of heart failure.

Pathophysiology

- Pathogenesis and Etiology The typical chronic failure that occurs insidiously is by far the most common.
- It's caused by hypertension. High blood pressure causes an increase in systemic vascular resistance; the heart has to pump harder and harder to push the blood. It gets bigger and beefier to compensate. But just like any muscle, it putters out and eventually fails. The heart gets bigger, rounder, and eventually goes floppy. Pathologically, constant overstimulation by catecholamines first helps the heart overcome the hypertension. It eventually leads to neural hormonal remodeling, cardiac toxicity, and then fibrosis. Other etiologies are simply a matter of memorization.
- Diastolic CHF (CHF with preserved ejection fraction) is caused by the things that prevent relaxation. Generally, it's a hypertrophic or restrictive cardiomyopathy. Pericardial disease and deposition disease can do it too.



Failure	*Path*	*Etiology*	*EF*
Systolic Failure	**Forward** failure	**Leaky** valves = any regurgitation **Dead** Heart = Ischemia / infarction **Floppy** muscles = EtOH, HTN, Drug	⇩
Diastolic Failure	**Filling** failure	**Pericardium** = Pericardial Tamponade Constrictive Pericarditis **Cardiomyopathy** = Restrictive Hypertrophic	⇧

1. Underlying mechanism of reduced cardiac output

- **Heart failure with reduced ejection fraction (HFrEF)**

Reduced contractility → systolic ventricular dysfunction → decreased left ventricular ejection fraction (LVEF) → decreased cardiac output

- **Heart failure with preserved ejection fraction (HFpEF)**

Decreased ventricular compliance → diastolic ventricular dysfunction → reduced ventricular filling and increased diastolic pressure → decreased cardiac output (while the left ventricular ejection fraction remains normal)

- **Left-sided heart failure (HFrEF and/or HFpEF)**
  - Increased left ventricular afterload: increased mean aortic pressure (e.g., arterial hypertension), outflow obstruction (e.g., aortic stenosis)
  - Increased left ventricular preload: left ventricular volume overload (e.g., backflow into the left ventricle caused by aortic insufficiency)
- **Right-sided heart failure**
  - Increased right ventricular afterload: increase in pulmonary artery pressure (e.g., pulmonary hypertension)
  - Increased right ventricular preload: right ventricular volume overload (e.g., tricuspid valve regurgitation, left-to-right shunt)

1. Consequences of decompensated heart failure

- **Forward failure:**

reduced cardiac output → poor organ perfusion → organ dysfunction (e.g., hypotension, renal dysfunction)

- **Backward failure**
  - Left ventricle: increased left-ventricular volumes or pressures → backup of blood into lungs → increased pulmonary capillary pressure → cardiogenic pulmonary edema (presenting with orthopnea) and increased pulmonary artery pressure
  - Right ventricle: increased pulmonary artery pressure → reduced right-sided cardiac output → systemic venous congestion → peripheral edema and progressive congestion of internal organs (e.g., liver, stomach)

1. Compensation mechanisms

- **Increased adrenergic activity**: increase in heart rate, blood pressure, and ventricular contractility
- **Increase of renin-angiotensin-aldosterone system activity (RAAS)**: activated following decrease in renal perfusion secondary to reduction of stroke volume and cardiac output ↑ Angiotensin II secretion results in:
  - Peripheral vasoconstriction → ↑ systemic blood pressure → ↑ afterload
  - Vasoconstriction of the efferent arterioles; → ↓ net renal blood flow and ↑ intraglomerular pressure → maintained GFR
  - ↑ Aldosterone secretion → ↑ renal Na^+ and H_2O resorption → ↑ preload
- **Secretion of brain natriuretic peptide (BNP)**
  - ↑ intracellular smooth muscle cGMP → vasodilation → hypotension and decreased pulmonary capillary wedge pressure

- Identify the symptoms and signs suggestive of heart failure

	Left-side HF	Right-side HF
Symptoms	- Exertional Dyspnea (shortness of breath limiting walking) - Orthopnea (shortness of breath that's worse when lying flat) - Paroxysmal Nocturnal Dyspnea (PND) (awakening after 1 to 2 hours of sleep due to acute SOB) - Nocturnal Cough (non-productive) (worse in recumbent position) - Confusion and memory impairment (occur in advanced CHF as a result of inadequate brain perfusion) - Diaphoresis And Cool extremities at rest (occuring in desperately ill patients)	- edema - Nocturia
Signs	- Displaced PMI - Pathologic S3 - S4 gallop - Crackles/rales at lung bases - Signs of pleural effusion - pulmonary HTN	- Peripheral pitting edema - Jugular Venous Distention(JVD) - Hepatomegaly/hepatojugular reflux - Ascites - Right Ventricular Heave (found with pulmonary HTN)

- most patients have left and right failure together
- Symptoms like an S3 heart sound and Jugular Venous Distension are signs of acute exacerbation
- In the chronic setting, it's critical to determine what class they are. Here, we use NYHA, as it directs treatment.

Symptoms

Left Ventricular Failure	Right Ventricular Failure
Orthopnea, Crackles, Rales	Hepatosplenomegaly, **JVD**
Dyspnea on Exertion, **S3,**	Peripheral Edema,
Paroxysmal Nocturnal Dyspnea	Dyspnea on Exertion, ↑JVP

S3 and JVD poor prognostic sign in acute exacerbation

- List the initial diagnostic testing for patients presenting with heart failure.

Diagnosis.

- **echocardiography:**
  - Is the best test to confirm the diagnosis of HF and classify the type.
  - Can be used to determine ejection fraction and identify valvular heart disease as well as other cardiac anomalies (dilated ventricle, thickened ventricle, etc.).
- **Chest x-ray**
  - It may show cardiomegaly, vascular redistribution, Kerley B-lines, or interstitial edema.
- **Electrocardiogram (ECG)**
  - is used to identify ventricular hypertrophy and/or the presence of ischemic heart disease, arrhythmias, or conduction delays which may cause or precipitate HF.
- **Brain natriuretic peptide (BNP**) (or type B natriuretic peptide)
  - is a polypeptide secreted by the heart in response to excessive stretching of the myocytes.
  - It is a valuable screening tool in the evaluation of patients with presumed HF or decompensated HF in the acute setting.
  - BNP is best used for ruling out HF, and a normal BNP generally excludes CHF as the cause of dyspnea.
  - BNP is almost always elevated (97% sensitivity) in patients with decompensated HF. the only exception is obesity, where BNP can be falsely low.
  - BNP lacks specificity (renal failure can lead to elevated BNP). A positive BNP warrants a follow-up echocardiogram.

If CHF is confirmed, investigate for:

- Underlying causes (consider coronary angiogram, chest imaging, and advanced cardiac imaging)
- Modifiable risk factors (e.g., hypertension, coronary artery disease)

- To able to describe the treatment strategies used in heart failure

Treatment

There are two goals: reduce fluid (preload) and reduce afterload.

Reduce fluid (preload):

- it's important to restrict salt intake (< 2g/day of NaCl) and reduce fluid intake (< 2L H20/day). Everybody gets this.
- Once the patient reaches class II, keep the fluid off by using diuretics like furosemide.
- At class III, Isosorbide Dinitrate is added.

Afterload reduction:

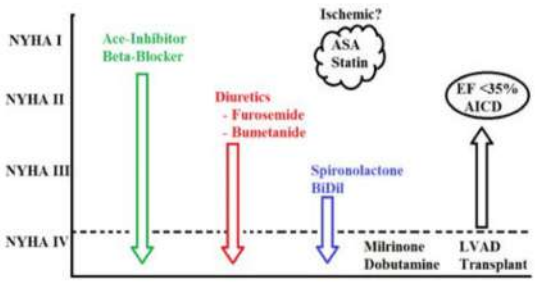
- Achieved with ACE-inhibitors (also ARBs).
- When CHF gets really bad (Class III and greater), add Spironolactone or Hydralazine. Isosorbide Dinitrate (preload) and Hydralazine (afterload) are given as a combination medication BiDil®.
- When the situation is dire (class IV) it's time to add inotropes like Dobutamine (which is a continuous infusion) while preparing for a transplant or ventricular assist device bridging them to transplant. Ambulatory infusion devices are available.

Other:

- To reduce the risk of sudden cardiac death: Beta-blockers are used to reduce arrhythmia and neuro-hormonal remodeling.
- Other considerations are the placement of an AICD if the EF < 35% and they're NOT class IV.
- Digoxin can be used if there's need of symptom relief (it won't change mortality).

Patient	*Treatment*
Everybody	**Salt <2g** per day **H_2O < 2L** per day **ACE-i** or **ARB** (best mortality benefit) **Beta-Blocker**
Preload Reduction	Diuretics such as **Furosemide** Nitrates such as **Isosorbide Dinitrate** Dietary Modifications (NaCl, H_2O)
Afterload Reduction	ACE-i or ARB Hydralazine Spironolactone

Special	*Treatment*
EF < 35%	**AICD** (must be Class I-III)
Ischemic	**ASA** and **Statin**
Class IV	**Inotropes** like **Dobutamine** (ICU) VAD bridge to transplant **Transplant**



Acute Exacerbation

- The precipitant of a CHF exacerbation (which usually means volume overload) can be a product of:
  - dietary noncompliance
  - medication noncompliance
  - blood pressure control
  - ischemia or arrhythmia
- The goal is the same as for chronic management:
  - afterload reduction (aka blood pressure control)
  - preload reduction (diuresis and nitrates)
- Ruling out acute ischemia (which should be treated as an MI) and other causes of dyspnea is important.
- But the person who is overtly overloaded (JVD, crackles, peripheral edema) with an elevated BNP needs aggressive diuresis with IV Furosemide and blood pressure control.
- Never start or increase a Beta-Blocker during an exacerbation.

Renal Disorders

Lectures List

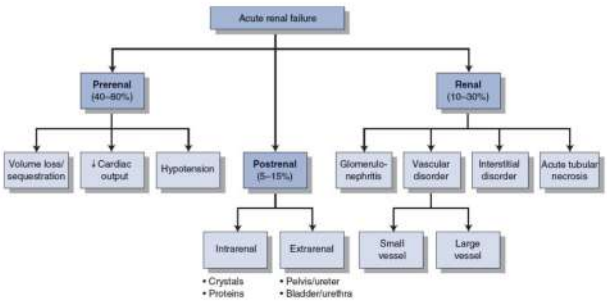
Renal disorders	
1	Acute kidney injury - To be able to identify stages, causes and initial work-up of acute kidney injury. - Identify indications for urgent dialysis. - To be able to distinguish between acute kidney injury and chronic kidney disease.
2	Chronic kidney disease and Renal replacement therapy - Recall the epidemiology of chronic kidney disease - Understand the definition of chronic kidney disease. - To be able to recall the classification of chronic kidney disease. - To be able to identify symptoms and signs of Uremia and its complications. - To be able to list key points in the management of chronic kidney disease.
3	Glomerular disease & Tubulointerstitial diseases - To understand nephrotic and nephritic range proteinuria. - To list common causes of nephritic range proteinuria. - To be able to approach patients with nephrotic syndrome. - Understand pathophysiology of glomerulonephritis and its common causes and complications and basic management. - Understand pathophysiology of Tubulointerstitial diseases and its common causes and complications and basic management.
4	Electrolytes imbalance and acid-base disorder - To be able to identify the type of hyponatremia (euvolemic-hypovolemic-hypervolemic) based on clinical presentation and laboratory finding. - Recognize true and pseudo-hyponatremia. - To be able to manage a patient with hypokalemia/ hyperkalemia. - To be able to Interpret arterial blood gases. - To be able calculate respiratory and metabolic compensation for acid/base disturbances. - To be able calculate anion gap with correction for serum albumin.

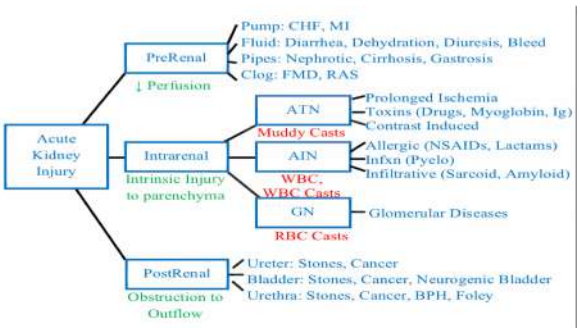
Acute kidney injury

- To be able to identify stages, causes and initial work-up of acute kidney injury.

The diagnosis of AKI requires an acute increase in serum creatinine and/or decrease in urine output (see the criteria for different stages in the table below); therefore, renal function tests should be done in every patient with suspected AKI
Additional laboratory investigations and imaging should be guided by the suspected cause.

Stages of AKI by Kidney Disease Improving Global Outcomes (KDIGO, 2012)		
Stage	Serum creatinine	Urine output
1	• Increase of 0.3 mg/dL (26.5 µmol/L) within 48 h or • 1.5–1.9 times baseline within 7 days	• < 0.5 mL/kg/h for 6–12 h
2	• 2–2.9 times baseline	• < 0.5 ml/kg/h for ≥12 h
3	• ≥ 3 times baseline or • Increase to ≥ 4 mg/dL (354 µmol/L) or • Initiation of renal replacement therapy or • Patients < 18 years: decrease in eGFR to < 35 mL/min/1.73 m^2	• < 0.3 mL/kg/h for ≥ 24 h or • Anuria for ≥ 12 h





❖ **Prerenal failure**

1. Most common cause of AKI; potentially reversible
2. **Etiology** (decrease in systemic arterial blood volume or renal perfusion leading to renal ischemia)-can complicate any disease that causes hypovolemia, low cardiac output, or systemic vasodilation
    a. Hypovolemia-dehydration, excessive diuretic use, poor fluid intake, vomiting, diarrhea, burns, hemorrhage
    b. CHF, cardiorenal syndrome Hypotension (systolic BP below 90 mm Hg), from sepsis, excessive antihypertensive medications, bleeding, dehydration
    c. Renal arterial obstruction (kidney is hypoperfused despite elevated blood pressure)
    d. Cirrhosis, hepatorenal syndrome
    e. In patients with decreased renal perfusion, NSAIDS (constrict afferent arteriole), ACE inhibitors (cause efferent arteriole vasodilation), and cyclosporin can precipitate prerenal failure.

3. **Clinical features**-signs of volume depletion (dry mucous membranes, hypotension, tachycardia, decreased tissue turgor, oliguria/anuria)

3. **Laboratory findings**
    a. Oliguria-always found in prerenal failure (this is to preserve volume)
    b. Increased BUN-to-serum Cr ratio (>20:1 is the classic ratio)-because kidney can reabsorb urea to increase sodium and water retention
    c. Increased urine osmolality (>500 mOsm/kg H2O)–because the kidney is able to appropriately reabsorb water
    d. Decreased urine Na+ (<20 mEq/L with fractional excretion of sodium [FENa] <1%) because Na+ is avidly reabsorbed
    e. Increased urine-plasma Cr ratio (>40:1)–because much of the filtrate is reabsorbed (but not the creatinine)
    f. Bland urine sediment, indicating lack of significant cellular damage to glomeruli or tubules

❖ **Intrinsic renal failure**

1. Kidney tissue (interstitium, glomeruli, tubules) is damaged such that glomerular filtration and tubular function are significantly impaired. Thus, kidneys are unable to concentrate urine effectively.
2. **Causes**
    a. Tubular disease (ATN)–can be caused by ischemia (most common cause), nephrotoxins
    b. Glomerular disease (acute glomerulonephritis [GN])–for example, Goodpasture syndrome, granulomatosis with polyangiitis, poststreptococcal GN, lupus
    c. Interstitial disease-for example, allergic interstitial nephritis, often due to a hypersensitivity reaction to medication
    d. Vascular disease-for example, renal artery occlusion, TTP, HUS
3. **Clinical features** depend on the cause. Edema is usually present. Recovery may be possible but takes longer than in prerenal failure.
4. **Laboratory findings**
    a. Decreased BUN-to-serum Cr ratio (<20:1, typically closer to 10:1 ratio) in comparison with prerenal failure. Both BUN and Cr levels are still elevated, but less urea is reabsorbed than in prerenal failure as kidney is no longer actively reabsorbing it.
    b. Increased urine Na+ (>40 mEq/L with FENa > 2% to 3%)-because Na+ is poorly reabsorbed
    c. Decreased urine osmolality (<350 mOsm/kg H2O)–because renal water reabsorption is impaired
    d. Decreased urine-plasma Cr ratio (<20:1)–because filtrate cannot be reabsorbed

	Prerenal	Intrinsic Renal
Urinalysis	Hyaline casts	Abnormal
BUN/Cr Ratio	>20:1	<20:1
FENa	<1%	>2–3%
Urine Osmolality	>500 mOsm	250–300 mOsm
Urine Sodium	<20	>40

❖ **Postrenal failure**

1. Least common cause of AKI
2. Obstruction of any segment of the urinary tract (with intact kidney) causes increased tubular pressure (urine produced cannot be excreted), which leads to decreased GFR. Blood supply and renal parenchyma are intact. Note that both kidneys must be obstructed (e.g., prostatic enlargement) for creatinine to rise.
3. Renal function is restored if obstruction is relieved before the kidneys are damaged.
4. Postrenal obstruction, if untreated, can lead to ATN.
5. **Causes**
    a. Urethral obstruction secondary to enlarged prostate (BPH) is the most common cause
    b. Obstruction of solitary kidney

● Identify indications for urgent dialysis.

- Metabolic acidosis of pH < 7.1
- Refractory hyperkalemia, hypercalcemia
- Toxic substances (e.g., lithium, toxic alcohols)
- Refractory fluid overload
- Signs of uremia, including pericarditis, encephalopathy, and asterixis on exam

Mnemonic for indications for dialysis: A-E-I-O-U → Acidosis, Electrolyte abnormalities (hyperkalemia), Ingestion (of toxins), Overload (fluid), Uremic symptoms

- To be able to distinguish between acute kidney injury and chronic kidney disease.

A detailed and accurate history is crucial for diagnosing acute kidney injury (AKI) and determining treatment. Distinguishing AKI from chronic kidney disease is important, yet making the distinction can be difficult; chronic kidney disease is itself an important risk factor for AKI. A history of chronic symptoms—months of fatigue, weight loss, anorexia, nocturia, sleep disturbance, and pruritus—suggests chronic kidney disease. AKI can cause identical symptoms, but over a shorter course.

TABLE 47-1 COMPARISON OF ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE

	Acute Kidney Injury	Chronic Kidney Disease
Onset	Sudden	Gradual, often over many years
Most common cause	Acute tubular necrosis	Diabetic nephropathy
Diagnostic criteria	Acute reduction in urine output and/or Elevation in serum creatinine	GFR <60 mL/min/1.73m^2 for >3 mo and/or Kidney damage >3 mo
Reversibility	Potentially	Progressive and irreversible
Primary cause of death	Infection	Cardiovascular disease

GFR, Glomerular filtration rate.

CKD & Renal replacement therapy

- Recall the epidemiology of chronic kidney disease
- Understand the definition of chronic kidney disease.

Chronic kidney disease (CKD) is defined as an abnormality of the kidney structure or function for ≥ 3 months. The most common causes of CKD in the United States are diabetes mellitus, hypertension, and glomerulonephritis. Since the kidneys have exceptional compensatory mechanisms, most patients remain asymptomatic until kidney function is significantly impaired. Patients **typically** present with symptoms of fluid overload (e.g., peripheral edema) and uremia (e.g., fatigue, pruritus). Laboratory studies show hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis. Management focuses mainly on treating the underlying disease and preventing possible complications, e.g., treating hypertension, avoiding nephrotoxic substances, and maintaining adequate hydration. If chronic kidney disease progresses to end-stage renal disease (ESRD), renal replacement therapy (i.e., dialysis or kidney transplantation) becomes necessary.

❖ Definition

Chronic kidney disease is defined as an eGFR < 60 mL/min/1.73 m2 and/or persistence ≥ 3 months findings indicating irreversible kidney damage, such as:

- Albuminuria (ACR > 30 mg/g) or hematuria
- Electrolyte imbalances
- Retention of nitrogenous wastes
- Acid-base imbalances
- Reduced production of erythropoietin, 1,25-(OH)2 vitamin D3 and/or renin
- Imaging showing structural abnormalities (e.g., polycystic kidney disease)

❖ Epidemiology

- CKD is more common in people aged 65 years or older (38%) than in people aged 45–64 years (12%) or 18–44 years (6%).
- CKD is slightly more common in women (14%) than men (12%).
- CKD is more common in non-Hispanic Black adults (16%) than in non-Hispanic White adults (13%) or non-Hispanic Asian adults (13%).
- About 14% of Hispanic adults have CKD.

- To be able to recall the classification of chronic kidney disease

Category	eGFR (mL/min/1.73 m^2)	Description
G1	> 90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

Albuminuria categories [8]			
Category	Urinary albumin excretion		Description
	mg/g	mg/mmol	
A1	< 30	< 3	Normal to mildly increased
A2	30–300	3–30	Moderately increased (microalbuminuria)
A3	> 300	> 30	Severely increased (macroalbuminuria)

Staging of CKD				
GFR category	eGFR (mL/min/1.73 m^2)	Albuminuria category		
		A1 < 30 mg/g or < 3 mg/mmol	A2 30–300 mg/g or 3–30 mg/mmol	A3 > 300 mg/g or > 30 mg/mmol
G1	> 90	G1A1	G1A2	G1A3
G2	60–89	G2A1	G2A2	G2A3
G3a	45–59	G3aA1	G3aA2	G3aA3
G3b	30–44	G3bA1	G3bA2	G3bA3
G4	15–29	G4A1	G4A2	G4A3
G5	< 15	G5A1	G5A2	G5A3

Interpretation

- **Not considered CKD** (unless there is evidence of kidney damage, e.g., imaging showing PCKD)
  - G1A1
  - G2A1
- **Mild CKD**
  - G1A2
  - G2A2
  - G3aA1
- **CKD**
  - G1A3
  - G2A3
  - G3aA2
  - G3bA1
- **End-stage kidney disease**
  - G3aA3
  - G3bA2, G3bA3
  - G4A1, G4A2, G4A3
  - G5A1, G5A2, G5A3

Stage	Description	GFR (ml/min/1.73m2)[5]
1	Kidney damage with normal or ↑ GFR You need evidence of kidney injury either by: ➔ Lab tests: high urea, high creatinine, hematuria, proteinuria or cast. ➔ Radiological evidence like cyst(s), shrinking kidney, kidney scars, kidney stones or hydronephrosis. انتبهوا للنقطة هذي انه لازم يكون فيه evidence.	≥ 90 شخص سليم معافى طبيعي بيكون ال GFR عنده اكثر من 100، لكن ما نقول عنه انت سليم ! ليه؟ لأن ماعنده Evidence of kidney injury
2	evidence of kidney injury + Mild ↓ GFR	60 – 89
3	evidence of kidney injury Moderate ↓ GFR	30 – 59
4	evidence of kidney injury Severe ↓ GFR	15 – 29
5	Kidney failure, (ESRD)	<15 or dialysis

- To be able to identify symptoms and signs of Uremia and its complications.

Definition: Uremia is defined as the accumulation of toxic substances due to decreased renal excretion. These toxic substances are mostly metabolites of proteins such as urea, creatinine, β2 microglobulin, and parathyroid hormone.

- **Constitutional symptoms**
  - Fatigue
  - Weakness
  - Headaches
- **Gastrointestinal symptoms**
  - Nausea and vomiting
  - Loss of appetite
- **Uremic fetor:** characteristic ammonia- or urine-like breath odor
- **Dermatological manifestations**
  - Pruritus
  - Skin color changes (e.g., hyperpigmentation, pallor due to anemia)
  - Uremic frost: uremia leads to high levels of urea secreted in the sweat, the evaporation of which may result in tiny crystallized yellow-white urea deposits on the skin.

- **Serositis**
  - Uremic pericarditis: a complication of chronic kidney disease that causes fibrinous pericarditis, Clinical features: chest pain worsened by inhalation, Physical examination findings: Friction rub on auscultation, ECG changes normally seen in nonuremic pericarditis (e.g., diffuse ST-segment elevation) are not usually seen.
  - Pleuritis
- **Neurological symptoms**
  - Asterixis
  - Signs of encephalopathy
  - Seizures
  - Somnolence
  - Coma
  - Peripheral neuropathy → paresthesias
- **Hematologic symptoms**
  - Anemia (caused by ↑ destruction of RBCs)
  - Leukocyte dysfunction → ↑ risk of infection
  - ↑ Bleeding tendency caused by abnormal platelet adhesion and aggregation

- To be able to list key points in the management of CKD

The overall management of chronic kidney disease is to prevent progression and manage complications.

❖ General measures

- **Diet**
  - Fluid intake: monitor appropriate fluid intake
  - Mediterranean diet, ↑ fruit and vegetable intake
  - Protein restriction to 0.55–0.6 g/kg/day
  - Electrolytes restriction: Sodium, Potassium and magnesium
- **Micronutrients:** vitamin D supplementation with cholecalciferol/ergocalciferol
- **Avoidance of nephrotoxic substances**
- **Vaccination**
  - Recommended immunizations: influenza, Pneumococcus, and varicella zoster, MMR and varicella for individuals who were vaccinated as infants or currently do not have immunity
- **Pharmacological Treatment**
  - Treat the hypertension, diabetes, dyslipidemia and any complications

Intervention	*Goal*	*Progression*
ACE-inhibitor	BP <130 / <80	HTN
Insulin	bG 80-110	DM

Complication	*Goal*	*Example*
Anemia	Hgb > 10	EPO, Iron
Secondary Hyperparathyroidism	PTH	Calcimimetics Phos Binders
Osteoporosis	Dexa > -2.5	Ca, 1,25VitD
Volume Overload	None	Loops Hemodialysis
Metabolic Acidosis	Bicarb > 20	NaBicarb

Glomerular disease & Tubulointerstitial diseases

- To understand nephrotic and nephritic range proteinuria.
- To list common causes of nephritic range proteinuria.

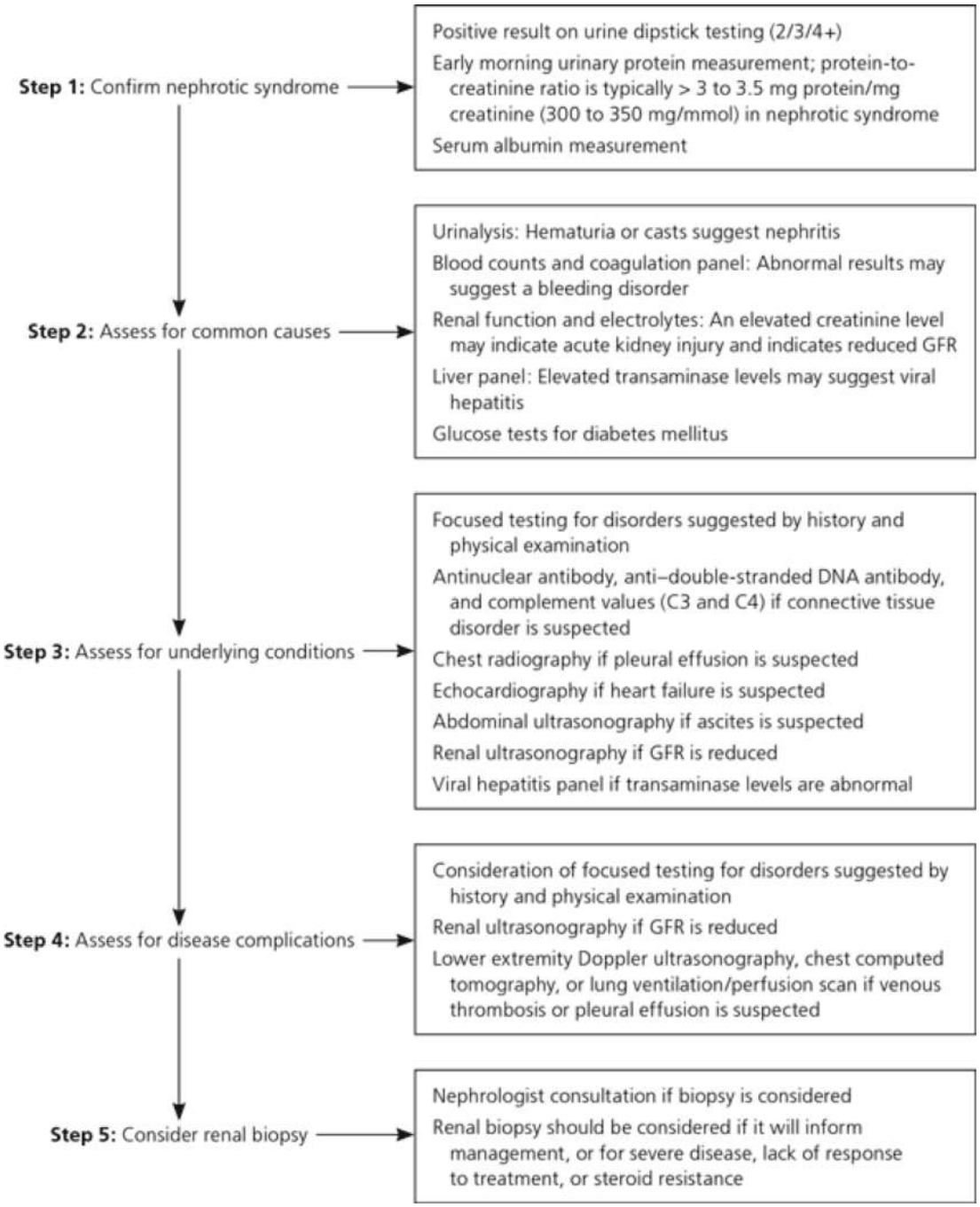
1. Nephrotic syndrome

- is a collection of signs and symptoms indicating damage to the glomerular filtration barrier.
- It is characterized by massive proteinuria (> 3.5 g/24 hours), hypoalbuminemia, and edema.
- **causes**
  - In adults, the most common causes of nephrotic syndrome include membranous nephropathy, followed by focal segmental glomerulosclerosis (FSGS) and membranoproliferative GN.
  - In children, nephrotic syndrome is most commonly caused by minimal change disease (MCD).
- Nephrotic syndrome can also be a manifestation of advanced renal disease in systemic conditions (e.g., diabetic nephropathy or amyloid nephropathy).
- Typical **laboratory findings** of nephrotic syndrome include hyperlipidemia and fatty casts on urinalysis.
- **Treatment** for FSGS, membranous nephropathy, and MCD usually includes immunosuppressive therapy.
- Nephrotic syndrome due to advanced renal disease is associated with a worse prognosis and is more difficult to treat.

2. Nephritic syndrome

- is characterized by glomerular capillary damage leading to hematuria, pyuria, water retention, and subsequent hypertension and edema.
- It can be **caused by** a variety of conditions including autoimmune, hereditary, and infectious diseases.
- Nephritic diseases can manifest with varying degrees of severity, ranging from asymptomatic hematuria to systemic involvement, as in rapidly progressive glomerulonephritis.
- The urine sediment is typically characterized by red blood cell casts, mild to moderate proteinuria (< 3.5 g/day), and sterile pyuria.
- **Diagnosis** of the underlying disease is often based on presentation and laboratory values, although renal biopsy may be indicated for confirmation.

- To be able to approach patients with nephrotic syndrome.



- Understand pathophysiology of glomerulonephritis and its common causes and complications and basic management.

	Nephritic syndrome	Nephrotic syndrome
Presentation	• Proteinuria (< 3.5 g/day) (can be in nephrotic range in severe cases) • **Hematuria** with acanthocytes • **RBC casts** in urine • Mild to moderate edema • Oliguria • Azotemia • **Hypertension** • Sterile pyuria	• **Heavy proteinuria (> 3.5 g/day)** • Hypoalbuminemia • **Generalized edema** • **Hyperlipidemia** and **fatty casts** in urine → frothy urine • Hypertension • ↑ Risk of thromboembolism: (via loss of antithrombin III) • ↑ Risk of infection (via loss of IgG and tissue edema which compromises the local blood supply and immune response)
Pathophysiology	• Inflammatory response within glomeruli → GBM disruption → loss of renally excreted RBCs (acanthocytes) and ↓ GFR → hematuria, oliguria, azotemia, and ↑ renin → edema and hypertension	• Damage to podocytes → structural damage of glomerular filtration barrier → massive renal loss of protein

Causes	• **Poststreptococcal glomerulonephritis**
	• **IgA nephropathy** (Berger disease)
	• Granulomatosis with polyangiitis
	• Microscopic polyangiitis
	• Eosinophilic granulomatosis with polyangiitis
	• **Goodpasture syndrome** (anti-GBM disease)
	• **Alport syndrome** (hereditary nephritis)
	• Thin basement membrane disease
	• **Rapidly progressive glomerulonephritis** (RPGN)
	• Lupus nephritis
	• Most common causes of nephritic-nephrotic syndrome:
	  ◦ Membranoproliferative glomerulonephritis
	  ◦ Diffuse proliferative glomerulonephritis
		• Due to primary or secondary podocyte damage
		  ◦ **Minimal change disease**
		  ◦ **Focal segmental glomerulosclerosis**
		  ◦ **Membranous nephropathy**
		• Due to secondary podocyte damage
		  ◦ **Diabetic nephropathy**
		  ◦ Amyloid light-chain (AL) **amyloidosis**, light chain deposition disease
		  ◦ Lupus nephritis

❖ Complications

Progression to sclerosis is rare in the typical patient; however, in 0.5-2% of patients with acute GN, the course progresses toward renal failure, resulting in kidney death in a short period.
Abnormal urinalysis (ie, microhematuria) may persist for years. A marked decline in the glomerular filtration rate (GFR) is rare.
Pulmonary edema and hypertension may develop. Generalized anasarca and hypoalbuminemia may develop secondary to severe proteinuria.
A number of complications that result in relevant end-organ damage in the central nervous system (CNS) or the cardiopulmonary system can develop in patients who present with severe hypertension, encephalopathy, and pulmonary edema. Those complications include the following:

- Hypertensive retinopathy
- Hypertensive encephalopathy
- Rapidly progressive GN
- Chronic renal failure
- Nephrotic syndrome

❖ **Treatment of:**

1. Nephritic syndrome:

- **Supportive therapy**
  - Low-sodium diet
  - Water restriction
- **Medical therapy**
  - If proteinuria and/or hypertension: angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
  - If severe hypertension and/or edema: diuretics
  - Sometimes immunosuppressive therapy is indicated (e.g., in lupus nephritis).
  - If RPGN from anti-GBM antibody disease: plasmapheresis
- **In the case of:**
  - Severe renal insufficiency or kidney failure: renal replacement therapy (e.g., hemodialysis, possibly transplantation)
  - Membranoproliferative glomerulonephritis (type 1 and type 2 MPGN):
    >> RAAS inhibitors are often added to treatment
    >> Prednisone alone or in combination with other immunosuppressants (cyclosporine OR tacrolimus)

2. Nephrotic syndrome:

- Control of the underlying disease, usually with glucocorticoids in the primary disorders.
- If steroids do not work, add cyclophosphamide or mycophenolate. Azathioprine may be useful.
- An ACE inhibitor or angiotensin receptor blocker (ARB) is used for all patients with proteinuria, but they do not reverse the underlying disease.
- The following may also be helpful:
  - Diuretics for edema
  - ACE inhibitors/ARBs (equal efficacy) for control of proteinuria and hypertension
  - Statins for hyperlipidemia
  - Anticoagulation if DVT or PE ensues
  - Good protein-calorie nutrition. Protein restriction is NOT indicated.

- Understand pathophysiology of Tubulointerstitial diseases and its common causes and complications and basic management.

Tubulointerstitial diseases

1. are characterized by acute or chronic inflammation of the renal tubules and interstitium.
2. Acute interstitial nephritis is commonly caused by hypersensitivity reactions to drugs, but infection or systemic disease may also precipitate the disease.
3. Common **causes** of chronic nephritis include drug toxicity (especially analgesics), metabolic disease (e.g., uric acid nephropathy), and other underlying conditions (e.g., multiple myeloma).
4. Typical **symptoms** in both acute and chronic nephritis are painless hematuria (without RBC casts) and pyuria.
    a. Depending on the underlying disease, nephritis may present with additional symptoms such as rash, arthralgias, and fever in the case of allergic interstitial nephritis.
5. The most important **diagnostic** modalities are lab tests (increased BUN and creatinine) and urinalysis, although a kidney biopsy may be indicated in selected cases.
6. **Treatment** usually consists of supportive measures and addressing the underlying cause (e.g., discontinuing medication).
7. All diseases affecting the renal tubules can ultimately lead to chronic renal failure.

Acute tubulointerstitial nephritis		
	Allergic interstitial nephritis [3]	**Crystal-induced acute kidney injury** [4]
Etiology	• **Antibiotics** (e.g., rifampin, penicillins, cephalosporins, sulfonamides), **NSAIDs**, diuretics, allopurinol, **proton pump inhibitors** (PPIs), phenytoin, quinolones [5]	• Medications (e.g, acyclovir, indinavir, ciprofloxacin, methotrexate)
Pathophysiology	• Drugs act as haptens, inducing a **type IV hypersensitivity reaction**.	• Drugs with low urine solubility **precipitate** within the renal tubules → tubular obstruction and toxicity to tubules
Clinical features	• Can be asymptomatic • Flank pain and costovertebral angle tenderness • Rash • Fever • Arthralgia	• Patients are usually asymptomatic. • Renal colic
Diagnostics	• Blood: elevated serum creatinine, eosinophilia • Urine: pyuria (typically eosinophiluria), microscopic hematuria • Renal biopsy: may show diffuse interstitial T-cell and monocyte infiltration	• Crystals on brightfield microscopy
Management	• Discontinue drugs and administer IV fluids [5]	
Prognosis	• Acute interstitial nephritis generally has a good prognosis, if it is recognized and managed early.	

Chronic tubulointerstitial nephritis		
Features	**Analgesic nephropathy** [7]	**Myeloma cast nephropathy** [8]
Etiology	• **NSAIDs** and **acetaminophen** • Formerly associated with phenacetin intake (no longer FDA-approved)	• Multiple myeloma
Pathophysiology	• NSAIDs: inhibition of prostacyclin synthesis → vasoconstriction of the medullary blood vessels → papillary ischemia and papillary necrosis • Acetaminophen: not very well understood [9]	• Excessive amounts of light chains are produced and filtered into the primary urine → precipitation of **light chains** in renal tubules → tubular obstruction and toxicity to renal tissue
Clinical features	• Painless hematuria • Pyuria • Fatigue • Nausea	
	• Possible colicky pain due to papillary necrosis	• Oliguria • Symptoms of multiple myeloma (e.g., bone pain, hypercalcemia, anemia) • Peripheral edema and dyspnea
Management	• Treat underlying disease • Monitor kidney function • Consider glucocorticoids • In selected cases, (temporary) dialysis	• Treatment of multiple myeloma (chemotherapy) and hypercalcemia (fluids and bisphosphonates) • Forced diuresis • If necessary, plasmapheresis/dialysis
Prognosis	• Usually progresses to ESRD • Associated with an increased risk of urothelial carcinoma	

Electrolytes imbalance & acid-base disorder

- To be able to identify the type of hyponatremia (euvolemic-hypovolemic-hypervolemic) based on clinical presentation and laboratory finding.
- Recognize true and pseudo-hyponatremia.

Causes of hypotonic hyponatremia			
	Hypovolemic hypotonic hyponatremia	Euvolemic hypotonic hyponatremia	Hypervolemic hypotonic hyponatremia
Description	• Low extracellular fluid volume	• Normal or minimal changes in extracellular fluid volume	• High extracellular fluid volume
Renal causes	• Acute or chronic renal failure with high urine output (polyuria) • Diuretics • Mineralocorticoid deficiency (Addison disease) • Recovery phase of acute tubular necrosis • Cerebral salt wasting syndrome	• SIADH • Medication use • Exercise-associated hyponatremia (EAH) • Acute or chronic renal failure • Glucocorticoid deficiency (adrenal insufficiency) [5] • Severe hypothyroidism [1][5]	• Acute or chronic renal failure with low urine output (i.e., failure to excrete free water)

Extrarenal causes	• Diarrhea
	• Vomiting
	• Dermal fluid loss (e.g., burns, sweating)
	• Third space fluid loss (e.g., peritonitis, ascites)
	• Bleeding/hemorrhage
		• Decreased salt intake (e.g., "tea and toast" diet)
		• Water intoxication (dilutional hyponatremia)
		  ◦ Excessive infusion of hypotonic (e.g., 0.45% NaCl) or sodium-free isotonic IV fluids
		  ◦ Primary polydipsia
		  ◦ Beer potomania
		  ◦ Reset osmostat syndrome
			• Congestive heart failure
			• Liver cirrhosis
			• Severe hypoproteinemia (e.g., nephrotic syndrome)

Fluid compartment changes in hyponatremia				
Defined by		Changes		
Tonicity	Volume status	Serum osmolality	Total body water	Total body sodium
Hypotonic hyponatremia	Hypovolemic hypotonic hyponatremia	↓	↓	↓↓
	Euvolemic hypotonic hyponatremia	↓	↑	↓ Or normal
	Hypervolemic hypotonic hyponatremia	↓	↑↑	↑
Isotonic hyponatremia (pseudohyponatremia)		Normal	↑	Normal
Hypertonic hyponatremia		↑	↓	Normal

Hyponatremia

Definition

Low serum sodium concentration < 135 mEq/L (and in hypotonic/true hyponatremia also low serum osmolality < 280 mOsm/kg H_2O).

Onset: acute (< 48 hours) or chronic (≥ 48 hours or duration unknown)

Etiology

Hypovolemic: e.g., GI/renal/dermal losses, third-spacing, hemorrhage

Euvolemic: e.g., SIADH, low salt intake, water intoxication

Hypervolemic: e.g., renal failure with oliguria, congestive heart failure

Diagnostics

Serum sodium (corrected for hyperglycemia) and osmolality

Further serum/urine studies to identify etiology

Treatment

Acute or severe symptoms: Correct sodium quickly with hypertonic saline, then treat underlying cause.

Chronic without severe symptoms: Correct sodium slowly (cause-specific treatment).

Complications

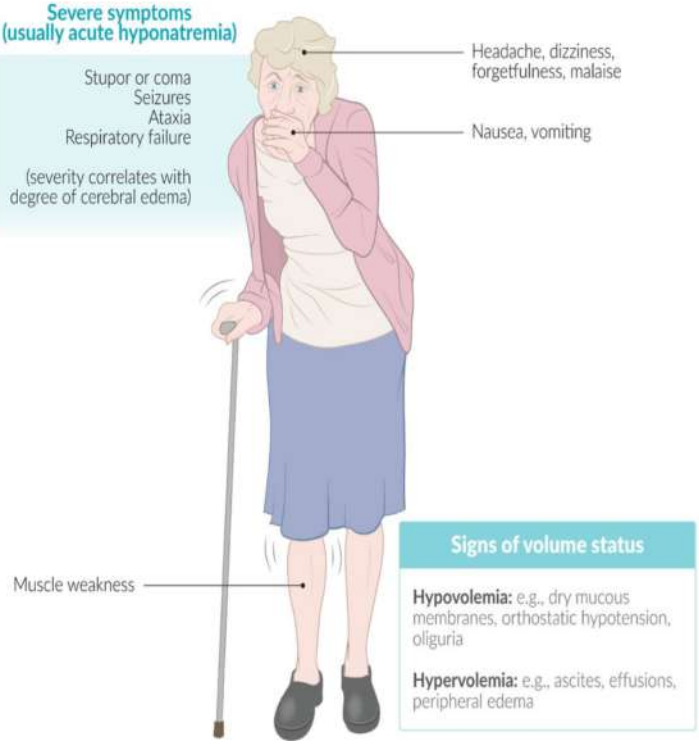
Secondary to hyponatremia: e.g., cerebral edema

Treatment-associated: e.g., osmotic demyelination syndrome

Severe symptoms (usually acute hyponatremia)

Stupor or coma
Seizures
Ataxia
Respiratory failure

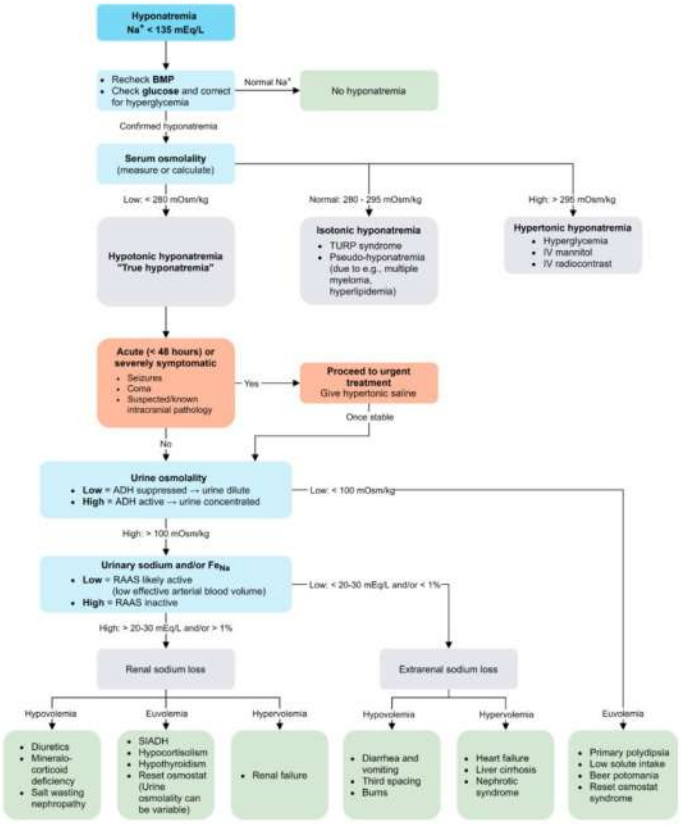
(severity correlates with degree of cerebral edema)



Signs of volume status

Hypovolemia: e.g., dry mucous membranes, orthostatic hypotension, oliguria

Hypervolemia: e.g., ascites, effusions, peripheral edema



- To be able to manage a patient with hypokalemia/ hyperkalemia.

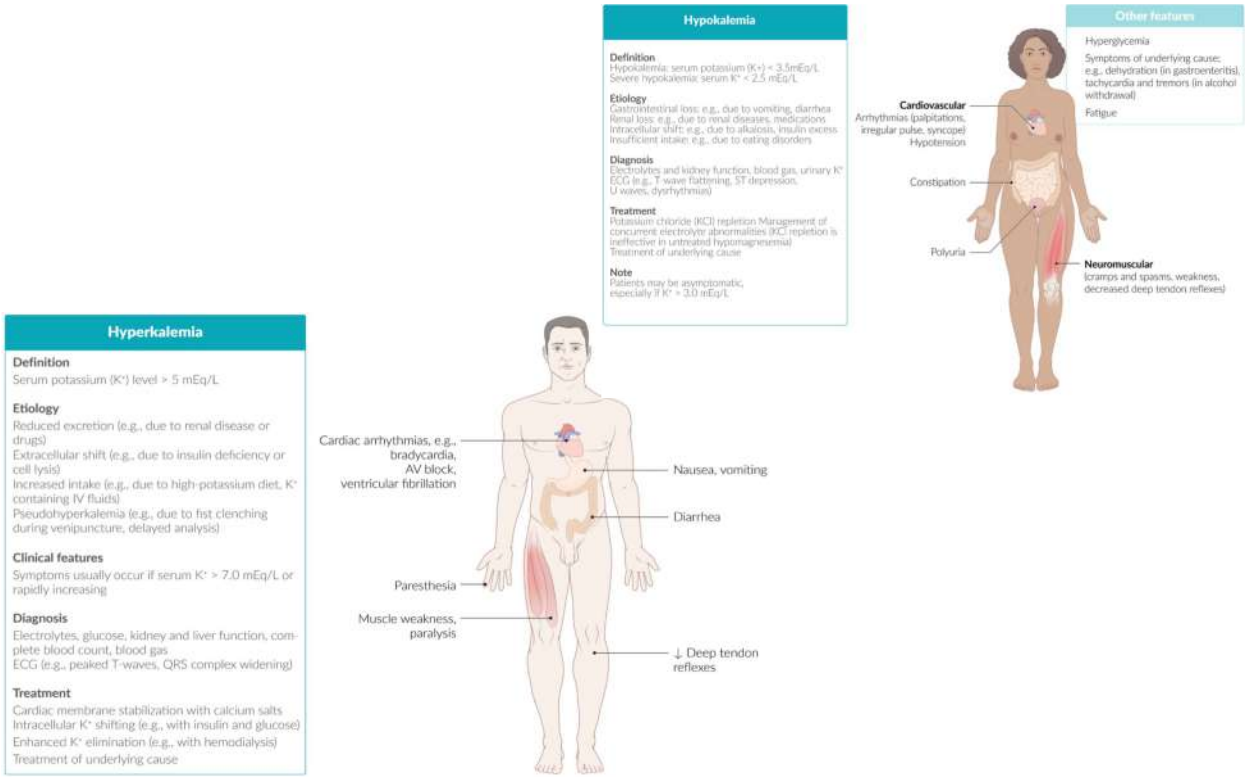
Therapeutic approach to hyperkalemia [14][21][9][2]		
Treatment strategy	**Acute hyperkalemia [24]**	**Chronic hyperkalemia**
Cardiac membrane stabilization	• If signs of cardiotoxicity: IV calcium chloride or calcium gluconate	• Not routinely required
Intracellular K^+ shifting	• **Short-acting insulin with glucose** • Consider inhaled SABAs.	

Enhanced K^+ elimination	• In refractory hyperkalemia:
	  ◦ Oliguria/ESRD: hemodialysis
	  ◦ Hypervolemia: Consider diuretics.
	  ◦ Metabolic acidosis: Consider IV 8.4% sodium bicarbonate.
	• Consider cation exchange medications
		• Consider one of the following:
		  ◦ Cation exchange medications
		  ◦ Diuretics
		  ◦ Oral sodium bicarbonate
		  ◦ If predialysis CKD: nephrology consult for renal replacement therapy

Reduced K^+ intake	• Low-potassium diet [10][25] • Consider dietitian consult.	

Treatment of underlying cause	• Medication review: Adjust medications that affect K^+ metabolism.
	  ◦ Decrease dose (or consider discontinuation) of drugs required to treat underlying conditions, e.g., RAAS inhibitors.
	  ◦ Recommend avoiding nonessential drugs associated with hyperkalemia (e.g., NSAIDs, OTC supplements).
	• Identify and treat other reversible conditions: e.g., primary adrenal insufficiency, AKI, tumor lysis syndrome.	

Monitoring and disposition	• Continuous cardiac monitoring if cardiotoxicity is present • Repeat serum K^+ every 2 hours • In refractory or severe hyperkalemia: Consider critical care consult.	• Serum K^+ prior to and after initiating drugs that affect K^+ metabolism • The frequency of serum K^+ monitoring should be tailored to the patient's comorbidities and prescribed medications. • Typically can be managed as outpatients



- To be able to Interpret arterial blood gases.
- To be able calculate respiratory and metabolic compensation for acid/base disturbances.
- To be able calculate anion gap with correction for serum albumin

Assessment of acid-base status

Start with an ABG and then proceed in the following order:

1. **Evaluate blood pH:**
    a. pH < 7.35 (acidemia): Primary disorder is an acidosis.
    b. pH > 7.45 (alkalemia): Primary disorder is an alkalosis.

2. **Evaluate pCO2 (partial pressure of carbon dioxide in blood, reference range: 33–45 mm Hg) to determine whether the primary acid-base disorder is respiratory or metabolic:**
    a. pH and pCO2 change in the opposite direction: respiratory disorder
        i. ↓ pH and ↑ pCO2: respiratory acidosis
        ii. ↑ pH and ↓ pCO2: respiratory alkalosis
    b. pCO2 and pH change in the same direction: metabolic disorder
        i. ↓ pH and ↓ pCO2: metabolic acidosis (calculate anion gap to identify the possible causes)
        ii. ↑ pH and ↑ pCO2: metabolic alkalosis
    c. Suspect a mixed acid-base disorder if:
        i. pCO2 or HCO3- is abnormal and pH is normal or did not change as expected (e.g., a very high pCO2 and a mild acidosis).
        ii. pCO2 and HCO3- shift towards acidosis (↑ pCO2 and ↓ HCO3-) or alkalosis (↓ pCO2 and ↑ HCO3-).
        iii. Lesser- or greater-than-expected compensatory response

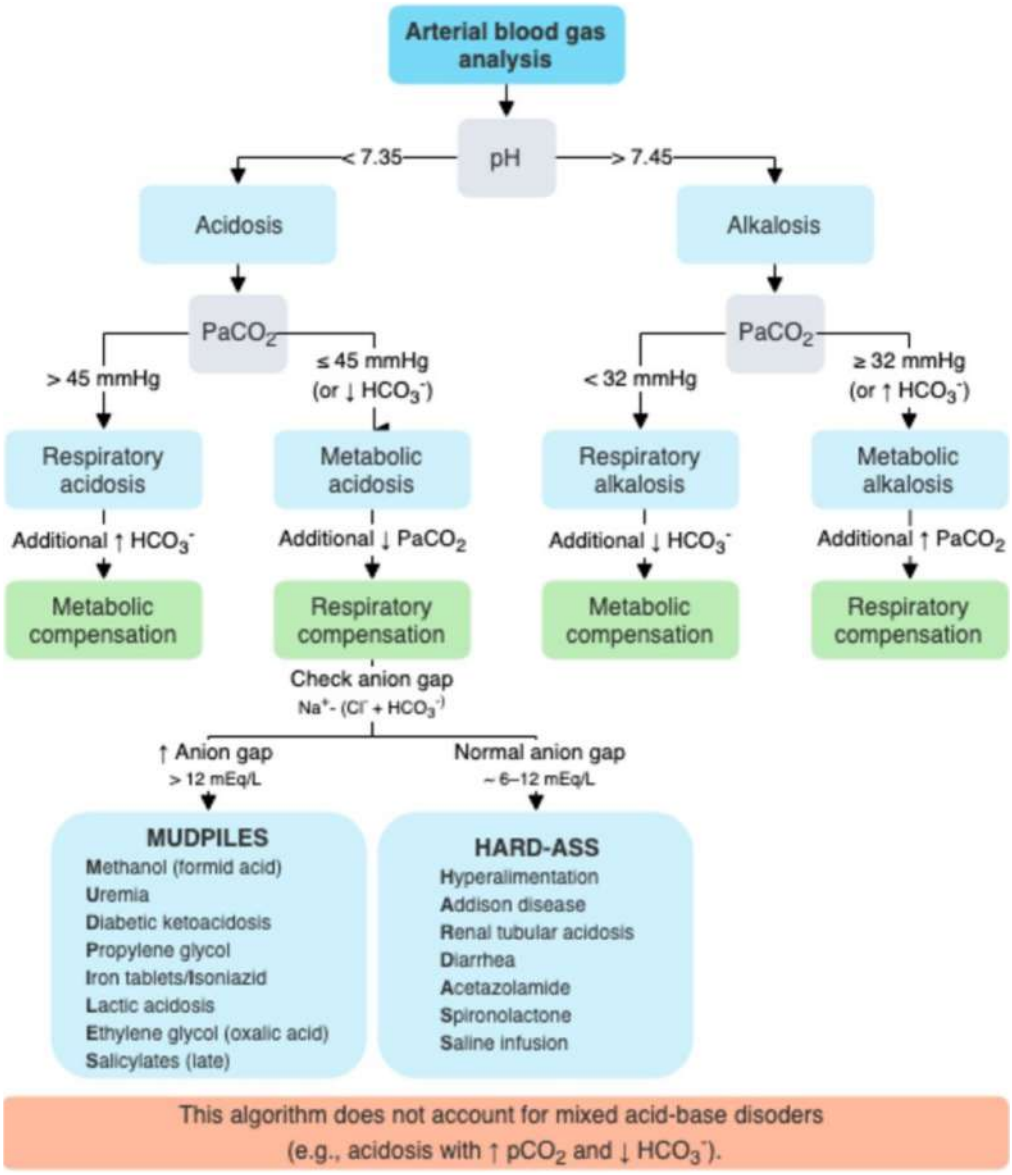
3. **Evaluate HCO3- (reference range: 22–28 mEq/L):**
    a. High: metabolic alkalosis or compensated respiratory acidosis
    b. Normal: uncompensated respiratory disorders
    c. Low: metabolic acidosis or compensated respiratory alkalosis

4. **Evaluate pO2:**
    a. High: hyperoxemia
    b. Low: hypoxemia

    Example:
    pH = 7.5, pCO2 = 20 mmHg, HCO3 = 22 mEq/L, pO2 = 70 mmHg
    Alkalosis (↑ pH), response disorder (↓ pCO2), uncompensated (normal HCO3), hypoxemia (↓ pO2): uncompensated respiratory alkalosis with hypoxemia

1. **Evaluate for anion gap**
    a. If potassium concentration is normal, anion gap ≈ [Na+] - ([Cl-] + [HCO3-]) (reference range: 6–12 mmol/L)

Compensation mechanisms in acid-base disorders			
Primary disorder		**Compensatory process**	**Expected compensation***
Metabolic acidosis		• ↓ Arterial and CSF pH (with ↓ HCO_3^-) → ↑ stimulation of the **medullary chemoreceptors** → ↑ **respiratory rate** and/or tidal volume (hyperventilation) → ↑ CO_2 washout → ↓ PCO_2	• **Winter formula** ◦ Expected PCO_2 = (1.5 x HCO_3^-) + 8 (+/- 2) ◦ Interpretation ▪ Measured PCO_2 > expected PCO_2: respiratory acidosis in addition to metabolic acidosis ▪ Measured PCO_2 < expected PCO_2: respiratory alkalosis addition to metabolic acidosis
Metabolic alkalosis		• ↑ Arterial and CSF pH (with ↑ HCO_3^-) → ↓ stimulation of the **medullary chemoreceptors** → ↓ **respiratory rate** and/or tidal volume (hypoventilation) → ↑ CO_2 retention → ↑ PCO_2	• Expected pCO2 = (0.7 x HCO_3^-) + 20 (+/- 5)
Respiratory acidosis	**Acute compensation**	• Buffers in blood	• Expected HCO_3^- = 24 + [0.1 x (pCO_2 - 40)] (+/- 3)
	Chronic compensation	• ↓ Arterial pH (with ↑ PCO_2) → ↑ **HCO_3^-** via: ◦ ↑ Reabsorption of HCO_3^- by the proximal convoluted tubule ◦ ↑ Excretion of H^+ as $H_2PO_4^-$ and NH_4^+ by the distal convoluted tubule and collecting duct	• Expected HCO_3^- = 24 + [0.4 x (pCO_2 - 40)] (+/- 3)
Respiratory alkalosis	**Acute compensation**	• Buffers in blood	• Expected HCO_3^- = 24 - [0.2 x (40 - pCO_2)] (+/- 3)
	Chronic compensation	• ↑ Arterial pH (with ↓ PCO_2) → ↓ **HCO_3^-** via: ◦ ↓ Reabsorption of HCO_3^- by the proximal convoluted tubule ◦ ↓ Renal excretion of H^+	• Expected HCO_3^- = 24 - [0.5 x (40 - pCO_2)] (+/- 3)
***If the expected compensation does not occur, a secondary acid-base disturbance will be present in addition to the primary disorder.**			



Rheumatological Disorders

Lectures List

	Rheumatological disorders
1	**Inflammatory joint diseases (include RA, Seronegative, crystal induce and joint infection**) - To identify the clinical presentation, radiographic features and appropriate investigations (labs, imaging) of inflammatory joint diseases - To be able to make a treatment plan for common Inflammatory joint diseases including (NSAIDs -DMARDs – biological therapy) and to know the most common side effects and precautions of drugs and the appropriate monitoring for the patients. - To be able to differentiate between inflammatory back pain from mechanical back pain and learn radiographic features that support diagnosis of Spondyloarthritis - To know extra-articular manifestations of Inflammatory joint disease - To be able to differentiate between gout, pseudogout and septic arthritis based on risk factors, radiological features and joint aspiration finding.
2	**Systemic connective tissue diseases (include SLE, Systemic sclerosis, Myositis*)** - To understand the clinical presentation of SLE, Systemic sclerosis and Myositis. - To know the systemic involvement of SLE, Systemic sclerosis, and Myositis. - To enlist the diagnostic modalities to establish the diagnosis of SLE, Systemic sclerosis and Myositis - To learn the treatment strategies for each system involved in SLE, Systemic sclerosis and Myositis - To learn the use and side effect of the drug used in treating Systemic connective tissue diseases (mainly Hydroxychloroquine, Mycophenolate, Azathioprine, Corticosteroid and cyclophosphamide) *Mainly dermatomyositis and polymyositis
3	**Osteoarthritis** - Understand the pathophysiology of osteoarthritis and its risk factors. - Recall the clinical manifestation and symptoms of osteoarthritis - To list the diagnostic modalities to establish the diagnosis and management.
4	**Vasculitis** - Understand the pathophysiology of vasculitis and recognize the common causes. - Identify the common presentations of different types of vasculitis. - List key management points for vasculitis

IJD (RA, Seronegative, crystal induce & joint infection)

- To identify the clinical presentation, radiographic features & appropriate investigations (labs, imaging) of inflammatory joint diseases
- To know extra-articular manifestations of Inflammatory joint disease

1. Rheumatoid arthritis

Clinical features of rheumatoid arthritis	
Clinical presentation	• Pain, swelling & morning stiffness in multiple joints • **Small joints** (PIP, MCP, MTP); spares DIP joints • Systemic symptoms (fever, weight loss, anemia) • **Cervical spine** involvement: subluxation, cord compression
Laboratory/imaging studies	• Positive rheumatoid factor & **anti-CCP antibodies** • C-reactive protein & ESR correlate with disease activity • **X-ray**: soft tissue swelling, joint space narrowing, bony erosions

Clinical Criteria
Symmetrical Arthritis, often of the hands, **Sparing DIP**
Morning Stiffness for > 60 minutes, improves with use
Multiple Joint Involvement (≥ **3**)
Radiographic Destruction of Joints (**erosions**)
+ Rheumatoid Factor or + **Anti CCP**
Rheumatoid Nodules

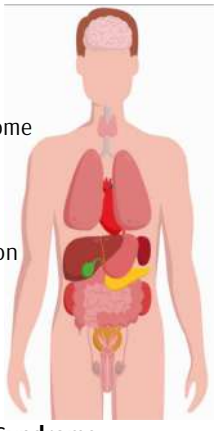
***N**obody **S**hould **H**ave **R**heumatoid **S**ymptoms **3** times (**X**)*
***N**: Nodules*
***S**: Symmetric*
***H**: Hands*
***R**: RF or CCP*
***S**: Stiffness*
***3**: 3 or more joints*
***X**: X-ray findings of erosions*

❖ Extra-articular manifestations

Constitutional
• Malaise, Anorexia, Some Weight Loss, Fever

Pulmonary
• Pleural effusions (very common)
• Pulmonary fibrosis
• Pulmonary infiltrates
• Rheumatic nodules in lungs -can cavitate or become infected

Cardiac
• Rheumatic nodules in heart can lead to conduction disturbances (heart block & bundle branch block)
• Pericarditis in 40%
• Pericardial effusion



Nervous System

Eyes
• Scleritis
• Scleromalacia-softening of the sclera
• Dry eyes, may develop Sjögren syndrome

Cutaneous
• Skin becomes thin and atrophic & bruises easily
• Vasculitic changes/ulcerations involving fingers, nail folds
• Subcutaneous rheumatoid nodules (elbows, sacrum, occiput) pathognomonic for RA

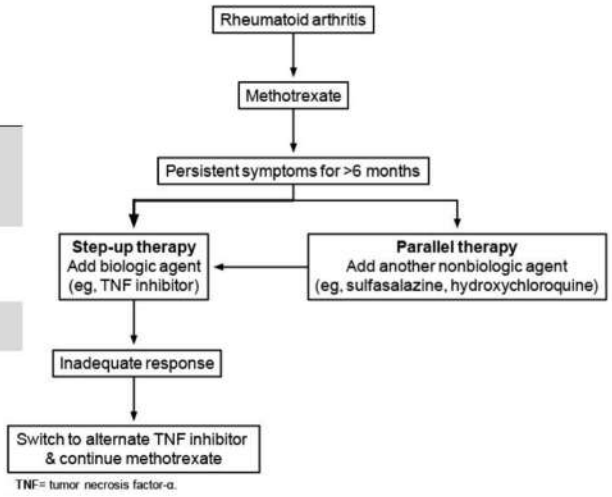
Felty Syndrome
• Triad of RA, neutropenia, and splenomegaly

❖ **Treatment**

- Start the treatment of RA with DMARDs as soon as possible.
- Methotrexate is the first line for RA.
- Leflunomide can be used if methotrexate can't be.
- Hydroxychloroquine and Sulfasalazine have long-acting effects that may be used together with methotrexate to avoid biologic therapy (doubling up is ok).
- Hydroxychloroquine is also appropriate for non-erosive mild disease and during pregnancy.
- The goal is treat-to-target (disease remission).
- If DMARDs fail add biologics.
    - Before starting biologics a TB screen and vaccines must be given as they significantly compromise immune function.
- Corticosteroids should be avoided
    - except during life threatening flares
    - to reduce long-term systemic side effects.
- NSAIDs can be used to control symptoms and are adjunctive therapy.

NSAIDs + DMARDS + Biologics .... Steroids
(Sxs) (everyone) (severe) (flares)

	Treatment
DMARD	Methotrexate (1st line) Leflunomide (2nd line) Hydroxychloroquine (pregnancy) Sulfasalazine (additive)
Anti-TNF	Etanercept Infliximab Rituximab
Glucocorticoid	Flares, get off this as soon as possible
NSAIDs	Supplemental only, NEVER MONOTHERAPY



2. Seronegative

Disease	*Presentation*	*Diagnosis*	*Extraarticular*	*Treatment*
Ankylosing Spondylitis	Back Pain + Morning Stiffness relieved by exercise (Sacroiliitis)	Bamboo spine on X-ray	IBD but independent of IBD course	NSAIDs Steroids Anti-TNF
Reactive Arthritis	Nongonococcal Urethritis Conjunctivitis Asymmetric Bilateral Arthritis	Ø PCR/DNA Chlamydia	Nongonococcal Urethritis (usually Chlamydia)	Doxycycline and NSAIDs
Psoriatic Arthritis	Psoriatic Patches Erosive pitting of nails MCP, DIP, PIP Arthritis	Ø	Psoriasis Arthritis may appear first	UV light NSAID (no skin) Methotrexate (skin)
Enteropathic Arthritis	Non-deforming, migratory, asymmetric Bilateral Arthritis In a patient with IBD	Ø	IBD and dependent of IBD course	Tx IBD with ASA compounds (mesalamine)

A. 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

In young patients with characteristic inflammatory back pain, plain x-rays of the pelvis showing sacroiliitis can confirm the diagnosis of AS. However, x-rays may be negative in early stages MRI can confirm sacroiliitis in such cases. Fusion of the vertebral bodies with ossification of intervertebral discs (bamboo spine) also suggests the diagnosis

B. Reactive Arthritis

- General Characteristics

- Reactive arthritis is asymmetric inflammatory oligoarthritis of lower extremities (upper extremities less common) The arthritis is preceded by an infectious process that is remote from the site of arthritis (1 to 4 weeks prior), usually after enteric or urogenital infections.
- It occurs mostly in HLA-B27–positive individuals.
- "Reiter syndrome" is an example of reactive arthritis, but most patients do not have the classic findings of Reiter syndrome (arthritis, uveitis, and urethritis), so the term reactive arthritis is now used.
- The organisms usually associated with reactive arthritis include Salmonella, Shigella, Campylobacter, Chlamydia, Yersinia.
- Look for evidence of infection (GI or genitourinary) 1 to 4 weeks before the onset of symptoms.

Antibiotics are not useful unless the patient is having an active infection

C. IBD-ASSOCIATED ARTHRITIS

A patient likely has inflammatory bowel disease (IBD) complicated by spondyloarthritis.
IBD, frequently presents in patients age 15-40 and again at age 50-80. Both CD and UC have multiple extraintestinal manifestations, including arthritis, eye (eg, uveitis, episcleritis) and skin (eg, pyoderma gangrenosum) involvement, and hepatobiliary disease (eg, primary sclerosing cholangitis). Arthritis occurs in up to 45% of patients with IBD and can involve axial (eg, spine) or peripheral (eg, knee) joints.
Patients with spondyloarthritis or sacroiliitis commonly report prolonged stiffness and low back or buttock pain that improves with activity. There are no specific tests for the diagnosis of IBD-associated arthritis. NSAIDs can RELIEVE arthritis symptoms but EXACERBATE the underlying bowel disease. Consequently, although NSAIDs are frequently tried, many of the medications (eg, sulfasalazine) used to treat the bowel disease itself are also used to treat joint disease.

D. Psoriatic arthritis

- Develops in 10% to 30% of patients with psoriasis. It is typically gradual in onset. Patients usually have skin disease for months to years before arthritis develops. Usually asymmetric and polyarticular. Characteristic dactylitis ("sausage digits") and nail pitting may also be present. Upper extremities most often involved; smaller joints more common than large joints.
- PsA Radiologic Features: Characteristic peripheral joint destruction progresses to cause "pencil in cup" Appearance

Arthritis in the presence of psoriasis is the key to clinical diagnosis.

Clinical features of psoriatic arthritis	
Arthritis	• DIP • ***Asymmetric* oligoarthritis** • ***Symmetric* polyarthritis**, similar to RA • **Arthritis mutilans** (deforming & destructive arthritis) • Spondylarthritides (sacroiliitis & spondylitis)
Soft tissue & nail involvement	• Enthesitis (inflammation at site of tendon insertion into 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

- To be able to make a treatment plan for common Inflammatory joint diseases including (NSAIDs -DMARDs – biological therapy) & to know the most common side effects and precautions of drugs & the appropriate monitoring for the patients.

Treatment	Side effects
NSAIDs	stomach problems i.e(bleeding, ulcer, and stomach upset), kidney problems, high blood pressure or heart problems,rashes, or other allergic reactions.
Methotrexate	GI upset, oral ulcers (stomatitis), mild alopecia, bone marrow suppression (co administer with folinic acid), hepatocellular injury, pulmonary fibrosis. It increases liver enzymes in some patients.
Glucocorticoid	increased appetite, acne, thinned skin that bruises easily, increased risk of infections, mood swings and depression, diabetes, osteoporosis, fluid retention & high blood pressure.
Anti-TNF	The most significant side effects for all of the TNF inhibitors is an increased risk for all types of infections, including tuberculosis (TB), fungal infections Hepatitis B reactivation

Disease-modifying antirheumatic drugs (DMARDs)		
Agent	**Mechanism**	**Adverse effects**
Methotrexate	Folate antimetabolite	• Hepatotoxicity • Stomatitis • Cytopenias
Leflunomide	Pyrimidine synthesis inhibitor	• Hepatotoxicity • Cytopenias
Hydroxychloroquine	TNF & IL-1 suppressor	• Retinopathy
Sulfasalazine	TNF & IL-1 suppressor	• Hepatotoxicity • Stomatitis • Hemolytic anemia
TNF inhibitors (eg, adalimumab, certolizumab, etanercept, golimumab, infliximab)		• Infection • Demyelination • Congestive heart failure • Malignancy

Synthetic DMARDs for RA [22][30][34]		
Drug class	**Agent**	**Important considerations**
Conventional DMARDs	• **Methotrexate** (MTX): first-line treatment in patients with moderate to high disease activity [34][30]	• Adverse effects [34][26][30] ◦ Stomatitis ◦ Pancytopenia ◦ ↑ AST, ALT ◦ Teratogenicity ◦ Pneumonitis • To minimize adverse effects, administer folic acid. [30] • Avoid administering NSAIDs on the same day as MTX.
	• Hydroxychloroquine: Consider in patients with low disease activity. [30]	• Adverse effects [22] ◦ Hyperpigmentation ◦ Retinopathy [30][26] ◦ Severe rash
	• Sulfasalazine: Consider in patients with low disease activity if MTX is contraindicated, e.g., during pregnancy. [30]	• Adverse effects [22][30] ◦ Diarrhea ◦ Agranulocytosis ◦ Cutaneous hypersensitivity reactions
	• **Leflunomide**: Consider if all other conventional DMARDs are contraindicated. [30] ◦ Mechanism of action: reversibly inhibits dihydroorotate dehydrogenase → impaired pyrimidine synthesis → inhibition of T-cell proliferation ◦ Other indications: psoriatic arthritis	• Adverse effects ◦ High blood pressure ◦ ↑ AST, ALT ◦ Teratogenicity ◦ GI symptoms (e.g., nausea, diarrhea)
Targeted DMARDs (JAK inhibitors)	• Tofacitinib or baricitinib: second-line treatment	• Adverse effects ◦ Severe infections ◦ TB reactivation ◦ Anemia [30]

Biologic DMARDs

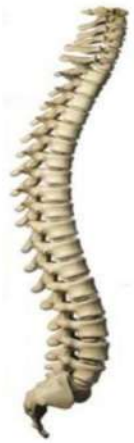
- Agents:
  - TNF-α inhibitors: e.g., adalimumab , infliximab , etanercept
  - Others: rituximab (anti-CD20), anakinra (IL-1 receptor antagonist, particularly for Still disease), tocilizumab (IL-6 receptor antagonist)
- Prevention and monitoring of adverse effects
  - Perform studies and vaccinations before the initiation of therapy based on the patient's individual risk and potential adverse effects of the prospective agent.
  - CBC, liver transaminases, and serum creatinine at baseline

a. Vaccinations for patients receiving biologic DMARDs: Influenza, pneumococcus, and hepatitis B

- Contraindications to anti-TNF-α treatment (infliximab, adalimumab, etanercept)
  - Pregnancy
  - Chronic infections, particularly tuberculosis: Rule out latent tuberculosis before starting therapy (the activity of TNF-α plays a major role in formation and stabilization of granulomas against Mycobacterium tuberculosis).
  - Multiple sclerosis
  - Malignancy
  - Immunosuppressed individuals
  - Systemic or localized infections
  - Moderate to severe heart failure (NYHA class III/IV)

- To be able to differentiate between inflammatory back pain from mechanical back pain & learn radiographic features that support diagnosis of Spondyloarthritis

IBP	MBP
Age of onset: <40 years (15-45)	Ex: Disc / Muscle strain ...etc Age of onset: any age
Insidious onset: **less likely to be acute**	Variable onset: may be acute
Pain improves with exercise Ptn keeps moving in waiting room and cant sit	Usually following trauma
Pain does not improve with rest	Pain may worsen with movement
Morning stiffness >30 minutes	Pain often improves with rest
Pain at night (especially in buttuck + alternating) which may wake patient during second half of the night	

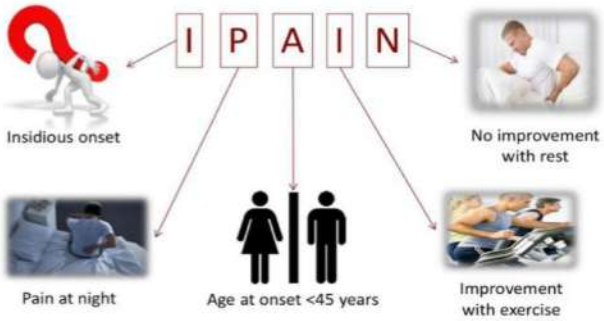


Spondyloarthropathy Patients will have symptoms of IBP not MBP!

Inflammatory back pain:

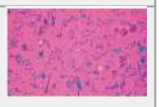
Chronic back pain (>3 months) IBP criteria are fulfilled if at least 4 out of 5 parameters are present:

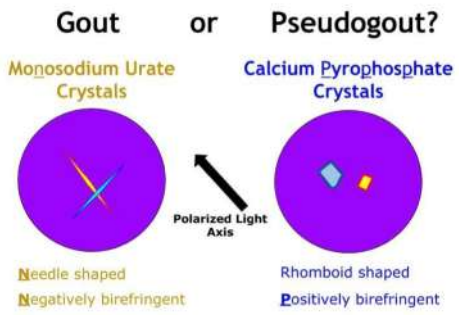
IPAIN:
Insidious onset
Pain at night
Age onset <45
Improves with Exercise
No improvement with rest



- To be able to differentiate between gout, pseudogout and septic arthritis based on risk factors, radiological features and joint aspiration finding.

Gout	
Risk factors	● Being male ● Being obese ● Underlying medical conditions (e.g CHF, CKD, HTN, Insulin resistance, Metabolic syndrome, Diabetes). ● medications, such as diuretics, Low dose ASA, Niacin, Cyclosporin, Pyrazinamide & ethambutol. ● Drinking alcohol. ● Diet, high in fructose or high in purines. * Purine-rich foods include red meat, organ meat, and some kinds of seafood, such as anchovies, sardines, mussels, scallops, trout, and tuna.
Radiological features	In chronic gout: Bone erosion, overhanging edges. 
joint aspiration findings	needle-shaped and negatively birefringent urate crystals. 

Pseudogout	
Risk factors	● Deposition increases with age and with OA of the joints. Therefore, pseudogout is common in elderly patients with degenerative joint disease. ● Other conditions that may increase crystal deposition include hemochromatosis, hyperparathyroidism, hypothyroidism, and Bartter syndrome.
Radiological features	chondrocalcinosis (cartilage calcification)
joint aspiration findings	rod-shaped and rhomboidal crystals, weakly positively birefringent 



Presentation of pseudogout is similar to gout, but typically occurs in larger joints (knee

Septic arthritis	
Risk factors	● Abnormal joint: OA, RA, prosthetic joint, gout ● Age >80 Risk ● Diabetes ● IV drug abuse, alcoholism ● Intra-articular glucocorticoid injections ● Synovial fluid analysis: leukocytosis Diagnosis (>50,000/mm), Gram stain, culture
Radiological features	● may be normal in the very early stage of the disease ● joint effusion may be seen ● narrowing of the joint space due to cartilage destruction in the acute phase ● destruction of the subchondral bone on both sides of a joint
joint aspiration findings	

	Colour	Clarity	Viscosity	WBC count (mm^3)	Neutrophil count	Gram stain	Crystals
Normal	Colourless	Translucent	↑	< 200 cells/mm^3	<25 %	Negative	Negative
Non-inflammatory	Straw like / yellow	Translucent	↑	200 - 2000 cells/mm^3	<25 %	Negative	Negative
Inflammatory	Yellow	Cloudy	↓	2000–50,000 cells/mm^3	>50 %	Negative	Positive
Septic	Yellow/green	Cloudy / opaque	↓	>50,000 cells/mm^3	>75 %	Positive	Negative
Haemarthrosis	Red/ xanthochromic	Bloody	Variable	200-2000 mm^3	50-75 %	Negative	Negative

Osteoarthritis

- Understand the pathophysiology of osteoarthritis & its risk factors.
- Recall the clinical manifestation & symptoms of osteoarthritis

The pathogenesis of OA involves a degradation of cartilage and remodelling of bone due to an active response of chondrocytes in the articular cartilage and the inflammatory cells in the surrounding tissues. The release of enzymes from these cells break down collagen and proteoglycans, destroying the articular cartilage. The exposure of the underlying subchondral bone results in sclerosis, followed by reactive remodelling changes that lead to the formation of osteophytes and subchondral bone cysts. The joint space is progressively lost over time.

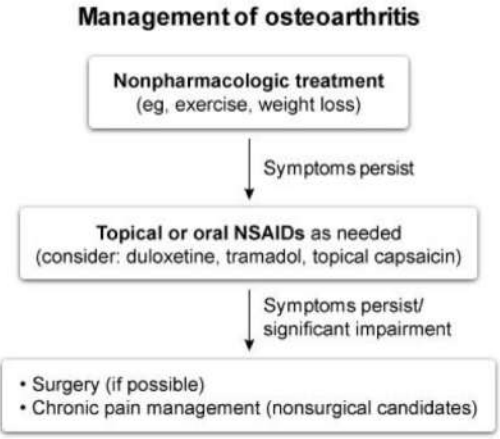
Risk factors for osteoarthritis	
Modifiable	**Non-modifiable**
• Sedentary lifestyle • Obesity • Occupational joint loading • Diabetes mellitus	• Advanced age • Female sex • Family history • Abnormal joint alignment • Prior joint trauma

Osteoarthritis	
Age of onset	• >40; prevalence 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

- To list the diagnostic modalities to establish the diagnosis & management.

❖ **Diagnosis**

1. Plain radiographs are the initial tests and should be obtained in all patients suspected of having osteoarthritis . Ideally, radiographs should be obtained in the standing position (for lower extremities). Findings include:
    a. Joint space narrowing (due to loss of cartilage)—key finding on radiographs
    b. Osteophytes
    c. Sclerosis of subchondral bony end plates adjacent to diseased cartilage—most severe at points of maximum pressure
    d. Subchondral cysts—occur as a result of increased transmission of intraarticular pressure to the subchondral bone
2. All blood tests are normal
3. MRI of the spine if indicated (neurologic findings, before surgery)



Osteoarthritis versus rheumatoid arthritis

	Osteoarthritis	Rheumatoid arthritis
Age of onset	>40; increases with age	40-60; often younger
Joint involvement	• Knees • Hips • DIP joint • 1st CMC joint	• MCP joint • PIP joint • Wrists
Morning stiffness	None/brief (<30 min)	Prolonged
Systemic symptoms	Absent	• Fever • Fatigue • Weight loss
Examination findings	• Hard, bony enlargement of joints	• Soft/spongy, warm joints

CMC = carpometacarpal; DIP = distal interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

Systemic connective tissue diseases

(include SLE, Systemic sclerosis & Myositis)

- To understand the clinical presentation of SLE, SS & Myositis.
- To know the systemic involvement of SLE, SS & Myositis.
- To enlist the diagnostic modalities to establish the diagnosis of SLE, SS & Myositis.
- To learn the treatment strategies for each system involved in SLE, SS & Myositis.

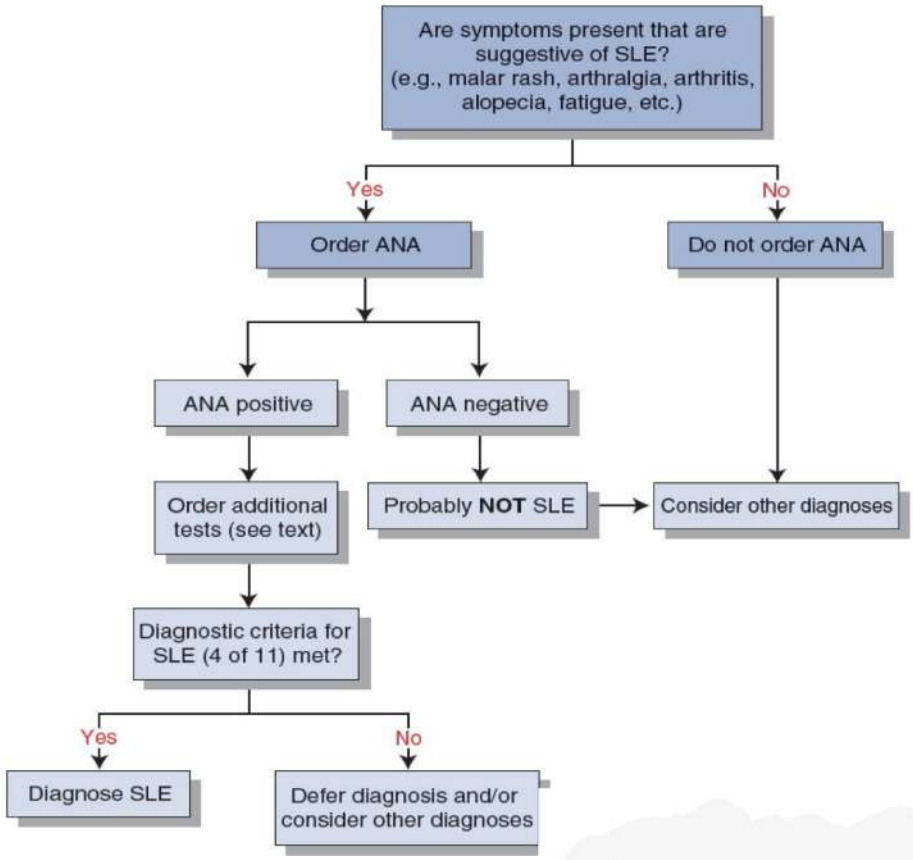
1. Systemic Lupus Erythematosus

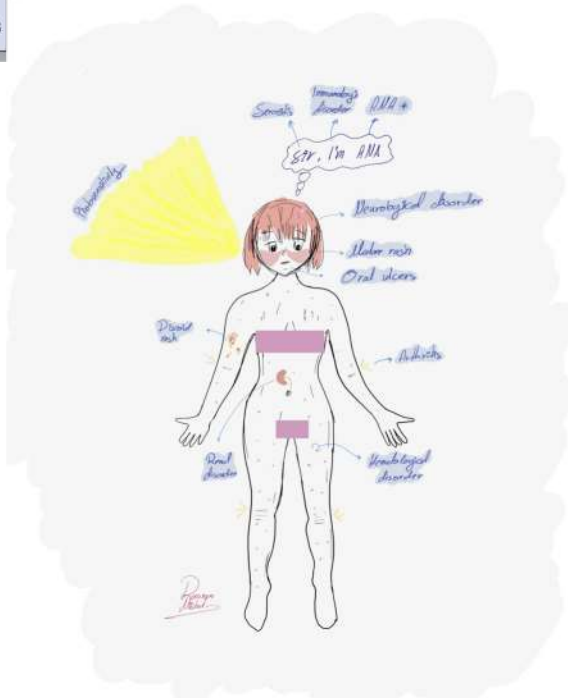
Manifestations of systemic lupus erythematosus	
Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • 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

❖ Diagnosis

There are two criteria classes of SLE,
ACR: American College of Rheumatology;
SLICC: Systemic Lupus International Collaborating Clinics





ACR criteria [1,2]		SLICC criteria [3]	
(4 of 11 criteria)*		(4 of 17 criteria, including at least 1 clinical criterion and 1 immunologic criterion; ¶ **OR** biopsy-proven lupus nephritis Δ)	
Criterion	**Definition**	**Criterion**	**Definition**
		Clinical criteria	
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds	Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); **OR** subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation		
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; **OR** discoid lupus/lichen planus overlap
		Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician	Oral or nasal ulcers	Palate, buccal, tongue, **OR** nasal ulcers (in the absence of other causes, such as vasculitis, Behçet syndrome, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion	Joint disease	Synovitis involving 2 or more joints, characterized by swelling or effusion **OR**
			Tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Serositis	Pleuritis – Convincing history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion **OR**	Serositis	Typical pleurisy for more than 1 day, pleural effusions, or pleural rub, **OR**
	Pericarditis – Documented by ECG, rub, or evidence of pericardial effusion		Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler syndrome
Renal disorder	Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation not performed **OR**	Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, **OR**
	Cellular casts – May be red cell, hemoglobin, granular, tubular, or mixed		Red blood cell casts
Neurologic disorder	Seizures **OR** psychosis – In the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)	Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); **OR** acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hematologic disorder	Hemolytic anemia – With reticulocytosis **OR**	Hemolytic anemia	Hemolytic anemia
	Leukopenia – Less than 4000/mm^3 total on 2 or more occasions **OR**	Leukopenia or lymphopenia	Leukopenia (<4000/mm^3 at least once) (in the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension), **OR**
	Lymphopenia – Less than 1500/mm^3 on 2 or more occasions **OR**		Lymphopenia (<1000/mm^3 at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
	Thrombocytopenia – Less than 100,000/mm^3 (in the absence of offending drugs)	Thrombocytopenia	Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
		Immunologic criteria	
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome	ANA	ANA level above laboratory reference range
Immunologic disorders	Anti-DNA – Antibody to native DNA in abnormal titer **OR**	Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
	Anti-Sm – Presence of antibody to Sm nuclear antigen **OR**	Anti-Sm	Presence of antibody to Sm nuclear antigen
	Positive antiphospholipid antibody on: 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies **OR** 2. A positive test result for lupus anticoagulant using a standard method **OR** 3. A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)
		Low complement	Low C3; low C4; **OR** low CH50
		Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

❖ Treatment

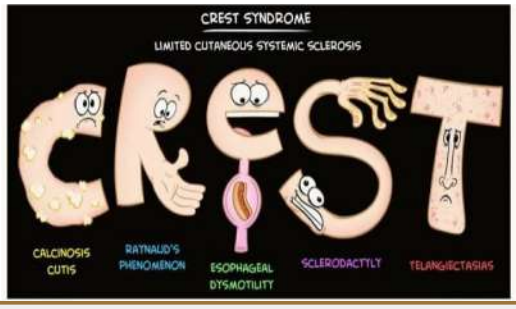
1. Avoid sun exposure because it can exacerbate cutaneous rashes
2. NSAIDs—for less severe symptoms
3. Either local or systemic corticosteroids —for acute exacerbations
4. Systemic steroids for severe manifestations
5. Best long-term therapy is antimalarial agents such as hydroxychloroquine —for constitutional, cutaneous, and articular manifestations. Hydroxychloroquine is continued as a preventative measure even after resolution of symptoms. Baseline and subsequent annual eye examinations are needed because of retinal toxicity.
6. Cytotoxic agents such as cyclophosphamide —for active glomerulonephritis
7. Monitor the following and treat appropriately:
    a. Renal disease, which produces the most significant morbidity
    b. HTN

2. Systemic sclerosis

❖ Clinical Features

1. Raynaud phenomenon: Present in almost all patients; usually appears before other findings
2. Cutaneous fibrosis: Tightening of skin of the face and extremities (sclerodactyly refers to a claw like appearance of the hand)
3. GI involvement:
    a. Occurs in most patients (both diffuse and limited)
    b. Findings include dysphagia/reflux from esophageal immobility (up to 90% of patients), delayed gastric emptying, constipation/diarrhea, abdominal distention, and pseudo-obstruction. Prolonged acid reflux may eventually lead to esophageal strictures.
4. Pulmonary involvement:
    a. Most common cause of death from scleroderma
    b. Interstitial fibrosis and/or pulmonary HTN may also be present
5. Cardiac involvement: pericardial effusions, myocardial involvement that can lead to CHF, arrhythmias
6. Renal involvement (renal crisis—rapid malignant hypertension) occurs in patients with diffuse disease (rare today)

Only diffuse scleroderma form has renal, lung, and heart involvement.



Systemic sclerosis subtype characteristics

Limited cutaneous	Diffuse cutaneous

• Scleroderma on head & distal UE
• Prominent vascular manifestations
  ○ Raynaud phenomenon
  ○ Cutaneous telangiectasia
  ○ Pulmonary arterial hypertension
• CREST syndrome
• Anticentromere antibodies
• Better prognosis
	• Scleroderma on trunk & UE
	• Prominent internal organ involvement
	  ○ Scleroderma renal crisis
	  ○ Myocardial ischemia & fibrosis
	  ○ Interstitial lung disease
	• Anti-Scl-70 (topoisomerase-1) antibodies
	• Anti-RNA polymerase III antibodies
	• Worse prognosis

❖ Diagnosis

- Autoantibodies:
  - Antinuclear antibodies (ANA) present in about 90% of cases
  - Limited SSc: anticentromere antibodies (ACA)
  - Diffuse SSc : anti-Scl-70 (anti-topoisomerase I antibody), Anti-RNA polymerase III
- Serum protein electrophoresis: ↑ γ-globulins
- Chest x-ray: detects possible pulmonary involvement
- Other tests: may be indicated based on organ-specific symptoms (e.g., signs of renal crisis).

❖ Treatment

Treatment focuses on organ-specific, symptomatic therapy. In the case of diffuse cutaneous disease or severe organ involvement, immunosuppressive therapy is indicated.

- General measures:
  - Physical therapy, massage
  - Prevent dry skin
  - Warm oil and paraffin baths
  - Avoid soap
  - Phototherapy
- Immunosuppressive therapy: e.g., methotrexate
- Organ-specific therapy
  - PPIs in cases of gastroesophageal reflux disease
  - CCBs for Raynaud phenomenon
  - D-penicillamine for skin and visceral complications
  - ACE inhibitors are used to prevent and treat renal hypertensive crisis

3. **Myositis** "dermatomyositis and polymyositis"

Polymyositis and dermatomyositis

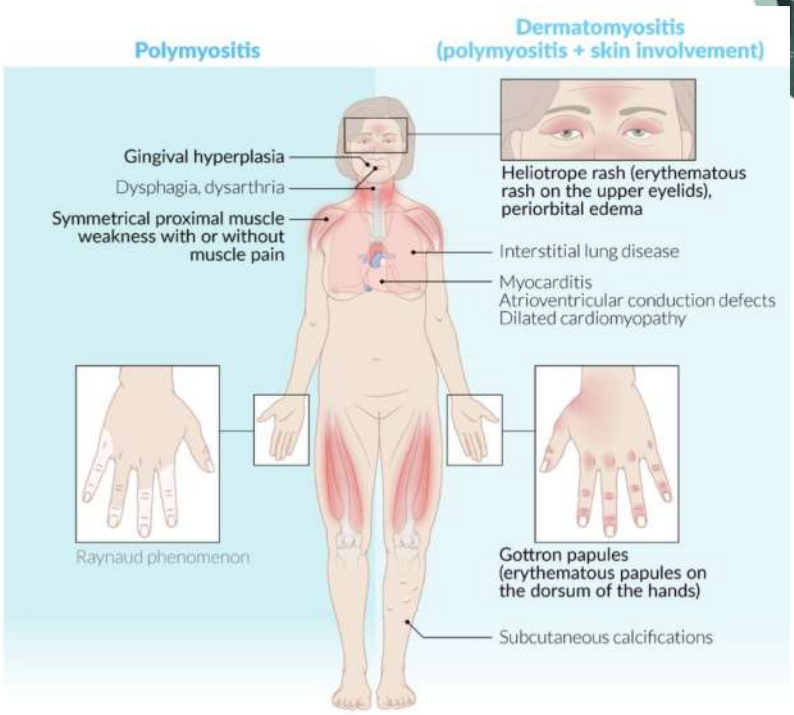
Etiology
Idiopathic; likely cell-mediated autoimmune cytotoxicity against skeletal muscle antigens
May be assoc. with viral infections (e.g., HIV, HTLV-1, and Coxsackie viruses) or malignancy (i.e., paraneoplastic syndrome)

Epidemiology
♀ > ♂
Peak age: 30–60 years

Serology
ANA (nonspecific)
Anti-Mi-2 antibodies (specific)
Anti-Jo-1 antibodies (specific)

Laboratory findings
↑↑ Serum creatine kinase,
↑ Aldolase, ↑ myoglobin, ↑ LDH,
↑ AST, ↑ ALT

Note
Associated with malignancy
(esp. in patients with dermatomyositis)



Characteristic presentations of idiopathic inflammatory myopathies (IIM) [2][6][15][16]			
	Muscle weakness	Cutaneous features	Systemic features

Dermatomyositis (DM)	• Progresses over weeks to months
	• Mild to moderately severe weakness
		• Typically present	• Common
			• Typically:
			  ◦ Increased risk of malignancy
			  ◦ Interstitial lung disease (may be severe)

Polymyositis (PM)		• Absent	

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.

❖ Diagnosis

1. Laboratory:
    a. CK level is significantly elevated. CK levels correspond to the degree of muscle necrosis, so one can monitor the disease severity.
    a. LDH, aldolase, AST, ALT are also elevated.
    b. ANA in over 50%
    c. Antisynthetase antibodies (anti-Jo-1 antibodies)—abrupt onset of fever, cracked hands, Raynaud phenomenon, interstitial lung disease and fibrosis, arthritis; does not respond well to therapy
    d. Antisignal recognition particle Cardiac manifestations (common) Worst prognosis of all subsets
    e. Anti-Mi-2 antibodies—better prognosis
1. EMG—abnormal in 90% of patients
2. Muscle biopsy
    a. Shows inflammation and muscle fiber fibrosis
    b. Dermatomyositis—perivascular and perimysial
    c. Polymyositis and inclusion body myositis—endomysial

❖ Treatment

Approach to treat inflammatory myopathy

- Refer to a rheumatologist experienced in the management of IIM.
- All patients: Start supportive therapies (physical, occupational, and/or speech therapy, as appropriate) as soon as possible.
- Patients with any form of IIM except IBM: Start pharmacological therapy.
- Advise patients with cutaneous manifestations to use photoprotective measures.
- Educate patients on the possible increased risk of malignancy and the importance of attending screenings.

Pharmacologic therapy

Initial treatment

- First-line: glucocorticoids
    - In severe disease or with multisystem involvement, consider an initial short course of pulsed IV methylprednisolone.
- AND (usually) a steroid-sparing immunosuppressive agent, e.g.: Methotrexate Azathioprine (to reduce steroid-induced side effects)

Subsequent treatment

Depending on the clinical presentation, additional medications may need to be added to the initial treatment regimen.

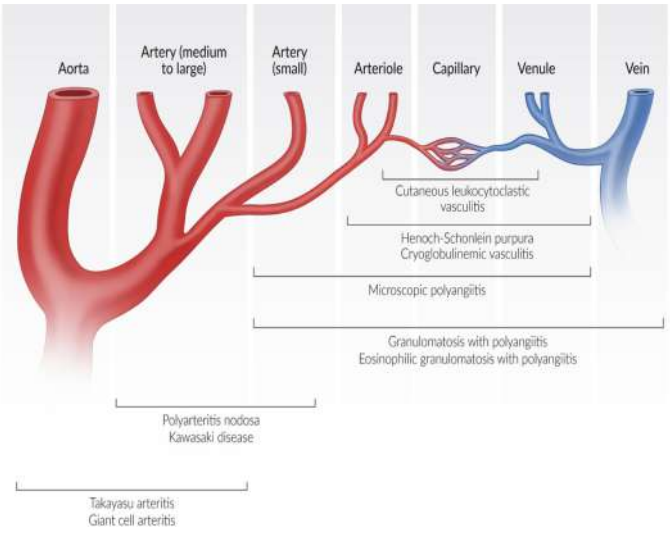
- Severe or refractory disease: Intravenous immunoglobulins
- Dysphagia: intravenous immunoglobulins
- Rapidly progressive ILD: Consider plasmapheresis.

- To learn the use & side effect of the drug used in treating Systemic connective tissue diseases (mainly Hydroxychloroquine, Mycophenolate, Azathioprine, Corticosteroid and cyclophosphamide)

Treatment	Uses	Side effects
Hydroxychloroquine	- **Malaria** Treatment and prophylaxis of malaria due to Plasmodium malariae, P. ovale, or P. vivax Strains of P. falciparum are usually resistant -**Rheumatic diseases**: used in mild courses ● Rheumatoid arthritis (basic therapy) ● Systemic lupus erythematosus and discoid lupus erythematosus (without organ involvement) -**Porphyria cutanea tarda** (in low doses)	● Gastrointestinal: Nausea with cramps (most common), Anorexia, Vomiting ● Visual disturbances: irreversible bilateral retinopathy "bull's eye maculopathy", Blurred vision, Photophobia ● Dermatologic: Pruritus, Photosensitivity, Alopecia, Whitening of hair ● Neurologic: Myasthenia-like muscle weakness, Sensorineural deafness, Tinnitus, Cranial nerve palsies ● Cardiac: torsades de pointes (due to possible QT prolongation), can cause sudden death ● Hematologic: e.g., thrombocytopenia, leukopenia ● Worsening of preexisting conditions: epilepsy, psoriasis, porphyria and preexisting retinal damage
Mycophenolate (glucocorticoid sparing)	- Lupus nephritis - Used in combination with cyclosporin or tacrolimus as transplant rejection prophylaxis - Rheumatic diseases (glucocorticoid sparing)	● Infection (especially with CMV) ● Vomiting and diarrhea ● Hyperglycemia ● Hypertension
Azathioprine	- Prophylaxis against renal transplant rejection - Autoimmune disease treatment (e.g., rheumatoid arthritis, Crohn disease, glomerulonephritis) - To wean patients off long-term steroid therapy - Steroid-refractory disease	● Hepatotoxicity ● Malignancies
Glucocorticoid	- Transplant rejection prophylaxis - To suppress various inflammatory and autoimmune reactions - Atopy and asthma - Adrenal insufficiency - Part of the regimen for the treatment of: 1. CLL 2. Non-Hodgkin lymphoma	increased appetite, acne, thinned skin that bruises easily, increased risk of infections, mood swings and depression, diabetes, osteoporosis, fluid retention & high blood pressure.
Cyclophosphamide	- Autoimmune disease therapy (e.g., SLE, autoimmune hemolytic anemias)	● SIADH ● Hemorrhagic cystitis

Vasculitis

- Understand the pathophysiology of vasculitis & recognize the common causes.
- Identify the common presentations of different types of vasculitis.
- List key management points for vasculitis



Vessel size	Vasculitis
Large-vessel vasculitis	Takayasu arteritis Giant-cell arteritis
Medium-vessel vasculitis	Polyarteritis nodosa Kawasaki disease
Small-vessel vasculitis	Granulomatosis with polyangiitis (GPA) Eosinophilic granulomatosis with polyangiitis (EGPA) Microscopic polyangiitis Anti-glomerular basement membrane (anti-GBM) Cryoglobulinemic vasculitis IgA vasculitis Hypocomplementemic urticarial vasculitis
Variable-vessel vasculitis	Behçet disease Cogan syndrome
Single-organ vasculitis	Cutaneous small-vessel vasculitis Testicular arteritis Central nervous system vasculitis

	Clinical presentation	Diagnostic clues	Treatment
Giant cell arteritis	• Elderly women, typically **> 50 years** • Visual impairment may result in **blindness**. • New-onset headache • Tender temporal artery • Jaw claudication • Associated with polymyalgia rheumatica	• **↑ ESR** • Autoantibodies absent • Halo sign around the vessel on duplex sonography • Temporal artery biopsy (gold standard) shows **granulomatous inflammation** with giant cells and intima proliferation that results in stenosis.	• High-dose glucocorticoids to prevent permanent vision loss
Takayasu arteritis	• Asian females, typically **< 40 years** • Disparity in blood pressure between arms (**"pulseless disease"**) • Bruit over the subclavian artery or abdominal aorta • Syncope and **angina pectoris**	• **↑ ESR** • Angiography shows stenosis of aortic arch and proximal great vessels (gold standard). • Biopsy shows granulomatous inflammation of the aorta and its major branches.	• Glucocorticoids
Kawasaki syndrome	• Children < 5 years • "CRASH (Conjunctivitis, Rash, Adenopathy, Strawberry tongue, Hand-foot changes) and BURN (≥ 5 days of fever)"	• ↑ ESR, ↑ CRP, thrombocytosis • Echocardiography may detect **coronary artery aneurysms**.	• High-dose ASA and IVIG
Polyarteritis nodosa	• 45–65 years, ♂ > ♀ • Fever, malaise • Abdominal, muscle, and joint pain • Renal impairment • Neurologic dysfunction (e.g., polyneuropathy, stroke) • Rash, ulcerations, nodules	• Association with **hepatitis B** and hepatitis C • **Spares the lungs** • ANCA-negative • Muscle biopsy shows transmural inflammation of vessels.	• Glucocorticoids, cyclophosphamide

Thromboangiitis obliterans (Buerger disease)	• Men < 45 years • Strong association with **tobacco use** • **Intermittent claudication** due to severe limb ischemia; acute necrosis of toes and fingers often requires amputation. • Raynaud phenomenon	• Angiography (confirmatory test): **nonatherosclerotic segmental occlusion** of arteries	• Smoking cessation
Granulomatosis with polyangiitis (Wegener)	• 35–55 years; ♂ > ♀ • Nasopharyngeal involvement: chronic sinusitis/rhinitis, saddle nose deformity • Chronic otitis media and mastoiditis • Treatment-resistant, pneumonia-like symptoms with cough, dyspnea, hemoptysis • Rapid progressive glomerulonephritis	• **PR3-ANCA/cANCA**-associated • Biopsy shows granulomatous, necrotizing inflammation of vessels, kidneys, and the lungs. • Chest x-ray/CT: multiple bilateral cavitating nodular lesions	• Glucocorticoids, cyclophosphamide
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	• Severe **allergic asthma, sinusitis** • Skin manifestations (e.g., tender nodules) • Peripheral neuropathy • Gastrointestinal, cardiac, renal involvement possible	• **MPO-ANCA/p-ANCA**-associated • Peripheral blood **eosinophilia** • ↑ **IgE** • Biopsy (confirmatory test): tissue eosinophilia and necrotizing granulomas	• Glucocorticoids, cyclophosphamide
Microscopic polyangiitis	• Hypertension and pauci-immune glomerulonephritis • Palpable purpura	• **MPO-ANCA/p-ANCA**-associated • Similar to granulomatosis with polyangiitis but spares the nasopharynx • Biopsy shows inflammation; **no granulomas**	• Glucocorticoids, cyclophosphamide
Immunoglobulin A vasculitis (Henoch-Schönlein purpura)	• Children; 90% < 10 years • **Palpable purpura** on lower limbs • Arthritis/arthralgia • Intestinal colic • Hematuria due to IgA nephropathy	• Often secondary to upper respiratory tract infections • ↑ **IgA** in serum • Biopsy: leukocytoclastic vasculitis with IgA and C3 immune complex deposition	• Supportive care (e.g., NSAIDs) in mild cases • Glucocorticoids and IV hydration in severe cases
Cryoglobulinemic vasculitis	• Fatigue • Arthralgia • Palpable purpura • Glomerulonephritis	• The majority of cases are secondary to **hepatitis C** infection. • Cryoglobulinemia	• Glucocorticoids; cyclophosphamide in severe cases • Treatment of **hepatitis C** infection (IFN-α, ribavirin)
Cutaneous small vessel vasculitis	• Palpable purpura	• Drug-induced, infections	• Discontinue drug intake
Behcet disease	• Most common in Turkey, the Middle East, and Japan • **Oral and genital ulcers** • Uveitis • Erythema nodosum	• Positive pathergy skin testing	• Glucocorticoids

Gastrointestinal And liver Disorders

Gastrointestinal and liver disorders

1	**Diseases of esophagus, stomach and duodenum (include GERD, PUD, gastritis)** - Identify common symptoms related to GERD, PUD and indication for an upper GI endoscopy. - To be able to initiate a diagnostic and management plans for patients suspected to have GERD or peptic ulcer disease. - To be able to implement invasive and non-invasive testing for H.pylori. - To list the medical therapy used for eradication of H.pylori.
2	**Gallbladder, bile duct, and pancreatic diseases** - To identify symptoms of cholangitis and choledocholithiasis and list the modalities of work-up and investigations. - To be able to initiate management plans for patients suspected cholangitis. - Identify common symptoms related to acute pancreatitis and initiate lab work to confirm diagnosis/cause - To be able to initiate the management plan for patient with acute pancreatitis and tailored therapy based on the cause.
3	**Inflammatory bowel disease and Irritable bowel syndrome** - Identify the risk factors and recognize clinical manifestations for inflammatory bowel disease. - To be able to act diagnostic plan for patients suspected to have inflammatory bowel disease. - To be able to establish a treatment plan for inflammatory bowel disease. - To identify the types of irritable bowel syndrome based on the history and examination. - List the key points in the management of irritable bowel syndrome.
4	**Malabsorption disorder (including Celiac disease, Whipple's disease, short bowel syndrome)** - Understand the pathophysiology of common Malabsorption disorders. - To be able to implement testing and interpret the results. - To recognize the histopathology pattern of intestinal of common Malabsorption disorders. - To understand the key points in the management of the common Malabsorption disorders.
5	**Approach to the Patient with Abnormal Liver Chemistry studies** - Describe and interpret abnormal liver enzymes. - Develop a differential diagnosis for abnormal liver enzymes and jaundice. - Describe the approach plan for patients with abnormal liver enzymes and jaundice. - To recognize the common causes for acute liver failure, understand the pathophysiology, clinical presentation, and formulate the work-up and management plan.
6	**Cirrhosis and complication of advanced liver disease** - List the common causes of liver cirrhosis in Saudi Arabia - List the complications of advanced liver disease. - To be able to identify patients with hepatic encephalopathy to understand the key elements in the management. - To be able to interpret the results of the ascitic tap to be able to diagnose the spontaneous bacterial peritonitis (SBP) - To understand the key points in the management SBP
7	**GI bleeding and ischemia** - List the causes of upper GI bleeding. - Identify the symptoms and signs for patients with GI bleeding. - Discuss the risk stratification and initial assessment for patients with GI bleeding or ischemia. - Illustrate important physical signs in patients with GI bleeding or ischemia. - Outline the investigations required and enlist key points in the management plan.
8	**Diarrhea** - List the common causes of acute diarrhea and chronic diarrhea - To be able to initiate a diagnostic and management plans for patient presenting with diarrhea. - To list the medical therapy used for C. Difficile

Diseases of esophagus, stomach & duodenum

(include GERD, PUD, gastritis)

- Identify common symptoms related to GERD, PUD and indication for an upper GI endoscopy.

❖ **Symptoms of:**

1. GERD

- Typical symptoms:
  - Retrosternal burning pain (heartburn)
  - Regurgitation
  - Dysphagia, odynophagia
- Atypical symptoms:
  - Pressure sensation in the chest/noncardiac chest pain
  - Belching, bloating
  - Dyspepsia, epigastric pain
  - Nausea
  - Halitosis
- Extraesophageal symptoms:
  - Chronic nonproductive cough and nighttime cough
  - Hoarseness
  - Dental erosions
- Aggravating factors:
  - Lying down shortly after meals
  - Certain foods/beverages

2. PUD:

PUD may be asymptomatic or manifest with a variety of clinical features, e.g., general dyspepsia or complications such as perforation or bleeding.

- Symptomatic PUD:
  - Abdominal pain: Commonly located in the epigastrium, Often described as “gnawing” or “burning”, Can be related to meal intake depending on the location of the ulcer
- Other associated symptoms:
  - Belching
  - Indigestion
  - Gastrointestinal reflux
  - Nausea and/or vomiting
  - Bloating/abdominal fullness

3. Gastritis

Many people with gastritis caused by a bacterial infection do not have any symptoms.
In other cases, gastritis can cause:

- indigestion
- gnawing or burning stomach pain
- feeling and being sick
- feeling full after eating

❖ **Symptoms or indications for which endoscopy is usually appropriate:**

- Gastrointestinal bleeding
- Unexplained iron deficiency anaemia
- Positive occult blood test result
- Dysphagia (food sticking)
- Odynophagia (painful swallowing)
- Severe upper abdominal pain
- Moderate, long standing upper abdominal pain
- Recurrent vomiting
- Unexplained weight loss
- Severe heartburn
- "Suspicious" barium meal result
- Gastric ulcer
- Check gastric ulcer for healing
- Achalasia
- Suspected coeliac disease

- To be able to initiate a diagnostic and management plans for patients suspected to have GERD or peptic ulcer disease.
- To be able to implement invasive and non-invasive testing for H.pylori.

❖ **Diagnosis of**

1. GERD:

1. Endoscopy with biopsy—the test of choice but not necessary for typical uncomplicated cases.
    a. Indicated if heartburn is refractory to treatment, or is accompanied by dysphagia, odynophagia, or GI bleeding.
    b. A biopsy should also be performed to assess changes in esophageal mucosa.
2. Upper GI series (barium contrast study)—this is only helpful in identifying complications of GERD (strictures/ulcerations), but cannot diagnose GERD itself.
3. Twenty-four–hour pH monitoring in the lower esophagus—this is the most sensitive and specific test for GERD. It is **the gold standard,** but is usually unnecessary.
4. Esophageal manometry—use if a motility disorder is suspected.

2. PUD:

1. Endoscopy
    a. Most accurate test in diagnosing ulcers.
    b. Essential in diagnosis of gastric ulcers because biopsy is necessary to rule out malignancy.
    c. Preferred when severe or acute bleeding is present (can perform electrocautery of bleeding ulcers).
    d. Can obtain endoscopic biopsy for diagnosis of H. pylori.
2. Barium swallow
    a. Sometimes used initially but is less reliable than endoscopy.
    b. Double-contrast techniques preferred due to improved accuracy.
3. Laboratory test—for diagnosis of H. pylori infection
    a. Biopsy: Histologic evaluation of endoscopic biopsy is the gold standard.
    b. **Stool antigen test**—High sensitivity and ease of testing makes this ideal for screening.
    c. Urease detection via **urea breath test** is highly sensitive and specific. It documents active infection and helps to assess the results of antibiotic therapy.
    d. Serology (lower specificity)—antibodies to H. pylori can remain elevated for months or even years after eradication of infection.
        i. The following may lead to false-negative test results: PPIs, bismuth, many antibiotics, and upper GI bleeding.
4. Serum gastrin measurement—if considering Zollinger–Ellison syndrome as a diagnosis.

Diagnostic approach for suspected PUD [22]

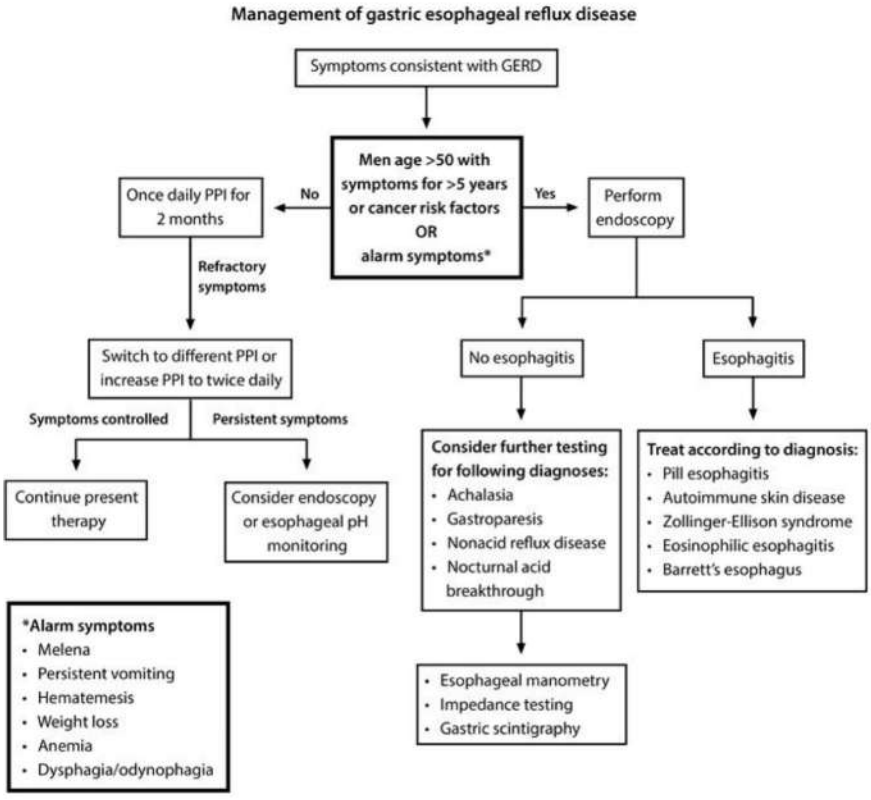
	Patient group	Testing strategy
Initial evaluation	• All patients	• Screen for common etiologies on history, e.g., NSAID use (see "Etiology") • Consider the following if there is suspicion for occult bleeding: ◦ CBC and BMP ◦ Fecal occult blood test
	• Patients ≤ 60 years of age without red flags for dyspepsia	• Begin with noninvasive testing for *H. pylori* infection (H. pylori test-and-treat strategy). ◦ Urea breath test ◦ H. pylori stool antigen test
	• Patients > 60 years of age, or > 45 years of age in areas with high gastric cancer prevalence • Patients with red flags for dyspepsia: on a case-by-case basis [22] • Patients unresponsive to empiric medical therapy (e.g., H. pylori eradication therapy, PPI trial therapy)	• Refer directly for EGD (or other indicated diagnostic study, e.g., liver chemistries and abdominal ultrasound for jaundice).
Further evaluation	• All patients with persistently uncertain etiology	• Consider specialized laboratory studies (e.g., secretin stimulation test for gastrinoma).

- To be able to initiate a diagnostic and management plans for patients suspected to have GERD or peptic ulcer disease.
- To list the medical therapy used for eradication of H.pylori.

Management of

1. GERD:

1. Initial treatment:
    a. Behavior modification—diet (avoid fatty foods, coffee, alcohol, orange juice, chocolate; avoid large meals before bedtime); sleep with trunk of body elevated; stop smoking
    b. Antacids—after meals and at bedtime
2. Add an H 2 blocker—can be used instead of or in addition to antacids for mild & intermittent symptoms
3. If above treatment fails or patient has severe GERD (e.g., erosive esophagitis), switch to a PPI
4. Antireflux surgery for severe or resistant cases
    a. Indications for surgery Intractability (failure of medical treatment) Respiratory problems due to reflux and aspiration of gastric contents Severe esophageal injury (ulcer, hemorrhage, stricture, Barrett esophagus)
    b. Types of surgery Nissen fundoplication (may be done open or laparoscopically)—procedure of choice for a patient with normal esophageal motility Partial fundoplication—when esophageal motility is poor
    c. Outcome of surgery—excellent results have been reported



2. PUD:

Medical:

Majority of patients with PUD can be successfully treated by curing H.pylori infection, avoidance of NSAIDs, and appropriate use of antisecretory drugs.

1. Supportive (patient directives)
    a. Discontinue aspirin/NSAIDs.
    b. Restrict alcohol use but do not restrict any foods.
    c. Stop smoking, decrease emotional stress.
    d. Avoid eating before bedtime (eating stimulates nocturnal gastric acid levels).
2. Acid suppression therapy
    a. PPIs—omeprazole (Prilosec), lansoprazole (Prevacid), block H+ /K + ATPase pump directly in parietal cell membrane. First line of therapy, most effective antisecretory agents.
    b. H2 receptor blockers—cimetidine (Tagamet) and ranitidine (Zantac). Block histamine-based parietal cell acid secretion. Less effective than PPIs.
    c. Antacids—somewhat outdated for primary therapy and more appropriately used for adjunctive therapy/symptomatic relief. Examples include aluminum hydroxide (Mylanta), calcium carbonate (Tums), bismuth subsalicylate (PeptoBismol).
3. Eradicate H. pylori with triple or quadruple therapy. Once infection is cleared, the rate of recurrence is very low.
    a. For initial therapy, triple therapy (PPI, amoxicillin, and clarithromycin) for 14 days.
    b. Quadruple therapy (PPI, bismuth, metronidazole, and tetracycline) indicated for patients with risk factors for macrolide resistance.
4. Cytoprotection
    a. Sucralfate—facilitates ulcer healing. Must be taken frequently, is costly, and can cause GI upset.
    b. Misoprostol—reduces risk for ulcer formation associated with NSAID therapy. Costly, and can cause GI upset (common side effect).
5. Treatment regimens
    a. If H. pylori test is positive, begin eradication therapy with either triple or quadruple therapy. Also begin acid suppression with antacids, an H2 blocker, or a PPI.
    b. If the patient has an active NSAID-induced ulcer, stop NSAID use (may switch to acetaminophen). Also begin with either a PPI or misoprostol. Continue for 4 to 8 weeks, depending on severity. Treat the H. pylori infection as above if present.
    c. Antisecretory drugs can be discontinued after 4 to 6 weeks in patients with uncomplicated ulcers who are asymptomatic. Patients at increased risk of recurrence (especially if underlying cause of ulcer is not reversed) may benefit from maintenance therapy.
    d. H. pylori–negative ulcers that are NOT caused by NSAIDs can be treated with antisecretory drugs (either H2 blockers or PPI).

Surgical

1. Rarely needed electively
2. Required for the complications of PUD (bleeding, perforation, gastric outlet obstruction)

❖ **Duodenal and gastric ulcer comparison**

Clinical symptoms of gastric and duodenal ulcers		
	Gastric ulcer	Duodenal ulcer
Findings common to both	• **Dyspepsia**: postprandial heaviness, early satiety, and gnawing, aching, or burning epigastric pain • Pain relief with antacids • Potential signs of internal bleeding (e.g., anemia, hematemesis, melena) • Stool sample positive for **occult blood** (see "Diagnostics" in "Gastrointestinal bleeding")	
Pain and eating	• Pain increases shortly after eating → weight loss	• Pain is relieved with food intake → weight gain • Pain increases 2–5 hours after eating.[16]
Nocturnal pain	• Less common[17]	• More common[17]

Gallbladder, bile duct, & pancreatic disease

- To identify symptoms of cholangitis and choledocholithiasis and list the modalities of work-up and investigations.

1. Choledocholithiasis:

❖ **Symptoms:**

- RUQ pain
  - More severe and prolonged (may last > 6 hours) than in cholelithiasis
  - Postprandial
  - May radiate to the epigastrium, right shoulder, and back (referred pain)
- Nausea, vomiting, anorexia
- Signs of extrahepatic cholestasis (e.g., jaundice, pale stool, dark urine, pruritus) may be present
- Features of complications: acute pancreatitis, acute cholecystitis, and acute cholangitis

❖ **Diagnosis:**

1. Laboratory Tests—total and direct bilirubin levels are elevated, as well as ALK-P.
2. RUQ ultrasound is usually the initial study,but is not sensitive study for choledocholithiasis. It detects CBD in only 50% of cases, so it cannot be used to rule out this diagnosis.
3. ERCP is the gold standard (sensitivity and specificity of 95%) and should follow ultrasound. ERCP is diagnostic and therapeutic
4. PTC is an alternative to ERCP.

2. Cholangitis

❖ **Symptoms:**

- Charcot cholangitis triad
  - Abdominal pain (most commonly RUQ)
  - High fever
  - Jaundice (least common feature)
- Reynolds pentad: Charcot cholangitis triad PLUS hypotension and mental status changes
- Features of sepsis, septic shock, and multiorgan dysfunction may be present, depending on the severity of disease at presentation.

❖ **Diagnosis:**

1. RUQ ultrasound is the initial study.
2. Laboratory findings-hyperbilirubinemia, leukocytosis, mild elevation in serum transaminases.
3. Cholangiography (PTC or ERCP).
    a. This is the definitive test, but it should not be performed during the acute phase of illness. Once cholangitis resolves, proceed with PTC or ERCP to identify the underlying problem and plan treatment.
    b. Perform PTC when the duct system is dilated (per ultrasound) and ERCP when the duct system is normal.

● To be able to initiate management plans for patients suspected cholangitis.

Empiric antibiotic therapy and urgent biliary drainage are the mainstays of treatment of acute cholangitis.
The choice and timing of both biliary drainage and any procedure to treat the underlying cause are dictated by the severity of the disease at presentation
Approach:

- Start supportive management and provide hemodynamic support
    - Identify and treat sepsis.
    - Provide hemodynamic and respiratory support as needed
    - NPO
    - IV fluid resuscitation
    - Electrolyte repletion
    - Analgesics (preferably NSAIDs), antiemetics, nasogastric tube insertion as needed
    - Close monitoring of hemodynamics, BP, and urine output is important.
    - Most patients respond rapidly. Once the patient has been afebrile for 48 hours, cholangiography (PTC or ERCP) can be performed for evaluation of the underlying condition.
- All patients: Administer empiric antibiotics
- Decompress CBD via PTC (catheter drainage); ERCP (sphincterotomy), or laparotomy (T-tube insertion) once the patient is stabilized, or emergently if the condition does not respond to antibiotics.
- Identify and treat concurrent choledocholithiasis
- Determine the need and timing for urgent biliary drainage; and treatment of the underlying cause, based on severity.
- Initiate supportive therapy and broad-spectrum antibiotics as early as possible!

Identify common symptoms related to acute pancreatitis and initiate lab work to confirm diagnosis/cause

❖ Symptoms:

- Constant, severe epigastric pain
  - Classically radiating towards the back
  - Worse after meals and when supine
  - Improves on leaning forwards
- Nausea, vomiting
- Fever
- If pulmonary complications are present: chest pain, dyspnea

❖ Signs:

- Signs of shock: tachycardia, hypotension, oliguria/anuria
- Possibly jaundice in patients with biliary pancreatitis
- Abdominal tenderness, distention, guarding
- Ileus with reduced bowel sounds and tympany on percussion
- Ascites
- Skin changes (rare)
- Cullen's sign: periumbilical ecchymosis and discoloration (bluish-red)
- Grey Turner's sign: flank ecchymosis with discoloration
- Fox's sign: ecchymosis over the inguinal ligament
- If pulmonary complications are present: signs of pleural effusion and/or ARDS

❖ Causes:

P arathyroid Hormone
A lcohol
N eoplasia
C alcium
R ocks (Gall Stones)
E strogens
A CE-i
T triglycerides
I nfarction (Ischemia)
T rauma (ERCP, MVA)
I nfection (Mumps)
S corpion Stings

- Biliary pancreatitis
- Alcohol-induced
- Idiopathic
- Severe hypertriglyceridemia (> 1,000 mg/dl)
- Hypercalcemia
- Post-ERCP
- Drug-induced pancreatitis (e.g., Steroids, Azathioprine, Sulfonamides, Loop and thiazide diuretics, Estrogen, Protease inhibitors, NRTIs, Anticonvulsants)
- Scorpion stings
- Viral infections (e.g., coxsackievirus B, mumps)
- Trauma (especially in children)
- Autoimmune and rheumatological disorders (e.g., Sjögren syndrome)
- Pancreas divisum
- Hereditary (e.g., mutation of PRSS1 gene, cystic fibrosis)

I GET SMASHED: Idiopathic, Gall stones, Ethanol, Trauma, Steroids, Mumps, Autoimmune, Scorpion poison, Hypercalcemia, Hypertriglyceridemia, ERCP, and Drugs are the most common causes of acute pancreatitis.

❖ **Diagnosis:**

Acute pancreatitis is diagnosed based on a typical clinical presentation, and either detection of highly elevated pancreatic enzymes or characteristic findings on imaging.

Tests to confirm clinical diagnosis

- ↑ Serum pancreatic enzymes
  - Lipase: if ≥ x3 Upper Limit of Normal → highly indicative of acute pancreatitis
  - Amylase (nonspecific)

Tests to assess severity

- Hematocrit (Hct)
  - Should be conducted at presentation as well as 12 and 24 hours after admissions
  - ↑ Hct (due to hemoconcentration) indicates third space fluid loss and inadequate fluid resuscitation
  - ↓ Hct indicates the rarer acute hemorrhagic pancreatitis
- WBC count
- Blood urea nitrogen (has the greatest prognostic information)
- ↑ CRP and procalcitonin levels
- ↑ ALT

Tests to determine etiology

- Alkaline phosphatase, bilirubin levels (evidence of gallstone pancreatitis)
- Serum calcium levels (Hypercalcemia may cause pancreatitis, which may then, in turn, cause hypocalcemia!)
- Serum triglyceride levels (fasting)

Imaging

- Ultrasound (most useful initial test): indicated in all patients
  - detection of gallstones and/or dilatation of the biliary tract (indicating biliary origin)
  - Signs of pancreatitis
    - Indistinct pancreatic margins (edematous swelling)
    - Peripancreatic build-up of fluid ; evidence of ascites in some cases
    - Evidence of necrosis, abscesses, pancreatic pseudocysts

- CT scan: not routinely indicated
  - Indications
    - At admission: only when the diagnosis is in doubt (e.g., not very highly elevated pancreatic enzymes, non-specific symptoms)
    - > 72 hours of symptom onset: if complications such as necrotizing pancreatitis or pancreatic abscess (e.g., persistent fever and leukocytosis, no clinical improvement or evidence of organ failure > 72 hours of therapy) are suspected
  - Findings
    - Enlargement of the pancreatic parenchyma with edema; indistinct pancreatic margins with surrounding fat stranding
    - Necrotizing pancreatitis: lack of parenchymal enhancement or presence of air in the pancreatic tissue
    - Pancreatic abscess: circumscribed fluid collection

- MRCP and ERCP
  - Indications: suspected biliary or pancreatic duct obstructions
  - MRCP is noninvasive but less sensitive than ERCP
  - ERCP can be combined with sphincterotomy and stone extraction; but **may worsen pancreatitis.**
- Conventional x-ray
  - Sentinel loop sign: dilatation of a loop of small intestine in the upper abdomen (duodenum/jejunum)
  - Colon cut off sign: gaseous distention of the ascending and transverse colon that abruptly terminates at the splenic flexure
  - Evidence of possible complications: pleural effusions, pancreatic calcium stones; helps rule out intestinal perforation with free air

- To be able to initiate the management plan for patient with acute pancreatitis and tailored therapy based on the cause.

Patients With Mild Acute Pancreatitis:

1. Bowel Rest (NPO)—goal is to rest the pancreas.
2. IV fluids
   a. patients may have severe intravascular volume depletion.
   b. Correct electrolyte abnormalities.
   c. Balanced crystalloids (lactated Ringer solution) are superior to normal saline, as normal saline can cause hyperchloremic metabolic acidosis. Acidosis will increase pancreatic zymogen activity which will then worsen autodigestion.

3. Pain Control
    a. be cautious in giving narcotics.
    b. Fentanyl And Meperidine preferred over morphine which causes an increase in sphincter of Oddi pressure.
4. Nasogastric Tube,if severe nausea/vomiting orileys present; routine use is controversial.
5. All patients with gallstone pancreatitis should have cholecystectomy after recovery from pancreatitis. These patients may benefit from early ERCP.
6. Prophylactic antibiotic therapy is not recommended.

Patients With Severe Pancreatitis:

1. Admit to the ICU.
2. Early enteral nutrition in first 72 hours is recommended through nasojejunal tube.
3. If the severe acute pancreatitis has not resolved in a few days, supplemental parenteral nutrition should be started.
4. If more than 30% of the pancreas necrosed, prophylactic antibiotics (imipenem) should be considered to prevent infection (which has high morbidity and mortality).

Other:

1. Fenofibrates: in hyperlipidemia-induced acute pancreatitis
2. Biliary pancreatitis
    a. Urgent ERCP and sphincterotomy (within 24 hours): in patients with evidence of choledocholithiasis and/or cholangitis; followed by cholecystectomy
    b. Cholecystectomy (preferably during same admission once the patient is stabilized; or within 6 weeks): in all patients with biliary pancreatitis

Acute Pancreatitis

Path	Autodigestion of the pancreas EtOH (#1) Gallstones (#2) Triglycerides
Patient	Boring epigastric pain radiating to the back, relief with leaning forward.
Dx	↑Lipase > 3x ULN ↑Amylase > 3x ULN (Lipase better) CT scan if unsure or for complications U/S if stones suspected → ERCP
Tx	NPO, IVF, Analgesia Feed when ready ~~Antibiotics~~ ~~Early Refeeding~~ ERCP only if worsening gallstone pancreatitis

IBD and IBS

- Identify the risk factors and recognize clinical manifestations for IBD.

❖ **Risk factors of UC**

- Genetic predisposition (e.g., HLA-B27 association)
- Ethnicity (white populations, individuals of Ashkenazi Jewish descent)
- Family history of inflammatory bowel disease
- Episodes of previous intestinal infection
- Increased fat intake (esp. saturated fat and animal fat)
- Oral contraceptive intake
- NSAIDs may exacerbate UC

❖ **Protective factors UC**

- Appendectomy
- Smoking has a protective effect

❖ **Risk factors of CD**

- Active and passive smoking of tobacco
- Familial aggregation
- Genetic predisposition (e.g., mutation of the NOD2 gene, HLA-B27 association)

	Crohn disease (CD)	**Ulcerative colitis (UC)**
Involvement	• Anywhere mouth to anus (mostly ileum & colon) • **Perianal disease** with **rectal sparing** • Skip lesions	• **Rectum (*ALWAYS*)** & colon • Continuous lesions
Microscopy	• Noncaseating granulomas	• No granulomas
Gross findings	• Transmural inflammation • **Linear** mucosal **ulcerations** • **Cobblestoning**, creeping fat	• Mucosal & submucosal inflammation • Pseudopolyps
Clinical manifestations	• Abdominal pain (often **RLQ**) • ***Watery* diarrhea** (**bloody** if colitis)	• **Abdominal pain** (*varying locations*) • **Bloody** diarrhea
Intestinal complications	• Fistulae, abscesses • Strictures (bowel obstruction)	• Toxic megacolon

- To be able to act diagnostic plan for patients suspected to have IBD.

❖ **Diagnosis**

- IBD is diagnosed with endoscopy and sometimes barium study.
- Anti–Saccharomyces cerevisiae antibodies (ASCA) are associated with CD, while antineutrophil cytoplasmic antibody (ANCA) is associated with UC.
    - If a patient is ASCA-positive and ANCA-negative, he has a >90% chance of having CD.
    - If a patient is ASCA-negative and ANCA-positive, he has a >90% chance of having UC
- With CD, prothrombin time may be prolonged because of vitamin K malabsorption.
- Also, kidney stones are more often seen because the fat malabsorption causes reduced calcium and increased absorption of oxalate. Use cholestyramine to treat calcium oxalate stones.
- (CD can cause deficiency of B12, K, calcium, and iron because of malabsorption.)

- To be able to establish a treatment plan for inflammatory bowel disease.

Crohn's Disease	Ulcerative Colitis
5-ASAs are often ineffective	Depends on severity of disease
Mild: For active disease prednisone or budesonide For maintenance azathioprine and 6-mercaptopurine	**Mild**: 4 bowel movements/day, mild bleeding, normal labs Mesalamine or sulfasalazine (causes reversible infertility in men and leukopenia by its sulfapyridine group)
Moderate: fever, weight loss, anemia, abdominal pain, nausea/vomiting For active steroids For maintenance azathioprine and 6-mercaptopurine or methotrexate For remission anti-TNF antibodies	**Moderate**: 4–6 bowel movements/day For active disease prednisone For remission budesonide For long-term maintenance azathioprine and 6-mercapto-purine (associated with drug-induced pancreatitis) to try to keep patients off steroids
Severe to fulminant: high fever, vomiting, rebound, obstruction For acute exacerbations, IV steroids or anti-TNF (**better choice**), possible surgery	**Severe**: >6 bowel movements/day, bleeding, fever, tachycardia, ESR >30 mm/h, anemia For acute exacerbations that fail steroids, and for maintenance if azathioprine and 6-mercaptopurine fail or are contraindicated, IV steroids followed by anti-TNF-alfa (infliximab, adalimumab, golimumab)
Fistula: anti-TNF For induction and maintenance anti-TNF antibodies (infliximab, adalimumab, certolizumab); if anti-TNF fails (can cause PML so check JC virus antibodies first) natalizumab (a monoclonal antibody to integrin-alfa-4 on leukocytes)	
For those with perianal disease ciprofloxacin and metronidazole For those who form fistulae or have disease refractory to other therapies infliximab	
Surgery is not very effective; disease tends to reoccur at the site of anastomosis	Surgery is curative; almost 60% of patients will require surgery within 5 years after diagnosis due to refractory symptoms or severe disease

- To identify the types of IBS based on the history and examination.

Clinical features of irritable bowel syndrome	
Rome IV diagnostic criteria	Recurrent **abdominal pain**/discomfort ≥1 day/week for past 3 months & ≥2 of the following: • Related to defecation (improves or worsens) • Change in stool frequency • Change in stool form
Alarm features	• Older age of onset (≥50) • GI bleeding • Nocturnal diarrhea • Worsening pain • Unintended weight loss • Abnormal labs (e.g., IDA, electrolyte disorders, ↑ CRP) • Positive fecal **lactoferrin** or **calprotectin** • FHx of early colon cancer or IBD

❖ Four different patterns are seen in the presentation of IBS:

IBS-D (diarrhea is the predominant symptom)
IBS-C (constipation is the predominant symptom)
IBS-M (mixed diarrhea and constipation)
IBS-A (alternating diarrhea and constipation)

- List the key points in the management of IBS.

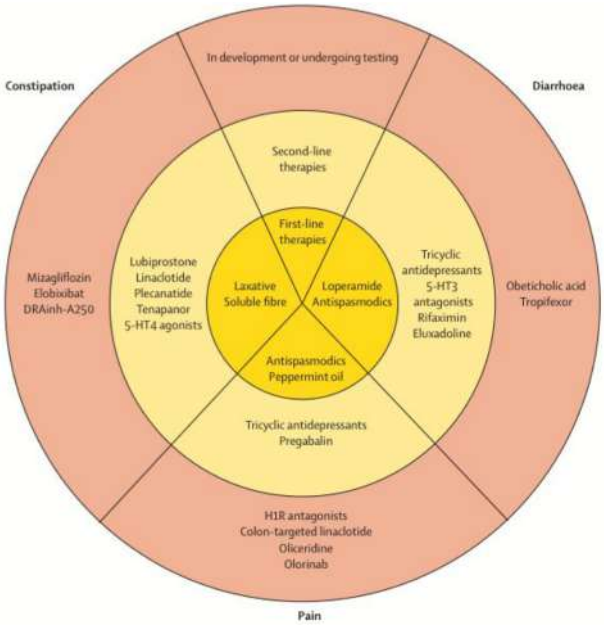
❖ **General measures**

- Regular consultations and reassurance that the disease, although chronic, is benign
- Lifestyle changes
    - Dietary adjustments (Plenty of fluid, High-fiber foods)
    - Avoidance of: Gas-producing foods (e.g., beans, onions, prunes), Fermentable, short-chain carbohydrates (e.g., foods with high fructose content: honey, apples, corn syrup), Lactose, Gluten
- Physical activity
- Stress management (identification of stress factors, avoidance techniques, relaxation therapy)
- Psychological therapy (patients with psychological conditions): e.g., cognitive-behavioral therapy

❖ **Medical therapy**

Medical therapy of IBS is symptom-directed:

- Diarrhea
    - Antidiarrheals (loperamide)
    - Rifaximin
    - Alosetron
- Constipation
    - Soluble fibers/bulk-forming laxatives (psyllium)
    - Osmotic laxatives (polyethylene glycol)
    - Lubiprostone (chloride channel activator)
- Cramping/pain
    - Antispasmodics (dicyclomine, hyoscyamine)
    - Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)



Malabsorption disorder (including Celiac disease, Whipple's disease, short bowel syndrome)

- Understand the pathophysiology of common Malabsorption disorders.

1. Celiac disease:

This is an autoimmune disorder caused by a gluten allergy; the body produces antibodies in reaction to gluten of wheat, rye, and barley.

Consumption of food containing gluten → tissue transglutaminase is released → modifies gliadin from gluten proteins → pathogenic T cells react to and are activated by modified gliadin → mediate chronic intestinal inflammation → epithelial damage resulting in villous atrophy, crypt hyperplasia, and loss of brush border → impaired resorption of nutrients in the small intestine (especially in the distal duodenum and proximal jejunum) → malabsorption symptoms

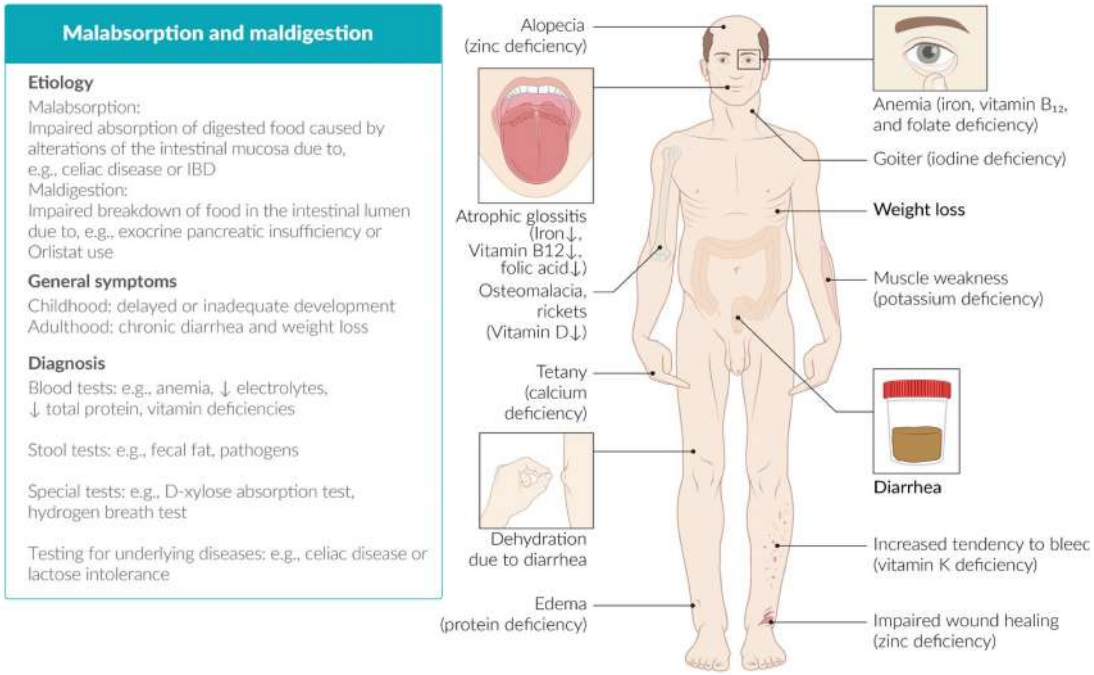
2. Whipple's disease:

Rare disease caused by infection by the bacterium Tropheryma whipplei. Inflammation secondary to the infection damages villi in the small intestine

3. Small intestine resection (short bowel syndrome)

Definition: a condition in which the small intestine is unable to adequately absorb nutrients, water, and electrolytes

Etiologies: surgical resection (e.g., for Crohn disease or trauma), congenital abnormalities



- To be able to implement testing and interpret the results.

1. Malabsorption

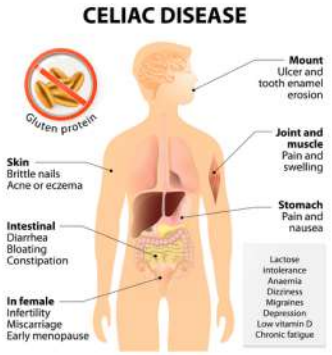
- Blood tests:
  - Macrocytic and/or microcytic anemia; ↓ electrolytes, ↓ total protein, vitamin deficiencies
- Stool tests
  - Analysis of fecal fat; over 72 hours (e.g., using Sudan stain)
  - Detection of pathogens
- D-xylose absorption test: assesses the absorptive function of the upper small intestine not routinely indicated (low sensitivity and specificity)
  - Interpretation:
    - ↓ D-xylose levels (urine and blood) occur in malabsorptive disorders that involve damage to the intestinal mucosa (e.g., celiac disease, Whipple disease) and in cases of bacterial overgrowth.
    - Normal (elevated) D-xylose levels suggest a different cause of malabsorption.
- Hydrogen breath test: assess the intestinal absorption of individual carbohydrates
- Lactulose breath test: determination of orocecal transit time (small intestine transit time)
- Glucose hydrogen breath test: if abnormal bacterial colonization of the small intestine is suspected
- Further testing (for underlying diseases): e.g., celiac disease or lactose intolerance

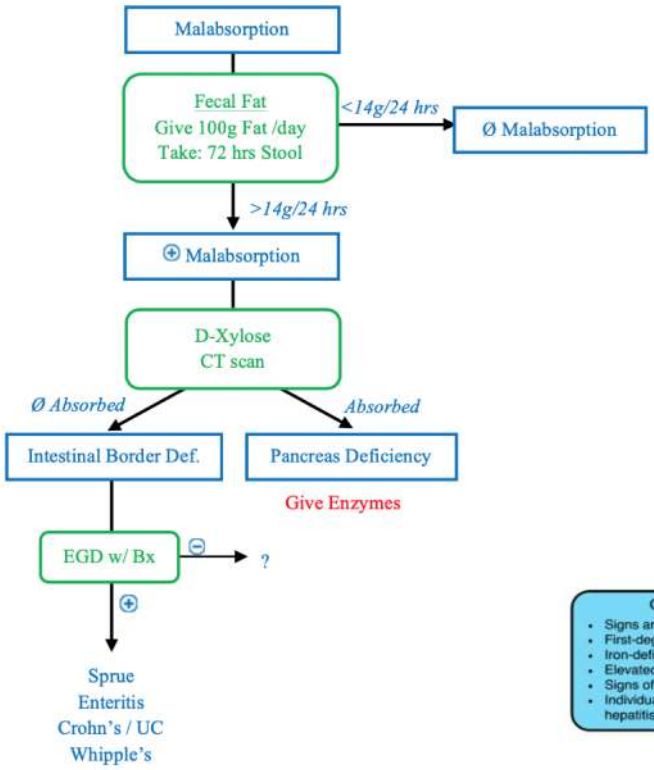
2. Celiac disease

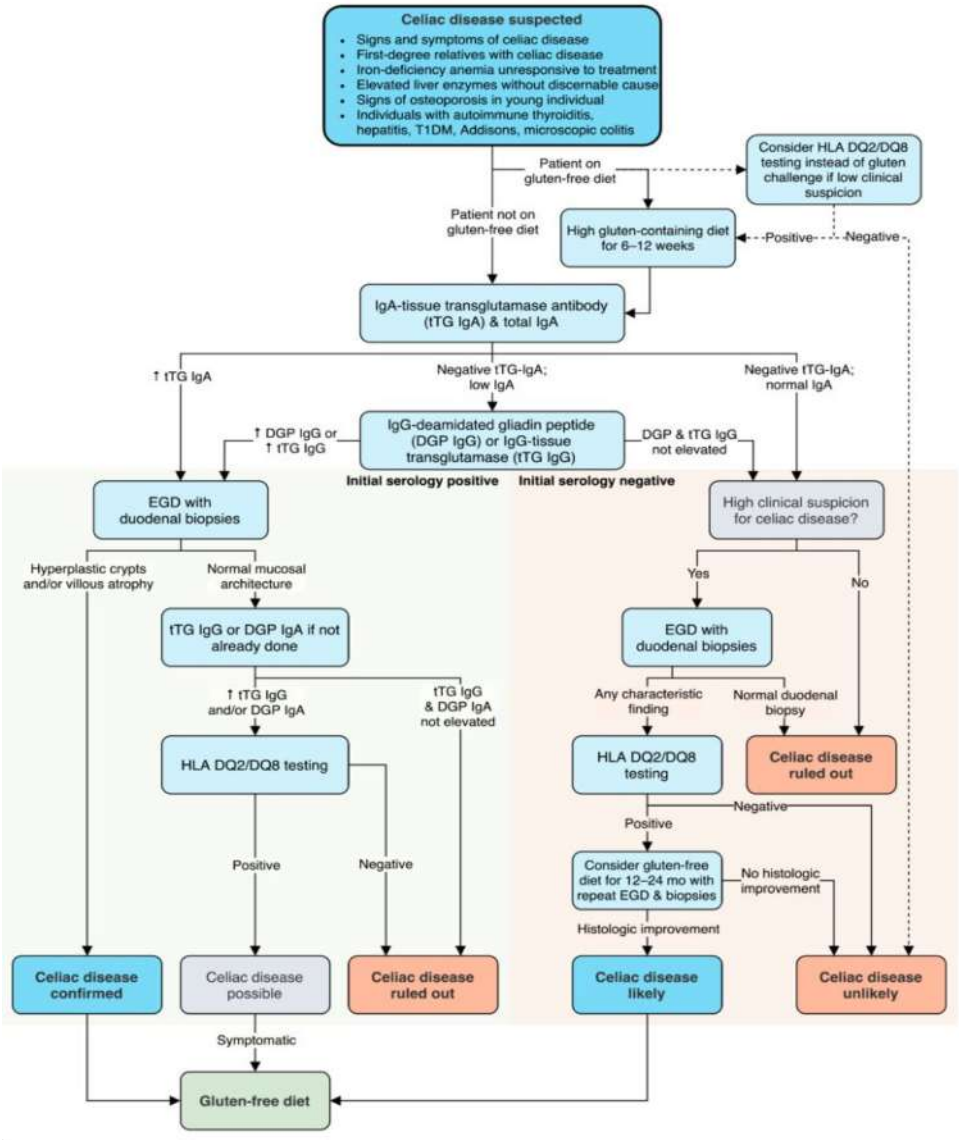
- Diagnosis is based on serology (initial testing) and EGD with duodenal biopsy (confirmation).

Routine studies

- **IgA tissue transglutaminase antibody (tTG IgA):** initial test
  - Risk of false negatives (e.g., in IgA deficiency, gluten-free diet)
- **Total IgA**
  - Indicated for all patients because of the high prevalence of IgA deficiency in patients with celiac disease
  - If patients have low IgA, perform further IgG-based testing.
- **EGD with small intestine biopsy** (confirmatory test)
  - Indications: positive serology or high clinical suspicion despite negative serology







Additional studies

- Deamidated gliadin peptide
  - IgG-based testing: indicated in IgA deficiency or discordant biopsy and serology
    - IgG-tissue transglutaminase (tTG IgG)
    - IgG deamidated gliadin peptide (DGP IgG): Test of choice (along with tTG IgA) in children under 2 years of age
  - IgA-based testing: IgA deamidated gliadin peptide (DGP IgA)
- HLA testing: second-line testing after unclear initial evaluation
  - Assesses for haplotypes HLA-DQ2 and HLA-DQ8
  - Indications include:
    - Uncertain diagnosis (e.g., disparity between serology and histopathology)
    - Gluten-free diet prior to diagnosis
    - Patients with Down syndrome
- Anti-endomysial antibody (EMA): Potential second-line confirmatory test (high-specificity)
- Video capsule endoscopy: if EGD is declined or as follow-up if symptoms persist despite treatment
- Nutrient deficiency screening: indicated in confirmed celiac disease
  - Ferritin, iron‹ Zinc, calcium‹ Vitamin B12 and B6, folate‹ Fat-soluble vitamins, especially vitamin D
- Associated autoimmune disorders: Consider further testing if there are symptoms for thyroiditis, autoimmune hepatitis, and/or diabetes.

3. Whipple's disease:

- EGD Biopsy
  - Microscopic examination showing periodic acid-Schiff stain (PAS)–positive macrophages in the lamina propria containing non–acid-fast gram-positive bacilli.
- PCR on the Blood/CSF can yield a positive result.

- To recognize the histopathology pattern of intestinal of common Malabsorption disorders.

1. Celiac disease:

- Intraepithelial lymphocytic infiltration
- Crypt hyperplasia
- Villous atrophy
- loss of brush border

2. Whipple's disease:

- Distended macrophages in lamina propria containing PAS+ (diastase resistant) granules and rod shaped bacilli by EM
- Dilated lymphatics or fat vacuoles
- Often multinucleated giant cells; rarely epithelioid granulomas in minority
- In mesentery or retroperitoneal nodes, resembles lipogranulomatous inflammation with round empty spaces

- To understand the key points in the management of the common Malabsorption disorders.

1. Celiac disease:

- Managing celiac disease mainly consists of maintaining a lifelong gluten-free diet.
- Iron and vitamin supplementation, if there are deficiencies (e.g., iron deficiency anemia)
- Consider osteoporosis screening in adult patients

2. Whipple's disease:

- Antibiotic therapy for 1 to 2 years.
- pick either Bactrim DS or Doxycycline

3. Short bowel syndrome:

Often, treatments change as the remaining intestine adjusts after surgery. The main goals of treating SBS are to maintain adequate nutrition, and manage symptoms and complications. This may involve a combination of:

- Dietary education, with the possible need for special nutrition support
- Medications
- Surgery

Disease	*Patient*	*Deficiency*	*Pathology*	*Diagnosis*	*Treatment*
Celiac Sprue	Adults	FIC	Autoimmune	Antibodies → Bx	Gluten Free Diet
Tropical Sprue	Tropics	B12	Infxn	Bx	Abx + B12
Whipple's Dz	Tropics	CNS, Joints	Infxn	Bx or PCR	Abx (Bactrim)
Lactase Deficiency	Asians	Dairy	↓ Enzyme	Relief w/ Tx	Lactase or Ø Dairy
Pancreatic Insufficiency	Cystic Fibrosis, Gallstones	ADEK	Ø Enzymes	CT/MRI/Bx	Add Enzymes

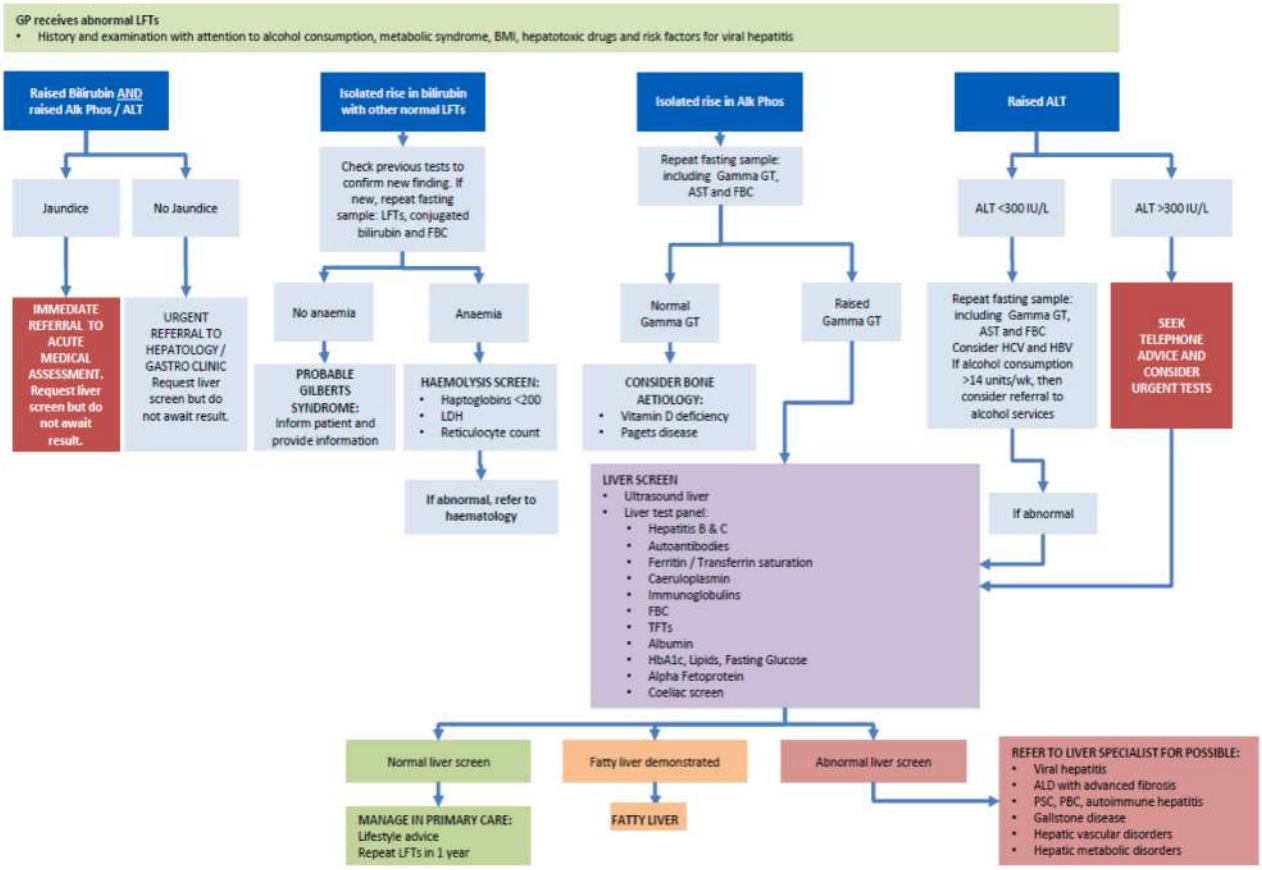
FATS ADEK and Steatorrhea
A = Night Blindness
D = Hypo Ca / Osteoporosis
E = Nystagmus
K = Bleeding (2,7,9,10) → INR

Protein Weight Loss and Edema

Proximal Bowel FIC vitamins
Folate = Megaloblastic Anemia
Iron = Microcytic Anemia
Calcium = Osteoporosis

Approach to the Patient with Abnormal Liver Chemistry studies

- Describe and interpret abnormal liver enzymes.
- Develop a differential diagnosis for abnormal liver enzymes and jaundice
- Describe the approach plan for patients with abnormal liver enzymes & jaundice



https://geekymedics.com/interpretation-of-liver-function-tests-lfts/

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU, ALT > AST	Normal to <3× normal elevation	Normal	Usually normal. If >5× above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT >2 suggests alcoholic hepatitis or cirrhosis	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation	Elevated, often >4× normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
(Obstructive jaundice)	Bilirubinuria	Rarely >500 IU		Normal	Normal
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation	Elevated, often >4× normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase		

- To recognize the common causes for acute liver failure, understand the pathophysiology, clinical presentation, and formulate the work-up and management plan.

1. Acute liver failure

❖ **Definition:**

- rapidly worsening liver function resulting in coagulopathy and hepatic encephalopathy in individual without preexisting liver disease or cirrhosis
- The presence of Hepatic encephalopathy differentiates acute liver failure from acute hepatitis, which has a much better prognosis than ALF

❖ **Treatment:**

depends on the underlying cause

- In general: early transfer to a liver transplant center
- Address underlying cause: e.g., in case of acetaminophen toxicity, administer intravenous N-acetylcysteine
- Address complications (e.g., cerebral edema, encephalopathy, coagulopathy, renal failure, and infection) in order to limit long-term damage
- Last resort: liver transplantation, for patients without sufficient regeneration of hepatocytes.

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)

Cirrhosis and complication of advanced liver disease

- List the common causes of liver cirrhosis in Saudi Arabia

❖ **Causes:**

1. Chronic hepatitis B and C infections–most common causes in SA
2. Nonalcoholic steatohepatitis (NASH)
3. Drugs (e.g., acetaminophen toxicity, methotrexate)
4. Alcoholic liver disease
    a. Refers to a range of conditions from fatty liver (reversible, due to acute ingestion) to cirrhosis (irreversible)
5. Autoimmune hepatitis
6. Primary biliary cirrhosis (PBC), secondary biliary cirrhosis
7. Inherited metabolic diseases (e.g., hemochromatosis, Wilson disease)
8. Hepatic congestion secondary to right-sided heart failure, constrictive pericarditis
9. α1-Antitrypsin (AAT) deficiency
10. Hepatic veno-occlusive disease–can occur after bone marrow transplantation

Patient has...	***Key Facts and Diagnosis***
Cirrhosis and COPD	A1-AT deficiency Get a biopsy = **PAS + Macrophages**
Cirrhosis, Diabetes, Tan Skin	Hemochromatosis Get a **ferritin** (very high) or **transferrin** then get a **biopsy** Transplant cures the cirrhosis, not the hemochromatosis
Cirrhosis, Chorea, and the "eye"	**Wilson's Disease** Start with a **slit lamp** (Kayser-Fleischer) Do NOT get Serum Copper - this is wrong Either **ceruloplasmin** or **urine copper** Transplant cures cirrhosis and disease
Cirrhosis and Inflammatory Bower Disease	**Primary Sclerosing Cholangitis** Start with an **MRCP** Biopsy / ERCP is NOT needed Do **NOT STENT** - ursodeoxycholic acid Can recur in transplant
Cirrhosis and alcohol consumption	**Alcoholic cirrhosis** Stop drinking alcohol Transplant curative
Cirrhosis and positive serology	**Viral hepatitis** Treat Hep B, Treat Hep C Vaccinate against A and B
Cirrhosis and a long list ensuring everything is negative	**NASH** Diagnosis of exclusion Treat symptoms and transplant

- List the complications of advanced liver disease.

❖ **Complications:**

1. Portal HTN
    a. Clinical features are listed above. Bleeding (hematemesis, melena, hematochezia) secondary to esophagogastric varices is the most life-threatening complication of portal HTN.
    b. Diagnose based on above features. Paracentesis can help in diagnosis.
    c. Treat the specific complication. Use transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressure.
2. Varices
    a. Esophageal/gastric Variceal hemorrhage has a high mortality rate. Patients with cirrhosis should be evaluated for the presence of varices and risk of hemorrhage. If varices are present, prophylactic measures are indicated (such as nonselective βblocker).
        i. Clinical features include massive hematemesis, melena, and exacerbation of hepatic encephalopathy.
        ii. Esophageal varices account for 90% of varices, and gastric varices for 10%. Initial treatment is hemodynamic stabilization (give fluids to maintain BP).
        iii. IV antibiotics are given prophylactically.
        iv. IV octreotide is initiated and continued for 3 to 5 days.
        v. Perform emergent upper GI endoscopy (once patient is stabilized) for diagnosis and to treat the hemorrhage either with variceal ligation or sclerotherapy.
        vi. Give nonselective β-blockers (propranolol, timolol, nadolol) as long-term therapy to prevent rebleeding.
    b. Rectal hemorrhoids
    c. Caput medusae (distention of abdominal wall veins)
3. Ascites
    a. Accumulation of fluid in the peritoneal cavity due to portal HTN (increased hydrostatic pressure) and hypoalbuminemia (reduced oncotic pressure). Ascites is the most common complication of cirrhosis. Patients without portal hypertension do not develop ascites.
    b. Clinical features: abdominal distention, shifting dullness, and fluid wave.
    c. Abdominal ultrasound can detect as little as 30 mL of fluid.
    d. Diagnostic paracentesis determines whether ascites is due to portal HTN or another process.
        i. Indications include new-onset ascites, worsening ascites, and suspected spontaneous bacterial peritonitis (SBP).
        ii. Examine cell count, ascites albumin, Gram stain, and culture to rule out infection (e.g., SBP).
        iii. Measure the serum ascites albumin gradient. If it is >1.1 g/dL, portal HTN is very likely. If <1.1 g/dL, portal HTN is unlikely, and other causes must be considered.
    e. Treatment A low-sodium diet and diuretics: spironolactone (used to reduce accumulation of fluid) and furosemide (used to prevent hyperkalemia caused by spironolactone).
    f. Perform therapeutic paracentesis if tense ascites, shortness of breath, or early satiety is present.
    g. Peritoneovenous shunt or TIPS to reduce portal HTN

1. Hepatic encephalopathy
    a. Toxic metabolites (there are many, but ammonia is believed to be most important) that are normally detoxified or removed by the liver accumulate and reach the brain.
    b. Occurs in 50% of all cases of cirrhosis, with varying severity.
    c. Precipitants include alkalosis, hypokalemia (e.g., due to diuretics), sedating drugs (narcotics, sleeping medications), GI bleeding, systemic infection, and hypovolemia.
    d. Clinical features Decreased mental function, confusion, poor concentration, even stupor or coma Asterixis ("flapping tremor"). (However, this is not a specific sign.)
        i. Rigidity, hyperreflexia Fetor hepaticus—musty odor of breath
    e. Treatment:

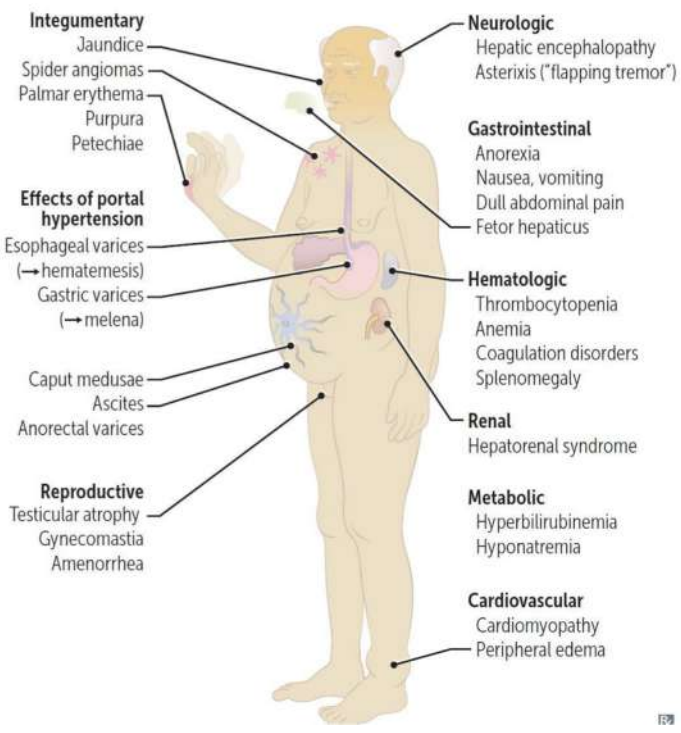
- Lactulose prevents absorption of ammonia. Metabolism of lactulose by bacteria in the colon favors formation of NH_4^+, which is poorly absorbed from GI tract, thereby promoting excretion of ammonia.
- Rifaximin (antibiotic): kills bowel flora; so decreases ammonia production by intestinal bacteria.
- Diet—limit protein to 30 to 40 g/day.

1. Hepatorenal syndrome—indicates end-stage liver disease
    a. Progressive renal failure in advanced liver disease, secondary to renal hypoperfusion resulting from vasoconstriction of renal vessels.
    b. Often precipitated by infection or diuretics.
    c. This is a functional renal failure—kidneys are normal in terms of morphology, and no specific causes of renal dysfunction are evident. This condition does not respond to volume expansion.
    d. Clinical features: azotemia, oliguria, hyponatremia, hypotension, low urine sodium (<10 mEq/L).
    e. Treatment: **Liver transplantation is the only cure**. In general, the prognosis is very poor, and the condition is usually fatal without liver transplantation.
2. SBP—infected ascitic fluid; occurs in up to 20% of patients hospitalized for ascites.
    a. Usually occurs in patients with ascites caused by end-stage liver disease; associated with high mortality rate (20% to 30%).
    b. Has a high recurrence rate (up to 70% in first year).
    c. Etiologic agents: Escherichia coli (most common) Klebsiella Streptococcus pneumoniae
    d. Clinical features: abdominal pain, fever, vomiting, rebound tenderness. SBP may lead to sepsis.
    e. Diagnosis is established by paracentesis and examination of ascitic fluid for WBCs (especially PMNs), Gram stain with culture, and sensitivities.
    f. Treatment Broad-spectrum antibiotic therapy: give specific antibiotic once organism is identified.

- Clinical improvement should be seen in 24 to 48 hours. Repeat paracentesis in 2 to 3 days to document a decrease in ascitic fluid PMN (<250).

7. Hyperestrinism—due to reduced hepatic catabolism of estrogens
    a. Spider angiomas—dilated cutaneous arterioles with central red spot and reddish extensions that radiate outward like a spider's web
    b. Palmar erythema
    c. Gynecomastia
    d. Testicular atrophy
8. Coagulopathy—secondary to decreased synthesis of clotting factors.
    a. Prolonged prothrombin time (PT); PTT may be prolonged with severe disease.
    b. Vitamin K supplementation ineffective because it cannot be used by diseased liver.
    c. Treat coagulopathy with fresh frozen plasma.

9. Hepatocellular carcinoma (HCC)—present in 10% to 25% of patients with cirrhosis. **All patients with cirrhosis should be screened for HCC, most commonly with serum AFP measurement and liver ultrasound every 6 months.**



What are the 5 variables of Child–Pugh classification?

- Bilirubin
- Albumin
- PT (or INR)
- Ascites
- Encephalopathy

Bake Another Pie At Eleven

Child–Pugh score estimates hepatic reserve in liver failure. It is used to measure disease severity and is a predictor of morbidity and mortality.

In HCC AFP+US: screening. CT or MRI (with contrast): confirmatory.
Liver biopsy recommended when both lab and imaging studies are inconclusive

- To be able to identify patients with hepatic encephalopathy to understand the key elements in the management.

HE is a reversible syndrome of impaired brain function occurring in patients with advanced liver disease.

❖ **common precipitants**:

- Drugs (benzodiazepines, narcotics or alcohol)
- Increased ammonia production, absorption or entry into the brain (excess dietary intake of protein (eating more meat), GI bleeding, infection, electrolyte disturbances such as hypoK, constipation (very important cause!) or metabolic alkalosis)
- Dehydration, like in elderly pts (e.g. vomiting, diarrhea, hemorrhage or diuretics – more than prescribed)
- Vascular occlusion (i.e. hepatic or portal vein thrombosis)
- Hepatocellular carcinoma (HCC)

❖ **Clinical features:**

Decreased mental function, confusion, poor concentration, even stupor or coma Asterixis ("flapping tremor")—have the patient extend the arms and dorsiflex the hands. (However, this is not a specific sign.)
Rigidity, hyperreflexia Fetor hepaticus—musty odor of breath

❖ **Management:**

1- IDENTIFY and TREAT precipitating factors for HE
2- Lactulose is the first choice (or rifaximin: non-absorbable antibiotic)

- To be able to interpret the results of the ascitic tap to be able to diagnose the spontaneous bacterial peritonitis (SBP)

❖ **Ascites**

- Accumulation of fluid within the peritoneal cavity
- 1500 ml of fluid must be present before flank dullness is detected clinically.
- Shifting dullness If no flank dullness is present less likely ascites (< 10%)
- Cause:
  - 85% of due to cirrhosis
  - 15% other causes

Rule of thumb: Any ascites needs to be tapped (when possible) to determine the cause of ascites and if there is infection!

❖ **Ascitic Fluid Analysis:**

• Routine tests on ascitic fluid:

1. Cell count and differential (see WBC+ RBC)
2. Albumin
3. Total protein

To evaluate the cause of ascites measure SAAG (Serum Albumin- Ascitic Gradient)

SAAG = Serum Albumin – Ascitic Albumin

≥ 1.1 g/dl **Portal Hypertension**	**< 1.1 g/dl** **Non Portal Hypertension**
- Chronic Liver Diseases - Budd-Chiari Syndrome - Congestive Heart Failure	- Nephrotic Syndrome - Pancreatitis - Peritoneal Tuberculosis - Peritoneal Carcinomatosis

• To understand the key points in the management of SBP

- **How do we diagnose SBP?**

• Do paracentesis and asses ascitic fluid polymorphonuclear leukocyte (PMN) (neutrophils) count ≥ 250 cells/mm3

• Usually one organism (gram negatives)

- E-coli or klebsiella , others: enterococcus, pseudomonas (mnemonic: KEEPs)

• If multiple organisms think of secondary peritonitis (perforation of colon and bacteria enters the ascites)

- **How to treat SBP?**

1. Antibiotics
2. Albumin – it reduces mortality in SBP.

GI bleeding and ischemia

- List the causes of upper GI bleeding.

Most common etiologies of GI bleeding [4]		
	(UGIB) [5]	(LGIB) [6]
Erosive or inflammatory	• **Peptic ulcer disease** (~ 30% of cases) • Esophagitis • Erosive gastritis and/or duodenitis	• **Diverticulosis** (~ 30% of cases) [7] • Inflammatory bowel disease (**IBD**), i.e., ulcerative colitis and Crohn disease • Invasive or inflammatory diarrhea (bacterial gastroenteritis, due to e.g., Shigella, EHEC)

Vascular	• **Esophageal varices** or gastric varices
	• Gastric antral vascular ectasia
	• **Dieulafoy lesion**: minor mucosal trauma to an abnormal submucosal artery (usually located in the proximal stomach) leads to major bleeding (acute upper GI bleeding)
	  ◦ It can be hard to visualize a Dieulafoy lesion on endoscopy because it is missing an ulcer base.
	  ◦ Treatment includes endoscopic hemostasis (injection therapy, hemoclips, etc.) or excision of the susceptible mucosa
		• **Hemorrhoids**
		• Ischemia (e.g., ischemic colitis, mesenteric ischemia)
		• Arteriovenous malformation
		• Rectal varices

	• **Angiodysplasia**: a common degenerative disorder of GI vessels (mostly venous) that can cause GI bleeding in the stomach, duodenum, jejunum, and colon [8]
	  ◦ Associated with age > 60 years, von Willebrand disease, aortic stenosis, and end-stage renal disease
	  ◦ Manifests with episodic bleeding (hematochezia) that ceases spontaneously in > 90% of cases
	  ◦ Diagnosis usually requires angiography.
	  ◦ Lesions are usually multiple tortuous dilated vessels, most commonly located in the right-sided colon (~ 75%).	

Tumors	• Esophageal cancer and/or gastric carcinoma	• Colorectal cancer and/or anal cancer • Colonic polyps
Traumatic or iatrogenic	• Hiatal hernias • Mallory-Weiss syndrome • Boerhaave syndrome	• Lower abdominal trauma • Anorectal trauma (e.g., anorectal avulsion, impalement injuries)
	• Following open or endoscopic surgery (e.g., anastomotic bleeding following a gastric bypass)	
Other causes	• Portal hypertensive gastropathy • Coagulopathies	• Anal fissures

- Identify the symptoms and signs for patients with GI bleeding

Clinical features:

- Anemia due to chronic blood loss
- Acute hemorrhage with significant blood loss
- Signs of circulatory insufficiency or hypovolemic shock
- Tachycardia, hypotension (dizziness, collapse, shock)
- Altered mental status
- Features of overt GI bleeding

	Description	Cause
Hematemesis	• Vomiting blood, which may be red or coffee-ground in appearance	• Most commonly due to bleeding in the upper GI tract (e.g., esophagus, stomach)
Melena	• Black, tarry stool with a strong offensive odor	• Most commonly due to bleeding in the upper GI tract • Can also occur in bleeding from the small bowel or the right color
Hematochezia	• The passage of bright red (fresh) blood through the anus (with or without stool) ◦ Colonic bleeding: maroon, jelly-like traces of blood in stools ◦ Rectal bleeding: streaks of fresh blood on stools	• Most commonly due to bleeding in the lower GI tract (e.g., in the distal colon) • Rapid passage of blood from the upper GI tract may also result in hematochezia.

***Both melena and hematochezia can be caused by either UGIB or LGIB.**

***Unexplained iron deficiency anemia (e.g., in men or postmenopausal women) should raise suspicion for GI bleeding.**

- Discuss the risk stratification and initial assessment for patients with GI bleeding or ischemia..
- Illustrate important physical signs in patients with GI bleeding or ischemia.
- Outline the investigations required and enlist key points in the management plan

1. UGIB

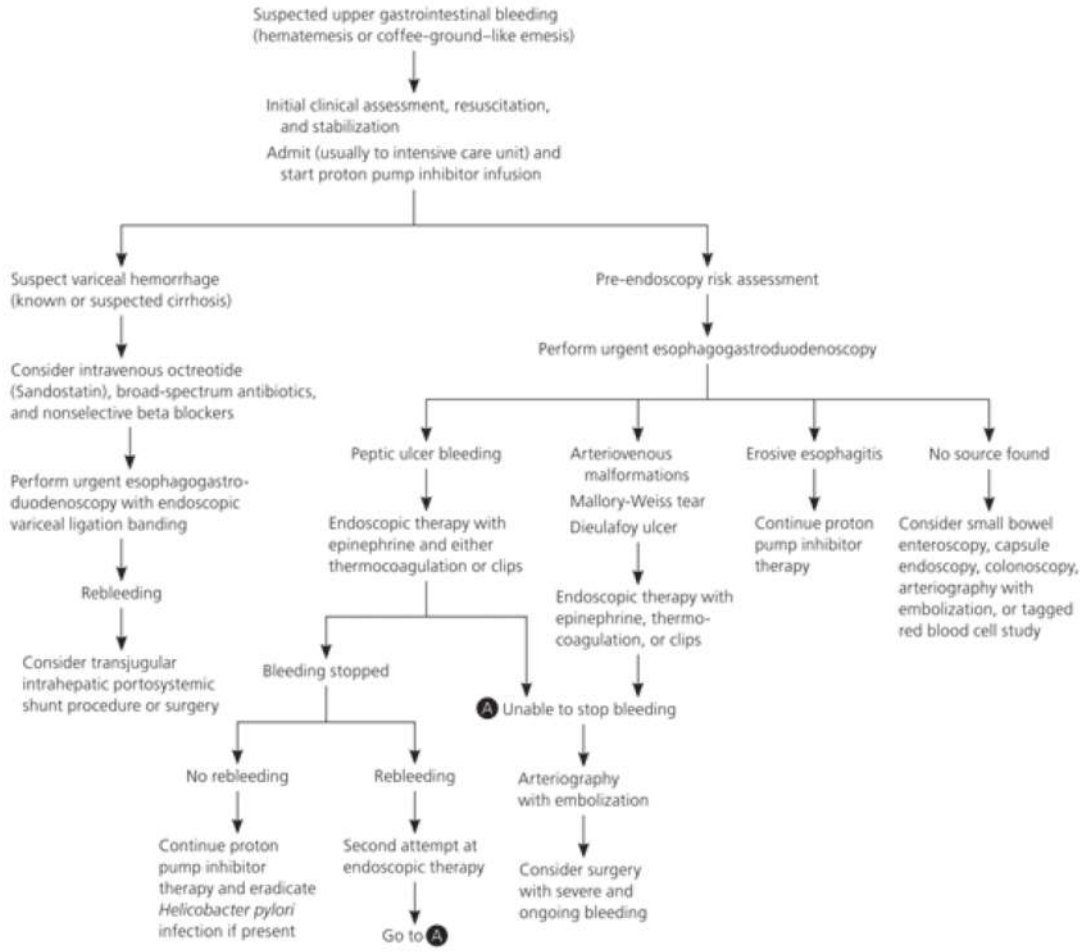
- scoring systems: e.g., the Glasgow-Blatchford score (GBS)

Glasgow Blatchford score [13][24]				
Parameters		Findings		Score
Laboratory features	BUN	< 18.2 mg/dL		0
		18.2 mg/dL–22.3 mg/dL		2
		22.4 mg/dL–27.9 mg/dL		3
		28 mg/dL–69.9 mg/dL		4
		≥ 70 mg/dL		6
	Hemoglobin	♂ : > 13 g/dL	♀ : > 12 g/dL	0
		♂ : 12–13 g/dL	♀ : 10–12 g/dL	1
		♂ : 10–12 g/dL	♀ : N/A	3
		♂ : < 10 g/dL	♀ : < 10 g/dL	6
Clinical features	Systolic blood pressure	> 110 mm Hg		0
		100–109 mm Hg		1
		90–99 mm Hg		2
		< 90 mm Hg		3
	Additional criteria	Heart rate ≥ 100/min		1
		Melena at presentation		1
		Syncope at presentation		2
		Liver disease		2
		Heart failure		2

Interpretation

- **Score 0: low-likelihood of rebleeding or need for urgent intervention**
- **Score ≥ 1: higher likelihood of rebleeding and/or need for urgent intervention [25]**

❖ **Approach to gi bleeding:**

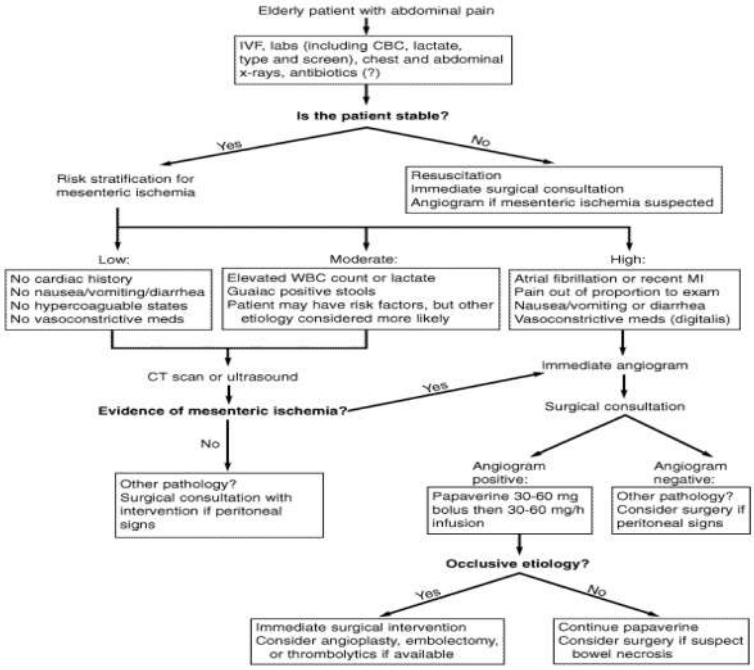


- Patients with upper (but not lower) GI bleeding often have an elevated blood urea nitrogen (BUN) and elevated BUN/creatinine ratio. Possible causes include increased urea production from intestinal breakdown of hemoglobin and increased urea reabsorption in the proximal tubule due to associated hypovolemia.

2. mesenteric ischemia

- AMI typically presents with sudden-onset, severe, poorly localized (visceral) mid abdominal pain accompanied by nausea and vomiting. Urge to defecate is common.
- In early-stage ischemia, physical examination is typically unremarkable (eg, mild diffuse tenderness) despite patients having **severe pain out of proportion to the examination findings.**
- If bowel infarction occurs, patients may develop more focal abdominal tenderness (due to local inflammation/infarction), peritoneal signs (eg, guarding, rebound tenderness), rectal bleeding, and sepsis.
- Leukocytosis, hemoconcentration, elevated amylase, and metabolic acidosis (lactate) are frequently seen on laboratory testing.
- Patients with evidence of bowel infarction should undergo immediate operative evaluation; otherwise, diagnosis can be confirmed radiologically by CTA.
- 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.

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 or 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 is unclear



❖ Initial Actions and Primary Survey of mesenteric ischemia

- Mesenteric ischemia is a time-sensitive disease process as delays in diagnosis will lead to increased morbidity and mortality, especially in elderly patients.
- The first and most important initial action is to consider mesenteric ischemia in the differential diagnosis of all elderly patients with abdominal pain. The importance of early consideration and diagnosis of mesenteric ischemia cannot be overemphasized.
- Other initial actions will include large bore intravenous access, fluid resuscitation, and telemetry monitoring.
- Obtain an ECG to see if the patient has atrial fibrillation which can put them at risk for an embolic cause of mesenteric ischemia.
- Discuss the case with the surgeons as early as possible so that they can monitor for changes in the patient's abdominal exam.
- An initial benign, soft abdominal exam can become peritoneal and that may lead the surgeons to take the patient to the operating room rapidly in order to preserve as much bowel as possible.
- Consider aggressive fluid administration early in the patients ED course as well as addressing any other abnormalities in the primary survey.
- If the patient is becoming hypoxic or has dyspnea due to fluid resuscitation, apply oxygen via nasal cannula, a non-rebreather mask, or non-invasive positive pressure ventilation via BiPAP. Consider intubation if their breathing worsens despite those measures.
- If the patient is hypotensive, make sure fluid resuscitation is adequate as vasopressors will worsen mesenteric blood flow and thereby worsen the amount of ischemia.
- Consider broad spectrum antibiotics and anticoagulation.

❖ Presentation

- The "classic" presentation for mesenteric ischemia will be in a patient over the age of 60.
- Women are three times more likely than men to have acute mesenteric ischemia.
- Patients will present with sudden abrupt onset of abdominal pain which may be associated with nausea, vomiting, and diarrhea.
- The abdominal pain will initially be severe and diffuse without any localization.
- One of the distinctive findings in mesenteric ischemia is that the **abdominal pain is out of proportion to their physical exam**. The patient may be screaming in pain, but their initial abdominal exam can be soft with no guarding or rebound. (This is because the ischemia is in the wall of the hollow viscus of the intestine and therefore does not cause the same peritoneal signs that would be present in appendicitis, cholecystitis, and other more localized processes.)
- As the disease progresses and the bowel infarcts, the patient will develop abdominal distension with guarding, rebound, and absence of bowel sounds. They may develop abdominal wall rigidity. Bloody diarrhea and heme-positive stools are a late finding after bowel has infarcted.

❖ **Treatment**

Definitive treatment options include the following:

- Acute mesenteric arterial embolism (AMAE)
  - Papaverine infusion, surgical embolectomy, and intra-arterial thrombolysis
- Acute mesenteric arterial thrombosis (AMAT)
  - Papaverine infusion and arterial reconstruction, either through aortosuperior mesenteric arterial bypass grafting or through reimplantation of the superior mesenteric artery (SMA) into the aorta
- Nonocclusive mesenteric ischemia (NOMI)
  - Papaverine infusion
- Mesenteric venous thrombosis (MVT)
  - Anticoagulation with heparin or warfarin, either alone or in combination with surgery; immediate heparinization should be started even when surgical intervention is indicated

All cases of mesenteric ischemia with signs of peritonitis or possible bowel infarction, regardless of etiology, generally warrant immediate surgical intervention for the resection of ischemic or necrotic intestines

Table 1. Acute mesenteric ischemia risk factors, symptoms, treatments, and mortality[1,5–7]

	ARTERIAL			VENOUS
	Occlusive		Nonocclusive (15%)	
	Embolic (60%)	Thrombotic (20%)		
Risk Factors	Atrial fibrillation MI CHF prior embolism (⅓)	CAD PAD tobacco use	ESRD CHF vasopressors	Prior DVT or PE (50%) Recent surgery Hypercoagulable
Symptoms	Acute-onset Hematochezia	Progressive worsening Chronic mesenteric ischemia symptoms (20-65%) - food fear, postprandial pain, early satiety, weight loss	Critically ill patient Hypotension Altered mental status	Insidious onset Asymptomatic
Treatments	Revascularization (endovascular or open surgery), laparotomy as indicated	Revascularization (endovascular or open surgery), laparotomy as indicated	Treat underlying cause, stop vasopressors, vasodilators, laparotomy as indicated	Anticoagulation, laparotomy as indicated
Mortality	18-88%	27-100%	50-83%, varies with underlying disease	25-69%

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; DVT, deep venous thrombosis; ESRD, end stage renal disease; MI, myocardial infarction; PAD, peripheral artery disease; PE, pulmonary embolism

Diarrhea

- List the common causes of acute diarrhea and chronic diarrhea
- To be able to initiate a diagnostic and management plans for patient presenting with diarrhea.

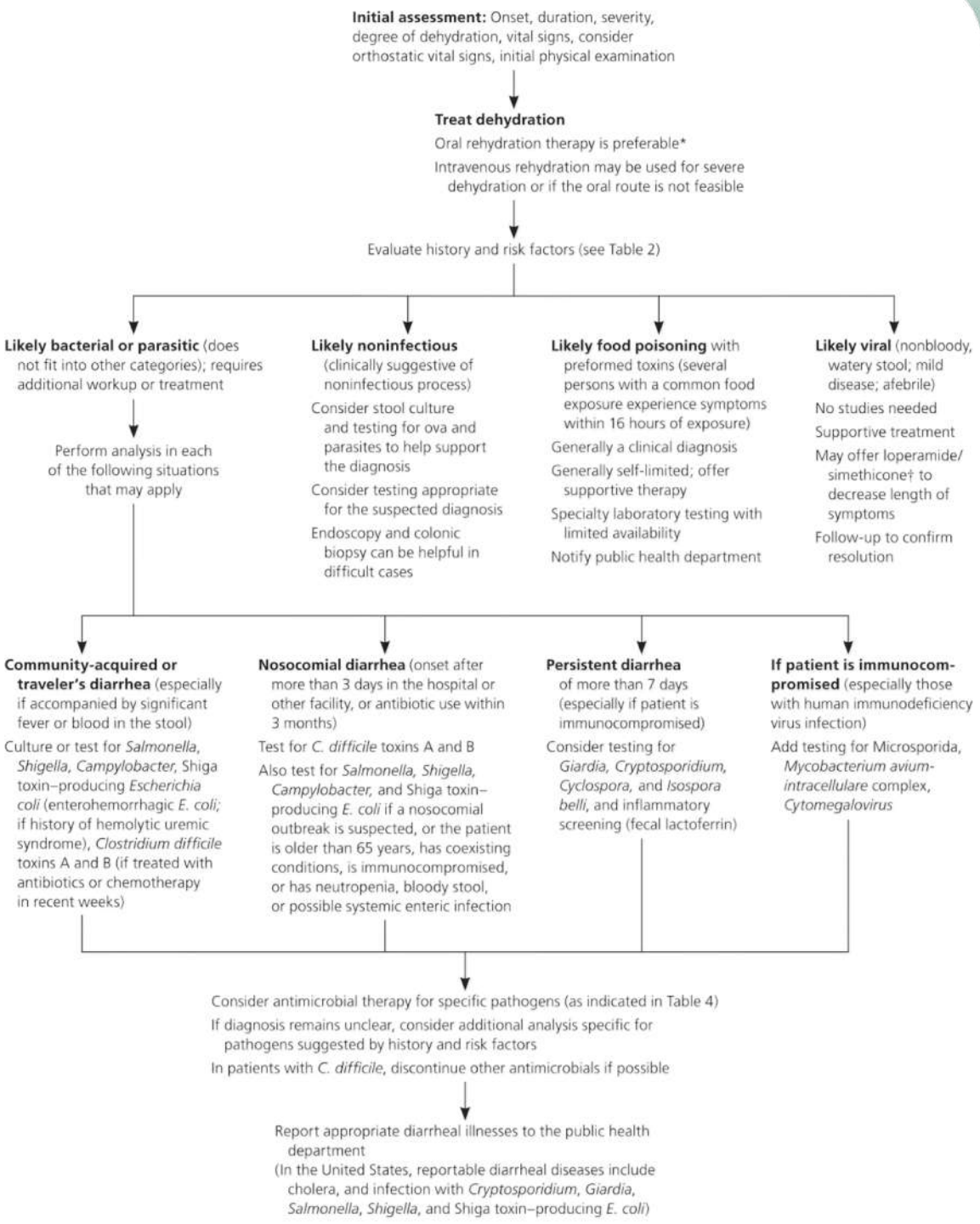
- Diarrhea is present if one of the following criteria is fulfilled:
  - Frequent defecation: ≥ 3 times per day
  - Altered stool consistency: increased water content
  - Increase in stool quantity: more than 200–250 g per day
  - Acute diarrhea: lasting ≤ 14 days
  - Persistent diarrhea: lasting > 14 days
  - Chronic diarrhea: lasting > 30 days

1. Acute diarrhea

Table 2. Clues to the Diagnosis of Acute Diarrhea

History	*Potential pathogen/etiology*
Afebrile, abdominal pain with bloody diarrhea	Shiga toxin–producing *Escherichia coli*
Bloody stools	*Salmonella, Shigella, Campylobacter,* Shiga toxin–producing *E. coli, Clostridium difficile, Entamoeba histolytica, Yersinia*
Camping, consumption of untreated water	*Giardia*
Consumption of food commonly associated with foodborne illness	
Fried rice	*Bacillus cereus*
Raw ground beef or seed sprouts	Shiga toxin–producing *E. coli* (e.g., *E. coli* O157:H7)
Raw milk	*Salmonella, Campylobacter,* Shiga toxin–producing *E. coli, Listeria*
Seafood, especially raw or undercooked shellfish	*Vibrio cholerae, Vibrio parahaemolyticus*
Undercooked beef, pork, or poultry	*Staphylococcus aureus, Clostridium perfringens, Salmonella, Listeria* (beef, pork, poultry), Shiga toxin–producing *E. coli* (beef and pork), *B. cereus* (beef and pork), *Yersinia* (beef and pork), *Campylobacter* (poultry)
Exposure to day care centers	*Rotavirus, Cryptosporidium, Giardia, Shigella*
Fecal-oral sexual contact	*Shigella, Salmonella, Campylobacter,* protozoal disease
Hospital admission	*C. difficile,* treatment adverse effect
Human immunodeficiency virus infection, immunosuppression	*Cryptosporidium,* Microsporida, *Isospora, Cytomegalovirus, Mycobacterium avium-intracellulare* complex, *Listeria*
Medical conditions associated with diarrhea	Endocrine: Hyperthyroidism, adrenocortical insufficiency, carcinoid tumors, medullary thyroid cancer Gastrointestinal: Ulcerative colitis, Crohn disease, irritable bowel syndrome, celiac disease, lactose intolerance, ischemic colitis, colorectal cancer, short bowel syndrome, malabsorption, gastrinoma, VIPoma, bowel obstruction, constipation with overflow Other: Appendicitis, diverticulitis, human immunodeficiency virus infection, systemic infections, amyloidosis, adnexitis
Medications or other therapies associated with diarrhea	Antibiotics (especially broad-spectrum), laxatives, antacids (magnesium- or calcium-based), chemotherapy, colchicine, pelvic radiation therapy Less common: Proton pump inhibitors, mannitol, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, cholesterol-lowering medications, lithium
Persistent diarrhea with weight loss	*Giardia, Cryptosporidium, Cyclospora*
Pregnancy	*Listeria*
Recent antibiotic use	*C. difficile*
Receptive anal intercourse, with or without rectal pain or proctitis	Herpes simplex virus infection, chlamydia, gonorrhea, syphilis
Rectal pain or proctitis	*Campylobacter, Salmonella, Shigella, E. histolytica, C. difficile, Giardia*
Rice-water stools	*V. cholerae*
Several persons with common food exposure have acute onset of symptoms	Food poisoning with preformed toxins Onset of symptoms within 6 hours: *Staphylococcus, B. cereus* (typically causes vomiting) Onset of symptoms within 8 to 16 hours: *C. perfringens* type A (typically causes diarrhea)
Travel to a developing country	Enterotoxigenic *E. coli* is most common Many other pathogens (e.g., *Shigella, Salmonella, E. histolytica, Giardia, Cryptosporidium, Cyclospora,* enteric viruses) are possible because of poorly cleaned or cooked food, or fecal contamination of food or water

Information from references 1, 7, 8, 14, and 15.



**—Use the new World Health Organization reduced-osmolarity oral rehydration solution or a substitute. It can be roughly duplicated by mixing 1/2 teaspoon of salt, 6 teaspoons of sugar, and 1 liter of water.*

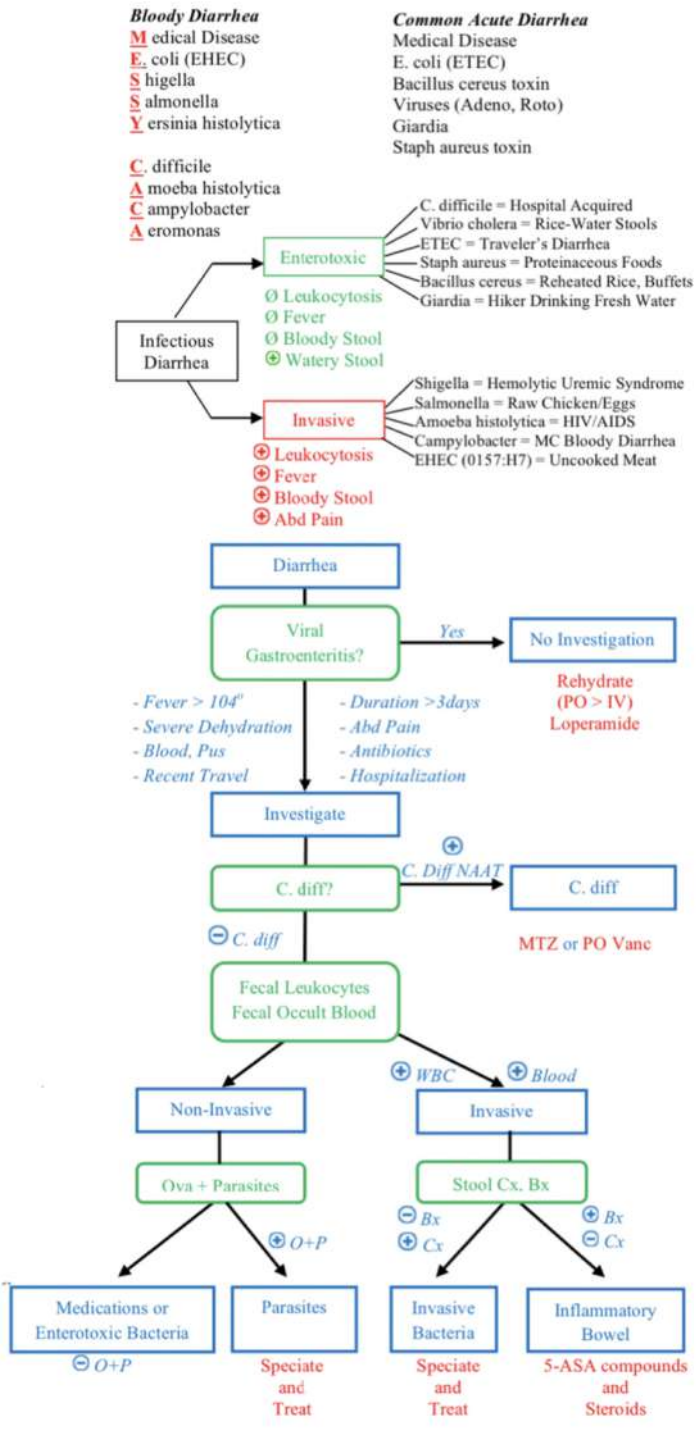
†—Dosing for loperamide/simethicone: 2 tablets (2 mg of loperamide/125 mg of simethicone per tablet) followed by 1 additional tablet after each unformed stool, up to 4 tablets in 24 hours (3 doses).

Table 4. Summary of Antibiotic Therapy for Acute Diarrhea

Organism	*Therapy effectiveness*	*Preferred medication*
Bacterial		
Campylobacter	Proven in dysentery and sepsis Possibly effective in enteritis	Azithromycin (Zithromax), 500 mg once per day for 3 to 5 days
Clostridium difficile	Proven	Metronidazole (Flagyl), 500 mg three times per day for 10 days
Enteropathogenic/ enteroinvasive *Escherichia coli*	Possible	Ciprofloxacin, 500 mg twice per day for 3 days
Enterotoxigenic *E. coli*	Proven	Ciprofloxacin, 500 mg twice per day for 3 days
Salmonella, non-Typhi species	Doubtful in enteritis Proven in severe infection, sepsis, or dysentery	—
Shiga toxin–producing *E. coli*	Controversial	No treatment
Shigella	Proven in dysentery	Ciprofloxacin, 500 mg twice per day for 3 days, or 2-g single dose
Vibrio cholerae	Proven	Doxycycline, 300-mg single dose
Yersinia	Not needed in mild disease or enteritis Proven in severe disease or bacteremia	—
Protozoal		
Cryptosporidium	Possible	Therapy may not be necessary in immunocompetent patients with mild disease or in patients with AIDS who have a CD4 cell count greater than 150 cells per mm^3
Cyclospora or *Isospora*	Proven	TMP/SMX DS, 160/800 mg twice per day for 7 to 10 days AIDS or immunosuppression: TMP/SMX DS, 160/800 mg twice to four times per day for 10 to 14 days, then three times weekly for maintenance
Entamoeba histolytica	Proven	Metronidazole, 750 mg three times per day for 5 to 10 days, plus paromomycin, 25 to 35 mg per kg per day in 3 divided doses for 5 to 10 days
Giardia	Proven	Metronidazole, 250 to 750 mg three times per day for 7 to 10 days
Microsporida	Proven	Albendazole (Albenza), 400 mg twice per day for 3 weeks

DS = double strength; TMP/SMX = trimethoprim/sulfamethoxazole.

Information from references 1, 14, 16, 44, and 45.



2. Chronic Diarrhea

Table 1. Differential Diagnosis of Chronic Diarrhea

Watery

Secretory (often nocturnal; unrelated to food intake; fecal osmotic gap < 50 mOsm per kg*)
- Alcoholism
- Bacterial enterotoxins (e.g., cholera)
- Bile acid malabsorption
- Brainerd diarrhea (epidemic secretory diarrhea)
- Congenital syndromes
- Crohn disease (early ileocolitis)
- Endocrine disorders (e.g., hyperthyroidism [increases motility])
- Medications (see Table 3)
- Microscopic colitis (lymphocytic and collagenous subtypes)
- Neuroendocrine tumors (e.g., gastrinoma, vipoma, carcinoid tumors, mastocytosis)
- Nonosmotic laxatives (e.g., senna, docusate sodium [Colace])
- Postsurgical (e.g., cholecystectomy, gastrectomy, vagotomy, intestinal resection)
- Vasculitis

Osmotic (fecal osmotic gap > 125 mOsm per kg*)
- Carbohydrate malabsorption syndromes (e.g., lactose, fructose)
- Celiac disease
- Osmotic laxatives and antacids (e.g., magnesium, phosphate, sulfate)
- Sugar alcohols (e.g., mannitol, sorbitol, xylitol)

Functional (distinguished from secretory types by hypermotility, smaller volumes, and improvement at night and with fasting)
- Irritable bowel syndrome

Fatty (bloating and steatorrhea in many, but not all cases)

Malabsorption syndrome (damage to or loss of absorptive ability)
- Amyloidosis
- Carbohydrate malabsorption (e.g., lactose intolerance)
- Celiac sprue (gluten enteropathy)–various clinical presentations
- Gastric bypass
- Lymphatic damage (e.g., congestive heart failure, some lymphomas)
- Medications (e.g., orlistat [Xenical; inhibits fat absorption], acarbose [Precose; inhibits carbohydrate absorption])
- Mesenteric ischemia
- Noninvasive small bowel parasite (e.g., *Giardia*)
- Postresection diarrhea
- Short bowel syndrome
- Small bowel bacterial overgrowth (> 10^5 bacteria per mL)
- Tropical sprue
- Whipple disease (*Tropheryma whippelii* infection)

Maldigestion (loss of digestive function)
- Hepatobiliary disorders
- Inadequate luminal bile acid
- Loss of regulated gastric emptying
- Pancreatic exocrine insufficiency

Inflammatory or exudative (elevated white blood cell count, occult or frank blood or pus)

Inflammatory bowel disease
- Crohn disease (ileal or early Crohn disease may be secretory)
- Diverticulitis
- Ulcerative colitis
- Ulcerative jejunoileitis

Invasive infectious diseases
- *Clostridium difficile* (pseudomembranous) colitis–antibiotic history
- Invasive bacterial infections (e.g., tuberculosis, yersiniosis)
- Invasive parasitic infections (e.g., *Entamoeba*)–travel history
- Ulcerating viral infections (e.g., cytomegalovirus, herpes simplex virus)

Neoplasia
- Colon carcinoma
- Lymphoma
- Villous adenocarcinoma

Radiation colitis

**—Fecal osmotic gap = 290 – 2 × (stool sodium + stool potassium). It helps differentiate secretory from osmotic diarrhea. Normal fecal osmolality is 290 mOsm per kg (290 mmol per kg). Although measurement of fecal electrolytes is no longer routine, knowing the fecal osmotic gap helps confirm whether watery stools represent chronic osmotic diarrhea (fecal osmotic gap greater than 125 mOsm per kg [125 mmol per kg]) or chronic secretory diarrhea (fecal osmotic gap less than 50 mOsm per kg [50 mmol per kg]).*[1]

Information from references 1 and 2.

Table 4. Common Causes of Chronic Diarrhea

Diagnosis	*Clinical findings*	*Tests*
Celiac disease	Chronic malabsorptive diarrhea, fatigue, iron deficiency anemia, weight loss, dermatitis herpetiformis, family history	Immunoglobulin A antiendomysium and antitissue transglutaminase antibodies most accurate; duodenal biopsy is definitive
Clostridium difficile infection	Often florid inflammatory diarrhea with weight loss Recent history of antibiotic use, evidence of colitis, fever May not resolve with discontinuation of antibiotics	Fecal leukocyte level; enzyme immunoassay that detects toxins A and B; positive fecal toxin assay; sigmoidoscopy demonstrating pseudomembranes
Drug-induced diarrhea	Osmotic (e.g., magnesium, phosphates, sulfates, sorbitol), hypermotility (stimulant laxatives), or malabsorption (e.g., acarbose [Precose], orlistat [Xenical])	Elimination of offending agent; always consider laxative abuse
Endocrine diarrhea	Secretory diarrhea or increased motility (hyperthyroidism)	Thyroid-stimulating hormone level, serum peptide concentrations, urinary histamine level
Giardiasis	Excess gas, steatorrhea (malabsorption)	*Giardia* fecal antigen test
Infectious enteritis or colitis (diarrhea not associated with *C. difficile*): bacterial gastroenteritis, viral gastroenteritis, amebic dysentery	Inflammatory diarrhea, nausea, vomiting, fever, abdominal pain History of travel, camping, infectious contacts, or day care attendance	Fecal leukocyte level, elevated erythrocyte sedimentation rate Cultures or stained fecal smears for specific organisms are more definitive
Inflammatory bowel disease: Crohn disease, ulcerative colitis	Bloody inflammatory diarrhea, abdominal pain, nausea, vomiting, loss of appetite, family history, eye findings (e.g., episcleritis), perianal fistulae, fever, tenesmus, rectal bleeding, weight loss	Complete blood count, fecal leukocyte level, erythrocyte sedimentation rate, fecal calprotectin level Characteristic intestinal ulcerations on colonoscopy
Irritable bowel syndrome	Stool mucus, crampy abdominal pain, altered bowel habits, watery functional diarrhea after meals, exacerbated by emotional stress or eating More common in women	All laboratory test results are normal Increased fiber intake, exercise, dietary modification should be recommended
Ischemic colitis	History of vascular disease; pain associated with eating	Colonoscopy, abdominal arteriography
Microscopic colitis	Watery, secretory diarrhea affecting older persons Nonsteroidal anti-inflammatory drug association possible No response to fasting; nocturnal symptoms	Colon biopsy

Diagnosis

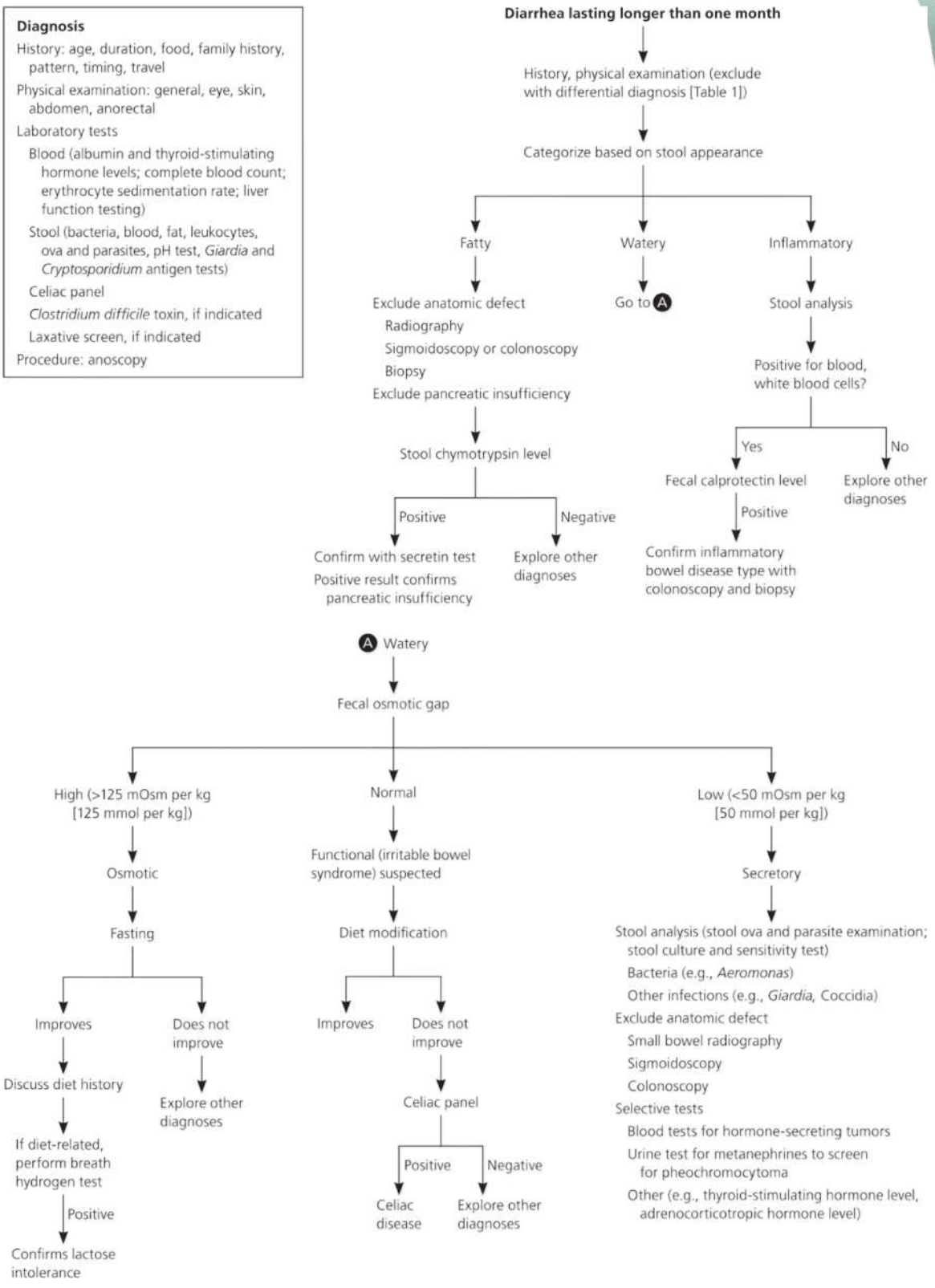
History: age, duration, food, family history, pattern, timing, travel

Physical examination: general, eye, skin, abdomen, anorectal

Laboratory tests

- Blood (albumin and thyroid-stimulating hormone levels; complete blood count; erythrocyte sedimentation rate; liver function testing)
- Stool (bacteria, blood, fat, leukocytes, ova and parasites, pH test, *Giardia* and *Cryptosporidium* antigen tests)
- Celiac panel
- *Clostridium difficile* toxin, if indicated
- Laxative screen, if indicated

Procedure: anoscopy



To list the medical therapy used for C. Difficile

- **General principles**
  - Antibiotic treatment is indicated in all symptomatic patients with CDI and should be guided by the severity of CDI.
  - Asymptomatic carriers do not require antibiotic therapy.
  - Fecal microbiota transplantation may be indicated in recurrent CDI, severe CDI, or fulminant CDI refractory to antibiotic therapy.
  - Surgical intervention may be necessary for critically ill patients or those with complications necessitating surgery.
- **Supportive measures**
  - Discontinue any precipitating antibiotic as soon as possible.
  - Correct fluid and electrolyte imbalances
  - Avoid antidiarrheals (e.g., loperamide) in patients not yet receiving antibiotics and those with fulminant CDI.

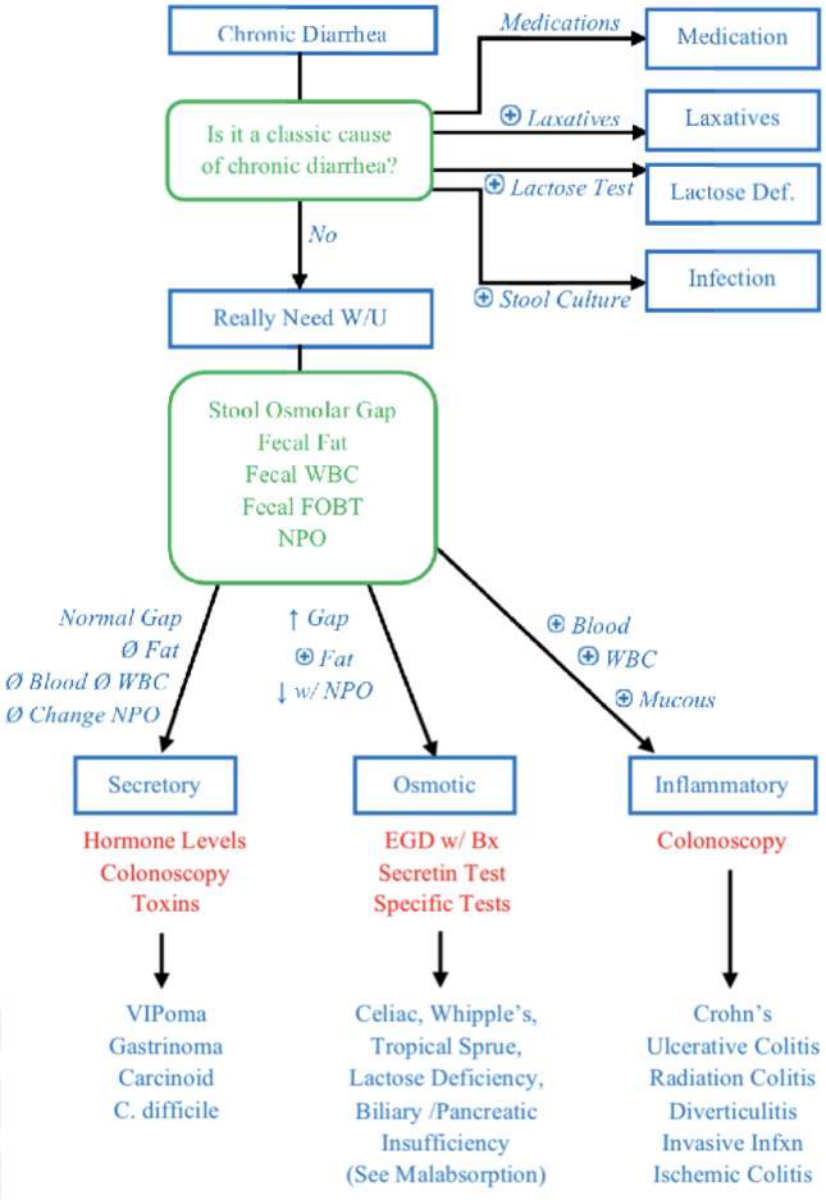
Antibiotic therapy for C. difficile infection in adults [1][2][3]

Category		Treatment options
Initial episode	Nonsevere CDI or severe CDI	• First-line ◦ Oral **fidaxomicin** [3] ◦ OR oral vancomycin • Second-line for **nonsevere** cases (if vancomycin and fidaxomicin are unavailable or inappropriate, e.g., in patients with allergies): oral metronidazole [2]
	Fulminant CDI	• First-line: high-dose oral vancomycin [2] • Consider adding IV metronidazole [2] • In patients with paralytic ileus, consider adding vancomycin enemas.
Recurrent CDI	First recurrence	• If the initial episode was treated with standard-dose vancomycin: ◦ Oral fidaxomicin [3] ◦ OR tapered and pulsed oral vancomycin • If the initial episode was treated with metronidazole: [2] ◦ Oral fidaxomicin ◦ OR standard-dose oral vancomycin
	Subsequent recurrences	• Any of the following: ◦ Oral fidaxomicin ◦ Standard-dose oral vancomycin followed by oral rifaximin ◦ Tapered and pulsed oral vancomycin

- **Fecal microbiota transplantation**
  - Healthy donor stool that is administered via capsules, colonoscopy, or enema
  - Can be considered in the following situations
    - Severe CDI or fulminant CDI with insufficient clinical improvement after 48–72 hours of maximum medical therapy.
    - Adult and pediatric patients with ≥ 2 recurrences despite appropriate antibiotic therapy for CDI
- **Surgical management**
  - Indications: critically ill patients with severe CDI or fulminant CDI refractory to antibiotic therapy, especially if ≥ 1 of the following are present
    - Factors associated with increased mortality, e.g., severe leukocytosis or serum lactate
    - Complications, e.g., toxic megacolon, ischemia, or bowel perforation

Secretory	*Osmotic*	*Inflammatory*
Secretagogues: VIP, Gastrin, Toxins	Ø Absorption = Fat, Protein, Osmolar Load,	
Nrml Osmotic Gap	**↑ Osmotic Gap**	⊕ **Blood**
Ø Blood Ø Mucous	Ø Blood Ø Mucous	⊕ **Mucous**
⊕ Nocturnal Sxs	Ø Nocturnal Sxs	
Ø Change with NPO	⊕ Change with NPO	
Normal Fecal Fat	↑ Fecal Fat	

Measure Stool Osmoles (reported value)	Calculated Stool Osmoles (Stool Na + Stool K) *2	= Osmotic Gap
280	110	= 170, Osmotic
280	278	– 2, Secretory



Infectious Disorders

Infectious disorders

1	**Hosp-acquired infection and approach to infectious control and antibiotic use/abuse** - Recognize the epidemiology, clinical presentation and morbidity of Hospital acquired infections - Understand features/mechanism involved in developing antibiotics resistance - Appreciate the challenges in the management of Hospital acquired infections - Discuss the antimicrobial treatments for hospital acquired infections - Define the necessary infection control guidelines.
2	**Meningitis** - Identify symptoms and signs suggestive of meningitis and encephalitis. - Identify common pathogens causing meningitis and encephalitis - To be able to approach a patient with meningitis and start the work-up with management. - Understand and interpret CSF analysis.
3	**HIV/AIDs** - Understand the pathophysiology of HIV. - Identify patients likely to have the acute retroviral syndrome and knows when to initiate the screen. - To be able to interpret the test results of HIV. - Recall the complications of AIDS and infections correlated with CD4 count level.
4	**Common Protozoal infections (including Malaria, Leishmaniasis, Amebiasis)** - Understand the pathophysiology and clinical presentation of malaria and outline management plans - Identify endemic areas of malaria and when/how to initiate the prophylaxis. - Recognize the malaria parasite in the peripheral blood smear. - Understand the pathophysiology and clinical presentation of Leishmaniasis - Understand the pathophysiology and clinical presentation of Amebiasis and outline management plans.
5	**Systemic bacterial infection (including Sepsis syndrome, Brucella, Osteomyelitis and Typhoid)** - Understand definition, pathophysiology and clinical presentation of sepsis - To be able to urgently recognize sepsis syndrome clinically and initiate work-up and treatment - Recognize clinical signs and symptoms of common systemic bacterial infection and Initiate investigation for it. - Identify key points in the treatment of Systemic bacterial infection.
6	**Urinary tract infection (UTIs) and sexual transmitted diseases (STDs)** - To be able to differentiate between asymmetric bacteria, simple and complicated urinary tract infections - Recite common organisms causes of urinary tract infection and sexual transmitted disease - Identify patients with pyelonephritis based on history and examination. - Recall the key points in the management of UTIs and STDs.
7	**Emerging infections and Bioterrorism** - Understand the pathophysiology, clinical presentation and complication of MERS-CoV and outline the essential key points in the management. - Understand the pathophysiology, clinical presentation and complication of SARS-COV 2 and outline the essential key points in the management. - Recite organisms with the potential for use in bioterrorism. - Identify features (clinical, situation, population) that may suggest a possible act of bioterrorism.

Hosp-acquired infection & approach to infectious control and antibiotic use/abuse

- Recognize the epidemiology, clinical presentation and morbidity of Hospital acquired infections

Hospital-acquired infections (HAI) affect 5–15% of all hospitalized patients and 40% of patients in ICU. The World Health Organization (WHO) estimates that the mortality from health-care-associated infections ranges from 12–80%.
HAI can occur in many forms, the most common of which in hospitalized patients is UTI.

urinary catheter-related infection (UTI):

- UTI accounts for 40% of all HAI; >80% of these infections are attributable to use of an indwelling urethral catheter.
- Adhering to strict indications for using indwelling catheters, maintaining sterile technique during catheter insertion and exercising prompt removal of the catheter when it is no longer required can help reduce the risk of a urinary catheter-related infection.

Central line associated bloodstream infection (CLABSI)

- is another common HAI, and among one of the most common infections observed in patients admitted to critical care units. It is estimated that 70% of hospital-acquired bloodstream infections occur in patients with central venous catheters.
- Symptoms include fever, chills, erythema at the skin surrounding the central line site and, in severe cases, hypotension secondary to sepsis.
- These infections can be associated with significant morbidity and mortality, increased length of hospital stay, and increased hospital cost.
- Checklists have been developed which provide best practices for the placement of central lines that lower the risk of infection (e.g., hand washing, gloving and gowning, sterile barriers, and early removal of central lines when possible).

Hospital-acquired pneumonia (HAP)

- is an infection that occurs more often in ventilated patients, typically ≥48 hours after admission to a hospital.
- These ventilator-associated pneumonias (VAP), a subtype of HAP, tend to be more serious because patients are often sicker and less able to mount effective immune responses.
- HAP is the second most common nosocomial infection.

- Common symptoms include coughing, fever, chills, fatigue, malaise, headache, loss of appetite, N/V, SOB, and sharp or stabbing chest pain that gets worse with deep breathing or coughing.
- Several methods have been undertaken to prevent HAP, including infection control (e.g., hand hygiene and proper use of gloves, gown, and mask), elevation of the head of the bed in ventilated patients, and other measures to reduce the risk of aspiration.

Surgical site infections (SSI)

- occur following a surgical procedure in the part of the body where the surgery took place.
- Some SSIs are superficial and limited to the skin, while others are more serious and involve deep tissue under the skin, body cavities, internal organs, or implanted material (e.g., knee or hip replacements).
- Symptoms include fever, drainage of cloudy fluid from the surgical incision or erythema, and tenderness at the surgical site.
- Most superficial SSIs (e.g., cellulitis) can be treated with appropriate antibiotics, whereas deeper infections (i.e., abscess) require drainage.
- Preoperative antibiotics have been effective in reducing the rate of SSIs.

• Understand features/mechanism involved in developing antibiotics resistance

Antibiotics act at different sites of the bacterium, either inhibiting essential steps in metabolism or assembly, or destroying vital components such as the cell wall.
Resistance to an antibiotic can be the result of:

1. **impaired or altered permeability of the bacterial cell envelope,**
    a. e.g. penicillins in Gram-negative bacteria
2. **active expulsion from the cell by membrane efflux systems alteration of the target site**
    a. (e.g. single point mutations inE. coli or a penicillin-binding protein in Strep. pneumoniae, leading to acquired resistance))
3. **over-production of the target site specific enzymes that inactivate the drug before or after cell entry**
    a. (e.g. ~-lactamases)
4. **development of a novel metabolic bypass pathway.**
    a. The development or acquisition of resistance to an antibiotic by bacteria involves either a mutation at a single point in a gene or transfer of genetic material from another organism (Fig. 11.4 next slide).
    b. Larger fragments of DNA may be introduced into a bacterium either by transfer of 'naked' DNA or via a bacteriophage (a virus) DNA vector.
    c. Both the former (transformation) and the latter (transduction) are dependent on integration of this new DNA into the recipient chromosomal DNA. This requires a high degree of homology between the donor and recipient chromosomal DNA.

5. **Finally, antibiotic resistance can be transferred from one bacterium to another by conjugation,**
    a. when extrachromosomal DNA (a plasmid) containing the resistance factor (R factor) is passed from one cell into another during direct contact. Transfer of such R factor plasmids can occur between unrelated bacterial strains and involve large amounts of DNA and often codes for multiple antibiotic resistance: for example, as for the fluoroquinolones.
    b. Transformation is probably the least clinically relevant mechanism, whereas transduction and R factor transfer are usually responsible for the sudden emergence of multiple antibiotic resistances in a single bacterium. Increasing resistance to many antibiotics has developed

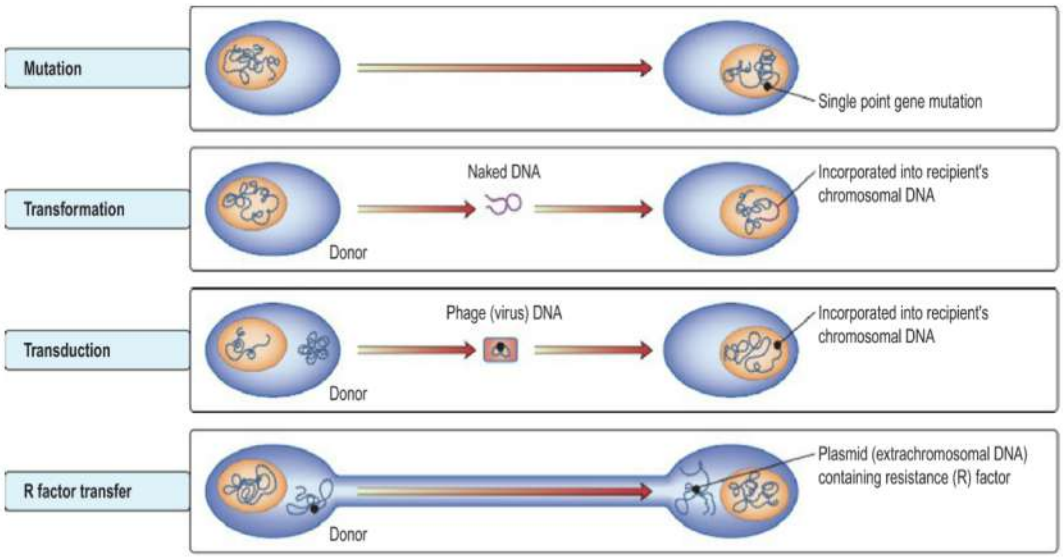


Figure 11.4 **Some mechanisms for the development of resistance to antimicrobial drugs.** These involve either a single point mutation or transfer of genetic material from another organism (transformation, transduction or R factor transfer).

- Appreciate the challenges in the management of Hospital acquired infections

Challenges in Management

- Increased number of severely ill patients and Increased numbers of immunocompromised patients
- Lack of rapid diagnostics for MDR pathogens extends the length of time that patients receive suboptimal antibiotic therapy
- Growing frequency of antimicrobial-resistant pathogens

Challenges in Prevention

- Lack of compliance with hand hygiene and other infection preventive measures (e.g., endoscope)
- Limited infection prevention resources

- Discuss the antimicrobial treatments for hospital acquired infections

Treatment of multiresistant pathogens [7]

Pathogen	Resistance		First-line therapy	Alternative therapy
Gram-positive				
MRSA	• All beta-lactam antibiotics (penicillins, cephalosporins, and carbapenems) • Potential resistance to: ◦ Aminoglycosides ◦ Macrolides ◦ Lincosamides ◦ Quinolones		• **Vancomycin**	• Linezolid • Daptomycin • Tigecycline • Ceftaroline • Doxycycline • Quinupristin/dalfopristin
Vancomycin-resistant enterococci (VRE)	• Vancomycin (possibly also teicoplanin) • Potential resistance to: ◦ Macrolides ◦ Most penicillins ◦ Quinolones ◦ Aminoglycosides ◦ Tetracyclines		• **Linezolid**	• Quinupristin/dalfopristin • Tigecycline • Daptomycin
Gram-negative				
ESBL pathogens (extended-spectrum β-lactamase)	• Penicillins • Cephalosporins	• MDRGNB [8] ◦ Fluoroquinolones ◦ Carbapenems ◦ Third and fourth generation cephalosporins ◦ Broad-spectrum penicillins	• MDRGNB: **carbapenems**	• In case of resistance to all four groups, consider last resort antibiotics: ◦ Colistin ◦ Linezolid ◦ Tigecycline
Pseudomonas aeruginosa	• Most penicillins • First, second, and third generation cephalosporins • Macrolides		• MDRGNB ◦ **Piperacillin** PLUS **tazobactam** ◦ Certain third generation cephalosporins (e.g., ceftazidime) ◦ Carbapenems ◦ All options can potentially be combined with an aminoglycoside.	• In case of resistance all four groups, give last resort antibiotics according to antibiogram: ◦ Colistin ◦ Polymyxin B

- Define the necessary infection control guidelines.

KEY ELEMENTS AT A GLANCE

1. Hand hygiene[1]

Summary technique:

- Hand washing (40–60 sec): wet hands and apply soap; rub all surfaces; rinse hands and dry thoroughly with a single use towel; use towel to turn off faucet.
- Hand rubbing (20–30 sec): apply enough product to cover all areas of the hands; rub hands until dry.

Summary indications:

- Before and after any direct patient contact and between patients, whether or not gloves are worn.
- Immediately after gloves are removed.
- Before handling an invasive device.
- After touching blood, body fluids, secretions, excretions, non-intact skin, and contaminated items, even if gloves are worn.
- During patient care, when moving from a contaminated to a clean body site of the patient.
- After contact with inanimate objects in the immediate vicinity of the patient.

2. Gloves

- Wear when touching blood, body fluids, secretions, excretions, mucous membranes, nonintact skin.
- Change between tasks and procedures on the same patient after contact with potentially infectious material.
- Remove after use, before touching non-contaminated items and surfaces, and before going to another patient. Perform hand hygiene immediately after removal.

3. Facial protection (eyes, nose, and mouth)

- Wear a surgical or procedure mask and eye protection (face shield, goggles) to protect mucous membranes of the eyes, nose, and mouth during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions.

4. Gown

- Wear to protect skin and prevent soiling of clothing during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.
- Remove soiled gown as soon as possible, and perform hand hygiene.

5. Prevention of needle stick injuries[2]

Use care when:

- handling needles, scalpels, and other sharp instruments or devices
- cleaning used instruments
- disposing of used needles.

6. Respiratory hygiene and cough etiquette

Persons with respiratory symptoms should apply source control measures:

- cover their nose and mouth when coughing/sneezing with tissue or mask, dispose of used tissues and masks, and perform hand hygiene after contact with respiratory secretions.

Health care facilities should:

- place acute febrile respiratory symptomatic patients at least 1 metre (3 feet) away from others in common waiting areas, if possible.
- post visual alerts at the entrance to health-care facilities instructing persons with respiratory symptoms to practise respiratory hygiene/cough etiquette.
- consider making hand hygiene resources, tissues and masks available in common areas and areas used for the evaluation of patients with respiratory illnesses.

7. Environmental cleaning

- Use adequate procedures for the routine cleaning and disinfection of environmental and other frequently touched surfaces.

8. Linens

Handle, transport, and process used linen in a manner which:

- prevents skin and mucous membrane exposures and contamination of clothing.
- avoids transfer of pathogens to other patients and or the environment.

9. Waste disposal

- Ensure safe waste management.
- Treat waste contaminated with blood, body fluids, secretions and excretions as clinical waste, in accordance with local regulations.
- Human tissues and laboratory waste that is directly associated with specimen processing should also be treated as clinical waste.
- Discard single use items properly.

10. Patient care equipment

- Handle equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of pathogens to other patients or the environment.
- Clean, disinfect, and reprocess reusable equipment appropriately before use with another patient.

[1] For more details, see: WHO Guidelines on Hand Hygiene in Health Care (Advanced draft), at: http://www.who.int/patientsafety/information_centre/ghhad_download/en/index.html.

Standard Precautions for All Patient Care

Standard Precautions are used for all patient care. They're based on a risk assessment and make use of common sense practices and personal protective equipment use that protect healthcare providers from infection and prevent the spread of infection from patient to patient.

More info
https://www.cdc.gov/infectioncontrol/basics/standard-precautions.html

Meningitis

- Identify symptoms and signs suggestive of meningitis and encephalitis.

1. Meningitis

- Classic triad of meningitis: fever, headache, and neck stiffness
- Altered mental status
- Photophobia
- Nausea, vomiting
- Malaise
- Seizures
- Possibly cranial nerve palsies

In the case of N. meningitidis

- Myalgia and, possibly, petechial or purpuric rash (especially in children)
- Possibly Waterhouse-Friderichsen syndrome

Common symptoms of viral meningitis :

- Prodrome with flu-like symptoms
- Low-grade fever
- Malaise, fatigue
- Myalgia
- Upper respiratory symptoms (e.g., sore throat)
- Pharyngitis, herpangina, and/or rash

Subarachnoid hemorrhage can manifest with the classic triad of meningitis but has a more sudden onset and patients often lose consciousness.

2. Encephalitis

- Patients often have a prodrome of headache, malaise, and myalgias.
- Within hours to days, patients become more acutely ill.
- Patients frequently have signs and symptoms of meningitis (e.g., headache, fever,photophobia, nuchal rigidity).
- In addition, patients have altered sensorium, possibly including confusion, delirium, disorientation, and behavior abnormalities.
- Focal neurologic findings (e.g., hemiparesis, aphasia, cranial nerve lesions) and seizures may also be present.

- Identify common pathogens causing meningitis and encephalitis

1. Meningitis

- Neonates—Group B streptococci, E. coli, Listeria monocytogenes.
- Children >3 months—Neisseria meningitidis, S. pneumoniae, H. influenzae.
- Adults (ages 18 to 50)—S. pneumoniae, N. meningitidis, H. influenzae.
- Elderly (>50)—S. pneumoniae, N. meningitidis, L. monocytogenes.
- Immunocompromised—L. monocytogenes, gram-negative bacilli, S. pneumonia.

2. Encephalitis

It is usually viral in origin. Nonviral causes, however, must also be considered

a. Viral causes

- Herpes (HSV-1) infection
- Arbovirus—for example, Eastern equine encephalitis, West Nile virus
- Enterovirus—for example, polio
- Less common causes—for example, measles, mumps, EBV, CMV, VZV, rabies, and prion diseases such as Creutzfeldt–Jakob disease

b. Nonviral infectious causes

- Toxoplasmosis
- Cerebral aspergillosis

c. Noninfectious causes

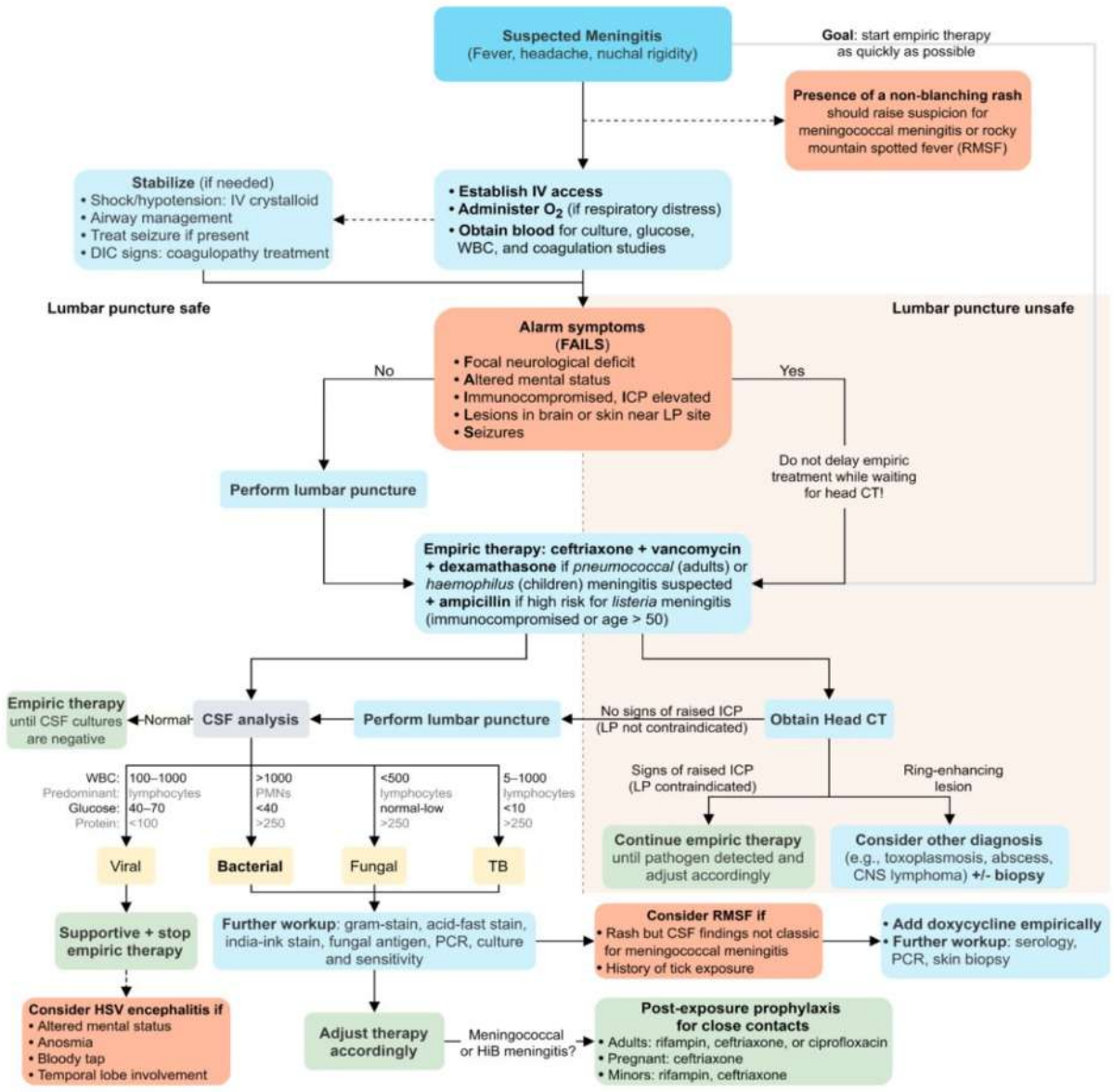
- Metabolic encephalopathies
- T-cell lymphoma

- To be able to approach a patient with meningitis and start the work-up with management

Approach

- Obtain samples immediately for blood cultures, routine laboratory tests, and screening for organ dysfunction
- Confirm the diagnosis with LP and CSF analysis (if no LP contraindications are present).

Start empiric antibiotics immediately after obtaining blood cultures and CSF samples. If LP is delayed for any reason (e.g., the need for a CT or hemodynamic stabilization), obtain blood cultures and administer antibiotics until it can be performed.



❖ Laboratory studies

Routine tests:

- Blood cultures (two sets): obtain before starting antibiotic therapy
- CBC
  - Normal/↑ WBC count
  - In severe infections, ↓ WBC count and thrombocytopenia
- BMP: Blood glucose is needed to analyze CSF glucose.
  - Common finding: mild electrolyte disturbances (e.g., hyponatremia from SIADH)
  - In critically ill patients: possible signs of acute kidney injury
- CRP: elevated

Additional tests

Assess for organ damage and complications.

- Coagulation panel: especially if there is suspicion for disseminated intravascular coagulation (e.g., petechiae, purpura)
- Blood gas: metabolic acidosis may be present in critically ill patients

Consider testing for atypical infections

Neuroimaging

Imaging is not necessary to establish the diagnosis of meningitis in most patients and should only be considered in patients with significant risk factors for complications.

Indications

- To assess the risk of brain herniation precipitated by LP
- Identify abscesses or other localized lesions (e.g., in postsurgical patients in whom infection is suspected)
- Suspected healthcare-associated ventriculitis/meningitis
- Patients with devices (e.g., CSF shunts)

Recommended criteria for imaging prior to LP in suspected meningitis;

- Focal neurological deficits
- Altered mental status
- Immunocompromised status (e.g., HIV, post-transplant, taking immunosuppressants)
- Papilledema
- History of CNS disease (e.g., mass, stroke, abscess)
- Seizures (new-onset)

Modalities

- CT head (with or without IV contrast): before LP if increased ICP is suspected
- MRI brain with IV contrast and diffusion: especially useful in patients with devices or after surgery

Supportive findings

- Usually normal or showing mild meningeal enhancement
- May identify predisposing factors for the infection (e.g., fractures, mastoiditis) or complications (e.g., abscess)

To remember the indications for imaging before LP, think of LP FAILS: Focal neurological deficits, Altered mental status, Immunocompromised or ↑ ICP, Lesions (space-occupying lesions in the brain), Seizures.

❖ **Management**

- Bacterial meningitis.

a. Empiric antibiotic therapy—Start immediately after LP is performed. If a CT scan must be performed or if there are anticipated delays in LP, give antibiotics first. Pathogen can often still be identified from CSF several hours after administration of antibiotics.

b. Intravenous (IV) antibiotics.

• Initiate immediately if the CSF is cloudy or if bacterial infection is suspected.

• Begin empiric therapy according to the patient's age

• Modify treatment as appropriate based on Gram stain, culture, and sensitivity findings.

c. Steroids—if cerebral edema is present.

d. Vaccination

• Vaccinate all adults >65 years for S. pneumoniae.

• Vaccinate asplenic patients for S. pneumoniae, N. meningitidis, and H. influenzae (organisms with capsules).

• Vaccinate immunocompromised patients for meningococcus.

e. Prophylaxis (e.g., rifampin or ceftriaxone)—For all close contacts of patients with meningococcus, give 1 dose of IM ceftriaxone.

2. Aseptic meningitis.

a. No specific therapy other than supportive care is required. The disease is self-limited.

b. Analgesics and fever reduction may be appropriate.

TABLE 10-3 Empiric Treatment for Acute Bacterial Meningitis

Age or Risk Factor	Likely Etiology	Empiric Treatment
Infants (<3 mo)	Group B streptococci, *E. coli*, *Klebsiella* spp., *L. monocytogenes*	Cefotaxime + ampicillin + vancomycin (aminoglycoside if <4 weeks)
3 mo to 50 yrs	*N. meningitidis*, *S. pneumoniae*, *H. influenzae*	Ceftriaxone or cefotaxime + vancomycin
>50 yrs	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*	Ceftriaxone or cefotaxime + vancomycin + ampicillin
Impaired cellular immunity (e.g., HIV)	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic gram-negative bacilli (including *P. aeruginosa*)	Ceftazidime + ampicillin + vancomycin

- Understand and interpret CSF analysis.

Cerebrospinal fluid analysis in meningitis [38][40]

	Normal	Bacterial meningitis	Viral meningitis
Appearance	• Clear fluid	• Cloudy, purulent fluid	• Clear fluid
Cell count and differential	• Cell count < 5/mm^3	• Elevated cell count with significant pleocytosis (leukocyte count > 1000/mm^3) • ↑ Granulocytes (> 80%)	• Variable cell count (leukocyte count 10–500/mm^3) • ↑ Lymphocytes
Opening pressure [42]	• 5–18 cm H_2O	• ↑↑	• Normal or ↑
Lactate [39]	• 1.2–2.1 mmol/L	• ↑↑	• Variable
Protein	• 15–45 mg/dL	• ↑	• Normal or ↑
Glucose	• 40–75 mg/dL	• ↓	• Normal
Gram stain and culture [39][40]	• No organisms present	• Positive gram stain and culture [39][40] ◦ Meningococci: gram-negative diplococci ◦ Pneumococci: gram-positive diplococci ◦ Listeria: gram-positive rods [39][40] ◦ Haemophilus influenzae: gram-negative coccobacilli	• No organisms present

HIV/AIDS

- Understand the pathophysiology of HIV.

Pathophysiology

- The most common virus associated with HIV is the HIV type 1 human retrovirus
- The virus attaches to the surface of CD4+ T lymphocytes (targets of HIV-1); it enters the cell and uncoats, and its RNA is transcribed to DNA by reverse transcriptase
- Billions of viral particles are produced each day by activated CD4 cells. When the virus enters the lytic stage of infection, CD4 cells are destroyed. It is the depletion of the body's arsenal of CD4 cells that weakens the cellular immunity of the host

- Identify patients likely to have the acute retroviral syndrome and knows when to initiate the screen.

High-risk individuals:

- homosexual or bisexual men
- IV drug abusers
- blood transfusion recipients before 1985 (before widespread screening of donor blood)
- heterosexual contacts of HIV-positive individuals,
- unborn and newborn babies of mothers who are HIV positive

Routine screening

For patients without risk factors for HIV infection, we recommend at least one-time HIV screening in adults and adolescents 13 to 75 years of age. In addition, pregnant women should be tested for HIV early in each pregnancy even if they have been screened during previous pregnancies.

Although one-time testing at a routine medical clinic visit is reasonable for most patients, annual or more frequent testing is recommended for high-risk persons including:

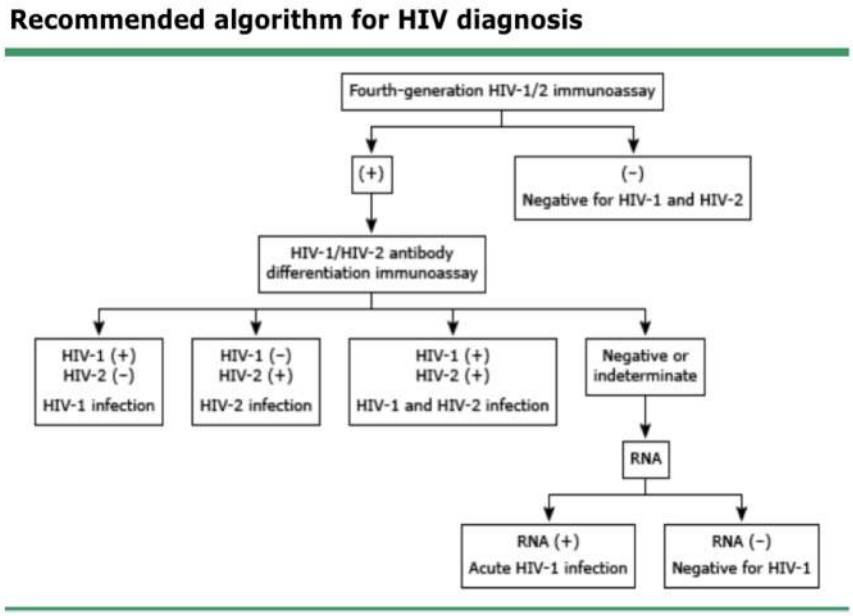
- Men who have sex with men (MSM) with sexual partners who are HIV-infected or have unknown serostatus. .
- Injection-drug users.
- Persons who exchange sex for money or drugs.
- Sex partners of persons who are HIV-infected, bisexual, or inject drugs.
- Persons who have sex with partners whose HIV status is unknown.

- To be able to interpret the test results of HIV.

Interpretation of results

The results of serologic testing algorithms are reported as positive, negative, or indeterminate:

- The criteria for a positive test are a positive combination assay or ELISA followed by a positive confirmatory assay.
- A negative test is a negative screening combination assay or ELISA.
- An indeterminate result is when the combination assay or ELISA is positive but the confirmatory test is indeterminate or negative.



- Recall the complications of AIDS and infections correlated with CD4 count level.

CD4 Count	*Infection*	*Treatment*
>500	Normal person with normal infections	Normal
200-500	Oral Leukoplakia	
	Pulmonary TB (>5mm)	INH (Latent), R.I.P.E (Active)
	Pneumococcal PNA	3rd Gen Ceph + Macrolide
	Thrush	Nystatin S+S
<200	PCP Pneumonia	Bactrim, Dapsone
	Crypto Meningitis	Amphotericin + Flucytosine
	Esophageal Candidiasis	Fluconazole
<100	HSV/CMV Esophagitis	Acyclovir/Ganciclovir
	Toxoplasmosis	Pyrimethamine Sulfadoxine
<50	Disseminated MAC	Clarithromycin + Ethambutol
	CMV Retinitis	Valaciclovir, Foscarnet

Common protozoal infection

- Understand the pathophysiology and clinical presentation of malaria and outline management plans.

❖ Pathophysiology

Asexual development in humans

1- Transmission of Plasmodium sporozoites via Anopheles mosquito bite → sporozoites travel through the bloodstream to the liver of the host

2-Liver: sporozoites enter hepatocytes → sporozoites multiply asexually → schizonts are formed containing thousands of merozoites → release of merozoites into the bloodstream

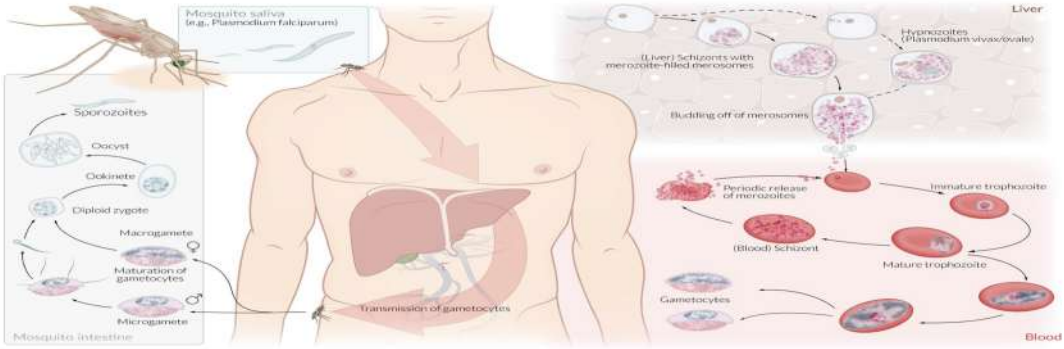
3-Circulatory system (two possible outcomes)

Merozoites enter erythrocytes → maturation to trophozoites → red cell schizonts are formed containing thousands of merozoites → release of merozoites into the bloodstream (which causes fever and other manifestations of malaria) → penetration of erythrocytes recurs

Merozoites enter erythrocytes → differentiation into gametocytes (male or female)

Sexual development in female Anopheles mosquito

A mosquito bites an infected human and ingests gametocytes → gametocytes mature within the mosquito intestines → sporozoites are formed and these migrate to the salivary glands → transmission of sporozoites to humans via mosquito bite



❖ Clinical feature

1. Symptoms may include fever and chills, myalgias, headache, nausea, vomiting, and diarrhea.

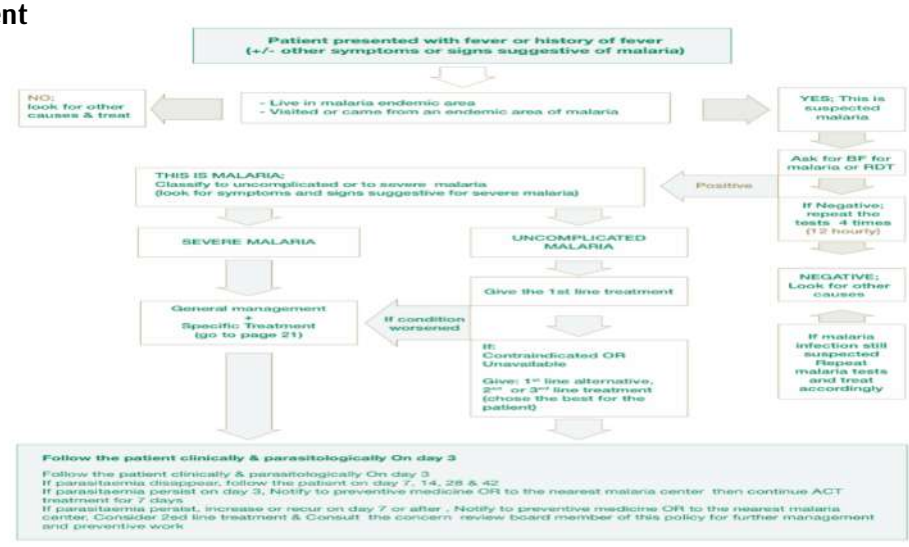
2. Fever pattern varies depending on cause
    a. P. falciparum—fever is usually constant
    b. P. ovale and P. vivax—fever usually spikes every 48 hours
    c. P. malariae—fever usually spikes every 72 hours

❖ Diagnosis

1. Identify organism on peripheral blood smear

2. Blood smear must have Giemsa stain

❖ Treatment



First line treatment of uncomplicated malaria: (ARTESUNATE + SP); alternative (ARTESUNATE + MEFLOQUINE)
Second Line Treatment of uncomplicated malaria:: (ARTEMETHER + LUMEFANTRINE)
Third Line Treatment of uncomplicated malaria: (oral QUININE + DOXYCYCLINE)

World Health Organization

وزارة الصحة
Ministry of Health

Kingdom of Saudi Arabia
Ministry of Health
Public Health Agency
Infectious Diseases Control General Directorate
Malaria Department

The national policy of malaria case management in The Kingdom of Saudi Arabia

1. Treatment of simple uncomplicated falciparum malaria:

1.1 First-line Treatment: *Artesunate (AS) + Sulfadoxine – Pyrimethamine* **(SP)**

Age in years	Weigh in Kgs	Day 1		Day 2	Day 3
		SP (500 S+25 P mg tab)	AS (50mg tab)	AS (50mg tab)	AS (50mg tab)
5 - 11 Months	5 - 10 Kgs	½	½	½	½
1 - 6 years	11 - 24 Kgs	1	1	1	1
7 - 13 years	25 - 50 Kgs	2	2	2	2
> 13 years	> 50 Kgs	3	4	4	4

❖ A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

1.2 Second-line Treatment: *Artemether* **20mg +** *Lumefantrine* **120mg**

Age in years	Weigh in Kgs	Day1		Day2		Day3	
		AM	PM	AM	PM	AM	PM
< 5		Not recommended					
<3 years	5 - 14	1	1	1	1	1	1
3 - 8 years	15 - 24	2	2	2	2	2	2
9 - 14 years	25 -34	3	3	3	3	3	3
>14 years	> 34	4	4	4	4	4	4

❖ A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

2. Treatment of malaria caused by P. vivax, or P. ovale and malariae:

Chloroquine 25mg base / kg divided over three (3) days, *(Chloroquine 4 tablets day 1, 4 tablets day 2, 2 tablets day 3)* combined with *Primaquine* 0.25 mg / kg bw taken daily with food for 14 days *for vivax and ovale , (Primaquine 15 mg tabs daily for 14 days for adult)*

3.Treatment of severe malaria:

Treatment		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		Time 0	12 hrs						
First option	Artesunate I.V / I.M.	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg
Second option	Artemether I.M	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg
Third option	Quinine I.V	20mg/kg in 5% Glucose(loading dose)		After 8hrs of loading dose start the maintenance dose as, 10mg/kg /8 hourly till the patient can take by mouth then shift to the oral.					

4. Treatment of malaria in pregnancy: **N.B.** Malaria in pregnancy should be considered severe and treated in hospital

Pregnancy in weeks	Uncomplicated malaria	Severe malaria
0-12 (1st trimester)	Quinine + Clindamycine	Quinine + Clindamycine
13- delivery (2nd &3rd trimester)	* First option: (AS + SP) * Second option: Quinine + Clindamycine	Artesunate Or Quinine + Clindamycine
Puerperium	AS + SP	Artesunate Or Quinine + Clindamycine

For any queries, Please call: 0112917743 or 0114738275

- **The onset of illness in malaria usually occurs weeks to months after infection, but it is dependent on the specific cause.**
- **P. falciparum infection is by far the most serious and life-threatening cause of malaria.**
- **Side effects of medications can be a factor in choosing appropriate malaria prophylaxis:**

• Atovaquone–proguanil is contraindicated in patients with renal disease and pregnancy.
• Mefloquine Is Contraindicated in patients with seizures and psychiatric conditions.
• Chloroquine is well tolerated and can be used in pregnancy.
Primaquine is contraindicated in patients with G6PD deficiency due to precipitation of hemolytic anemia.

- Identify endemic areas of malaria and when/how to initiate the prophylaxis.

5 of 72

).7 Chemoprophylaxis for the travelers to malaria endemic destinations, Table (6)

9.7.1 Mefloquine 250 mg once weekly is recommended for travelers to countries or regions with P. falciparum Chloroquine resistance.

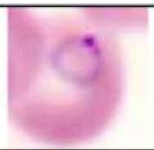
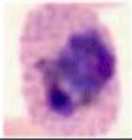
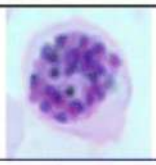
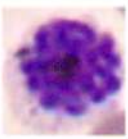
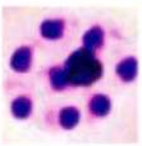
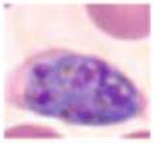
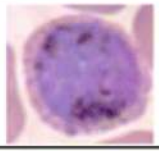
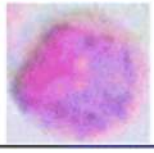
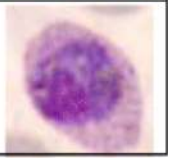
- Strat 2- 3 weeks before travel, continue throughout the stay and for 4 weeks after leaving the malaria endemic destination.
- Mefloquine is taken after meals with plenty of fluids
- Mefloquine chemoprophylaxis can be continued long periods of stay up to one year.

9.7.2 Contraindications to Mefloquine use are

- Allergy to mefloquine, quinine or quinidine.
- Current of previous history of psychiatric disorder including; depression, anxiety disorder, psychosis, schizophrenia, suicide attempts, suicidal thoughts, convulsions and epilepsy.
- Any of the above mentioned psychiatric disorders in a first-degree relative.
- Heart block and prolonged QT interval.
- Chronic liver disease.
- Blackwater fever.
- Children/ infants less than 5 kg weight
- Halofantrine use; avoid halofantrine use for 4 months after last dose of Mefloquine.
- Avoid Mefloquine in certain high-risk travelers like; pilots, divers, armed personnel, dangerous missions and travelers to countries with high prevalence of Mefloquine resistance like Thailand-Myanmar borders.

Prophylactic medication cannot prevent infection but instead suppresses the course of the disease and its symptoms by killing the parasite within the host before it can cause severe disease. There is no prophylactic medication that provides protection against all species of the Plasmodium genus.

- Recognize the malaria parasite in the peripheral blood smear.

Species / Stage	Falciparum	Vivax	Malariae	Oval
Ring Stage				
Trophozoite				
Schizont				
Gametocyte				

- Understand the pathophysiology & clinical presentation of Leishmanias

❖ **Etiology :**

Pathogen: Leishmania donovani (protozoan)

- **Cutaneous leishmaniasis**

- Americas: L. mexicana, L. braziliensis, L. guyanensis, L. panamensis (L. braziliensis, L. guyanensis, L. panamensis can also cause mucosal leishmaniasis)]
- Asia/Africa: L. major, L. tropica. L. aethiopica

- **Visceral leishmaniasis**: L. donovani, L. infantum

Transmission
Vector: phlebotomine sandflies
Reservoir: mammals (especially dogs, humans, and rodents)

1. Cutaneous leishmaniasis

Clinical features

- Localized cutaneous leishmaniasis

Incubation period: weeks to months
Manifestation: solitary or multiple reddish macules/papules around the sandfly bite that quickly increase in size and develop central ulceration

- Mucosal leishmaniasis

Some Leishmania subtypes (e.g., L. braziliensis, L. guyanensis, L. panamensis) cause mucosal leishmaniasis, which can develop months to years after cutaneous leishmaniasis that was not treated properly]
Manifestation: commonly affects the nasopharynx (mucosal bleeding, nasal blockage)

2. Visceral leishmaniasis

Clinical features

- Incubation period: 2–6 months
- Many patients are asymptomatic.
- Kala-azar (Hindi for "black fever," in reference to the darkening of the skin it can cause)
    - Usually insidious progression
    - Flu-like symptoms, spiking fevers
    - Weight loss
    - Lymphadenopathy
    - Hepatosplenomegaly
    - Ascites and edema
    - Pancytopenia
    - Possible darkened or gray skin color (especially on the palms and soles)
    - Immunosuppression may lead to secondary bacterial infections in advanced disease

- Understand the pathophysiology and clinical presentation of Amebiasis and outline management plans.

Amoebiasis

Amoebiasis is caused by Entamoeba histolytica; it is common throughout the tropics Infection can give rise to amoebic dysentery or extra-intestinal amoebiasis, e.g. amoebic liver abscess.

Clinical features:

- Intestinal amoebiasis or amoebic dysentery:

Cysts of E. histolytica are ingested in water or uncooked food contaminated by human faeces. The parasite invades the mucous membrane of the large bowel, producing ulceration. The incubation period of amoebiasis ranges from 2 wks to many years, followed by a chronic course with grumbling abdominal pains (often in the right lower quadrant, mimicking appendicitis) and two or more unformed stools a day. Diarrhoea alternating with constipation is common, as is mucus, sometimes with streaks of blood. There is a dysenteric presentation, with passage of blood and mucus simulating bacillary dysentery or ulcerative colitis, especially in the elderly and those with superadded pyogenic infection.

- Amoebic liver abscess:

This occurs when trophozoites enter the **liver** via the portal vein. In the liver, usually the right lobe, they multiply and rapidly destroy the parenchyma, forming an amoebic abscess. Local symptoms of an enlarged, tender liver, cough and pain in the right shoulder are characteristic, but symptoms may remain vague and signs minimal. A high swinging fever without much systemic upset is sometimes seen. A large liver abscess may rupture through the diaphragm into the lung, from where its contents may be coughed up. Rupture into the pleural cavity, the peritoneal cavity or pericardial sac is less common but more serious.

Investigations

- Fresh Stool Sample:may reveal motile trophozoites on microscopy.
- Sigmoidoscopy: typical flask-shaped ulcers may be seen and should be scraped for microscopy.
- Antibodies: detectable by immunofluorescence in 95% of patients with hepatic amoebiasis and intestinal amoeboma but in only ~60% of dysenteric amoebiasis.
- PCR: also sensitive but not widely available.

If the clinical picture suggests amoebic abscess, there may be a neutrophil leucocytosis and a raised right hemidiaphragm on CXR. Confirmation is by liver USS.

Management

Intestinal and early hepatic amoebiasis responds quickly to **oral metronidazole**. Diloxanide furoate should be given orally for 10 days after treatment to eliminate luminal cysts. Drainage/aspiration may be required for amoebic abscess to prevent rupture; this yields characteristic brown ‘anchovy sauce’ liquid. Surgical drainage is needed if rupture occurs.

Systemic bacterial infection

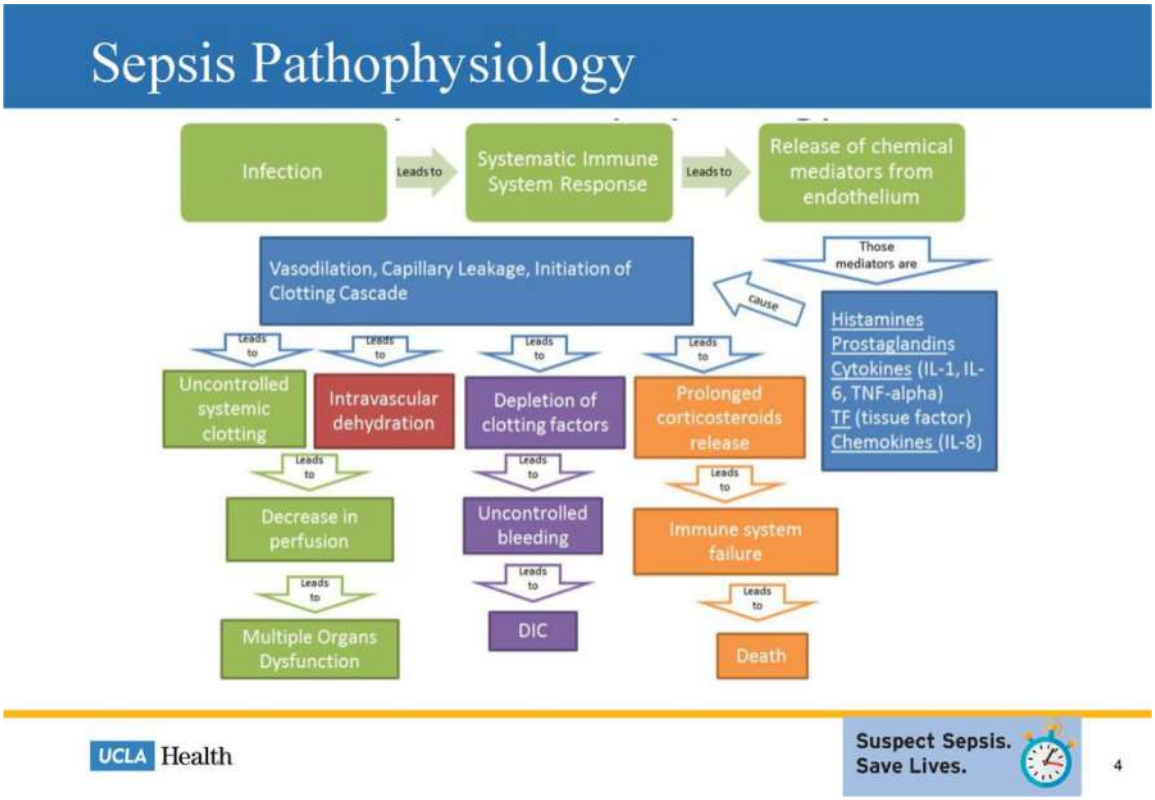
(including Sepsis syndrome, Brucella, Osteomyelitis and Typhoid)

- Understand definition, pathophysiology and clinical presentation of sepsis

  - **Sepsis:** a severe, life-threatening condition that results from a dysregulation of the patient's response to an infection, causing tissue and organ damage and subsequent organ dysfunction
  - **Septic shock:** a sepsis syndrome accompanied by circulatory and metabolic abnormalities that can significantly increase mortality

Diagnostic criteria

1. Persistent hypotension: Vasopressors are required to maintain MAP ≥ 65 mm Hg.
2. Persistent lactic acidosis: lactate › 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation



- To be able to urgently recognize sepsis syndrome clinically and initiate work-up and treatment

❖ Clinical features

- Fever , chills, and diaphoresis
- Tachycardia
- Tachypnea
- Features of organ dysfunction (see SOFA score)
    - CNS impairment: altered mental status
    - Cardiovascular failure: hypotension
    - Coagulopathy → disseminated intravascular coagulation → petechiae, purpura
    - Liver failure: jaundice
    - Kidney failure: oliguria
    - Respiratory failure: symptoms of acute respiratory distress syndrome (ARDS)
- Additionally in septic shock
    - Hypotension (MAP < 65 mm Hg)
    - Initially warm skin and normal capillary refill time (warm shock) → cold cyanotic, pale, or mottled skin with prolonged capillary refill time (cold shock)
- Features of the primary infection
- Generalized edema (capillary leak)

❖ Diagnosis

The main goals of the diagnostic workup in a patient with suspected sepsis are to determine the presence and severity of organ dysfunction and to identify the source of infection.

* Positive cultures are not mandatory for the diagnosis of sepsis.

- **Laboratory studies**

In addition to serum lactate and blood cultures (at least two sets), the following laboratory studies should be obtained to support the diagnosis and evaluate for organ dysfunction.

  - CBC: variable findings
    - Leukocytosis or leukopenia
    - Thrombocytosis or thrombocytopenia
  - CRP, procalcitonin: typically elevated
  - BMP and electrolytes
    - Renal function: ↑ BUN and ↑ creatinine
    - Glucose: hyperglycemia, hypoglycemia
    - Electrolyte derangements
  - Liver chemistry and synthetic function tests: hyperbilirubinemia, ↑ INR, ↑ ALT, ↑ AST
  - Coagulation panel, D dimer: ↑ prothrombin time, ↑ activated partial thromboplastin time, ↓ antithrombin III, ↑ D dimer may be present (DIC)
  - Consider amylase, lipase (if pancreatitis is suspected)
  - Blood gas: to identify possible acid-base disturbances and assess oxygenation

Identifying the source of infection

*In addition to blood cultures, consider additional cultures guided by clinical judgment

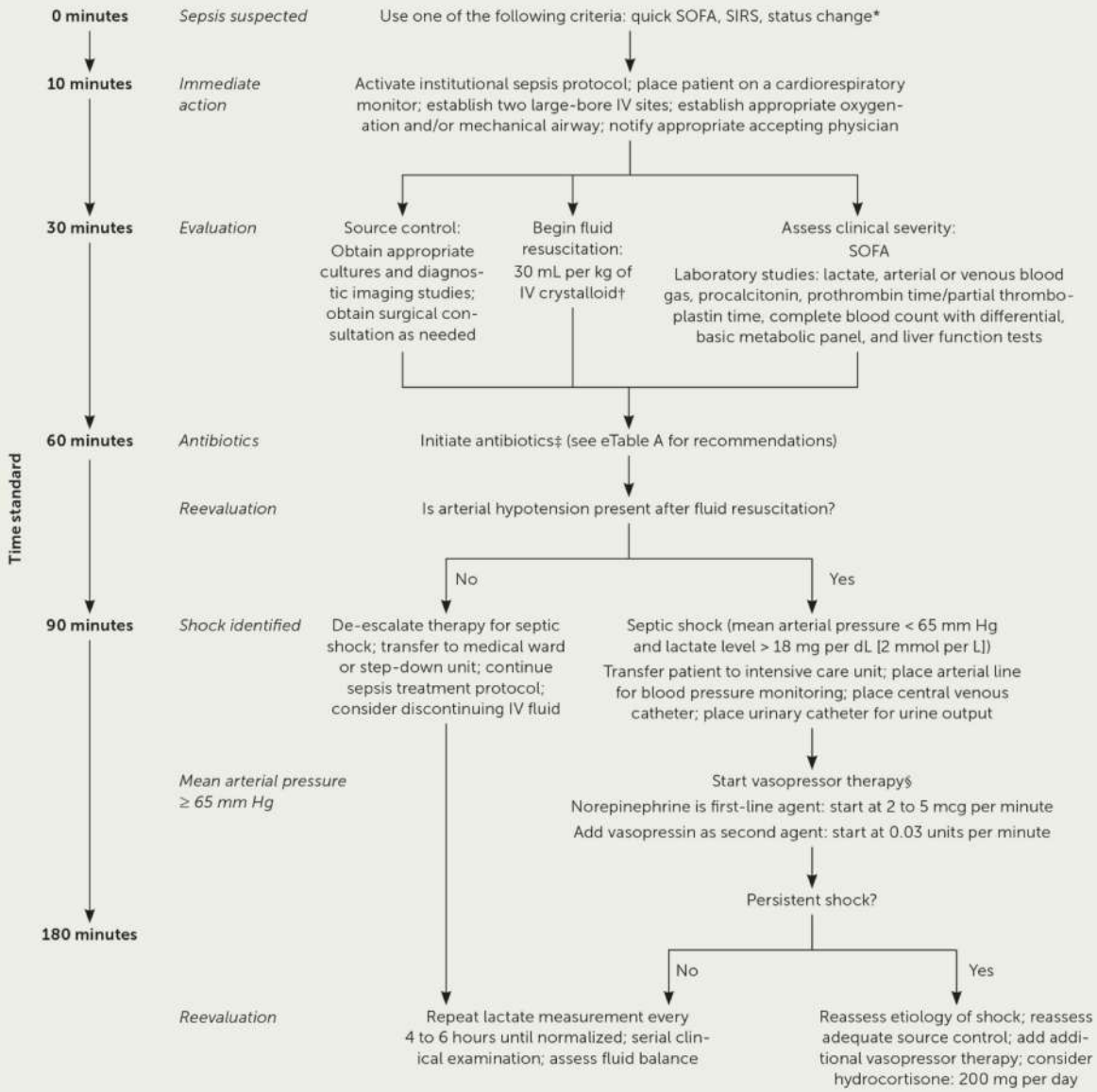
  - Urinalysis and urine culture
  - Sputum culture
  - Consider also: CSF , wound secretion, tissue/fluid
  - Diagnostic procedures as indicated to obtain samples for cultures (e.g., lumbar puncture, thoracentesis, paracentesis, arthrocentesis)

- **Imaging**

Direct decisions based on clinical suspicion. Examples of commonly performed imaging include:

  - Chest x-ray: if pneumonia is suspected and/or to determine if ARDS is present as a complication
  - Abdominal x-ray: if a perforation or obstruction is suspected (pneumoperitoneum, air-fluid levels)
    - Ultrasound
    - Abdominal ultrasound: initial abdomen assessment in most cases
    - Soft tissue: initial assessment of cellulitis and, in most cases, soft tissue abscess
  - CT scan: for a more detailed assessment of thoracic and abdominal/pelvic pathology
  - Echocardiography: to identify valve vegetations

❖ Approach



IV = intravenous; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment.

*—quick SOFA: 2 out of 3 points; SIRS: 2 out of 4 criteria (if data available); status change: presence of infection, heart rate increase of ≥ 30 beats per minute over previous baseline, systolic blood pressure decrease of ≥ 30 mm Hg in one hour, urine output ≤ 0.5 mL per kg per hour, lactate level ≥ 2 mmol per L.

†—Fluid resuscitation is still recommended in patients with end-stage renal disease, dialysis, pneumonia or acute lung injury requiring high flow oxygen, and heart failure. Frequent reassessment is required, and postresuscitation fluid should be adjusted as clinically indicated.

‡—Selection of antibiotics is based on the infections associated with septic shock and high risk of multidrug-resistant organisms.

§—Short-term, low-dose vasopressor therapy can be initiated through peripheral IV line. Long-term vasopressors and septic shock transferred to the intensive care unit should have a central venous catheter.

❖ Treatment

Diagnostic and treatment measures should be conducted simultaneously in a patient suspected of having sepsis. Success depends on early detection, early and effective resuscitation, and early antibiotic therapy.

- Initial resuscitation and ongoing clinical reassessment
- Provide hemodynamic support.

Fluid resuscitation: Many patients may benefit from around 30 mL/kg of crystalloid fluids

- If there is persistent hypotension during or after fluid resuscitation, start vasopressors and titrate to maintain a MAP ≥ 65 mm Hg.
- Start empiric broad-spectrum antibiotics

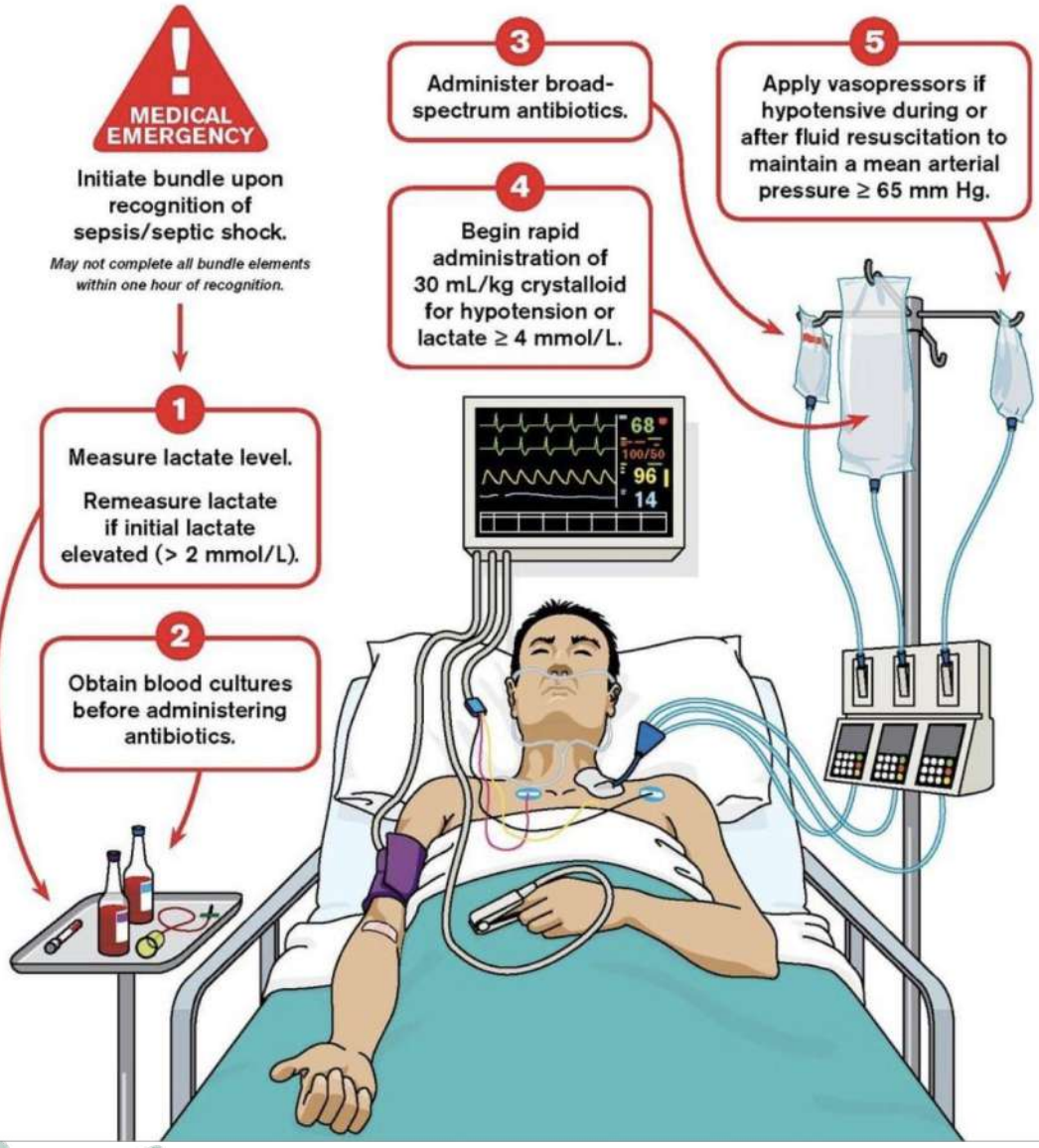
Empiric antibiotic regimens for sepsis with unclear source

Patient characteristics	Commonly used regimens
Unknown risk factors	• Vancomycin [30] • PLUS one of the following: ◦ Broad-spectrum carbapenem ▪ Meropenem [26] ▪ Doripenem ◦ Extended-range penicillin/B lactamase inhibitor ▪ Piperacillin/tazobactam [26] ▪ Ticarcillin/clavulanate ◦ Third-generation (or higher) cephalosporin [26] ▪ Cefotaxime ▪ Ceftriaxone ▪ Ceftazidime ▪ Cefepime
At risk for specific pathogens	• MRSA: Vancomycin [30] • Resistant gram-negative organisms (e.g., Pseudomonas) [29][26] ◦ At least one of the following: ▪ A carbapenem (e.g., meropenem) [26] ▪ Piperacillin/tazobactam ▪ Cefepime ◦ Consider the addition of one of the following: ▪ Polymyxin B [26] ▪ Colistin ▪ An aminoglycoside (e.g., gentamicin, amikacin) • Anaerobes: Consider adding metronidazole.
Neutropenia	• See "Empiric antibiotic therapy for neutropenic fever."

Hour-1 Bundle

Initial Resuscitation for Sepsis and Septic Shock

Surviving Sepsis Campaign



- Recognize clinical signs and symptoms of common systemic bacterial infection and Initiate investigation for it.
- Identify key points in the treatment of Systemic bacterial infection

1. Brucellosis

- is a zoonotic infection caused by different species of Brucella, a genus of gram-negative bacteria.
- The most common vectors of the disease are cattle, sheep, goats, and pigs.
- Transmission occurs through the ingestion of contaminated animal

❖ Risk factors:

- occupational or recreational exposure to infected animals and animal products (e.g., farmers, veterinarians, hunters, slaughterhouse workers, laboratory personnel)

❖ Pathophysiology:

- Brucella spp. survive and replicate within macrophages of the reticuloendothelial system → formation of noncaseating granulomas

❖ Clinical manifestations:

Brucellosis manifests with flu-like symptoms. However, hepatomegaly, splenomegaly, lymphadenopathy, and focal organ infection (e.g., osteomyelitis, endocarditis, spondylitis) may also occur.

❖ Diagnostics:

- Laboratory studies: may show anemia, neutropenia, mild elevation of liver enzymes
- Serology: serum agglutination (Rose Bengal test), ELISA
- Confirmatory test
    - Blood culture (may be false negative)
    - Lymph node or bone marrow biopsy specimen and culture
    - Histopathology: noncaseating granulomas
    - Culture medium for isolation: charcoal yeast extract agar (cysteine and iron buffered)

Blood culture is the most important diagnostic tool at disease onset, as stool cultures are often negative despite active infection.

❖ Antibiotic therapy:

- First-line therapy: doxycycline PLUS rifampin
- Second-line therapy: doxycycline PLUS streptomycin

2. Typhoid fever

❖ Pathogenesis

1. inactivated by gastric acids, so a large inoculum is required
2. crosses intestinal epithelium track through invasion of Peyer patches M cells
3. the bacteria then spread via lymphatics and bloodstream
4. may colonize the gallbladder in chronic carriers

❖ Prevention

- vaccines are recommended prior to traveling to endemic areas, oral live-attenuated vaccine 6 years of age or older
- parenteral vaccine containing Vi capsular polysaccharide 2 years of age or older

❖ Presentation

Symptoms

- fever lasting several days
- constipation initially, non-bloody diarrhea later
- abdominal pain
- malaise
- anorexia

Physical exam

- fever
- relative bradycardia
- pink macular rash that spreads from trunk to extremities (rose spots)
- abdominal tenderness
- hepatosplenomegaly
- signs of dehydration

❖ Diagnosis:

- Laboratory tests
  - CBC: Anemia, Leukopenia or leukocytosis , Absolute eosinopenia, Relative lymphocytosis
  - Abnormal liver function tests
- Pathogen detection
  - Blood cultures: Bacteremia is detectable starting in week 1 of the disease.
  - Stool cultures
  - Bone marrow cultures
  - Serology (Widal test)

❖ **Treatment**

antibiotics can increase the duration of gastrointestinal symptoms but are still recommended to prevent complications & relapse. choice of antibiotics should be guided by local resistance patterns

- Conservative
  - rehydration, correction of any electrolyte imbalances
- Medical
  - fluoroquinolones Is the first-line for all patients
  - azithromycin if resistance or intolerance of fluoroquinolone
  - Third-generation cephalosporins (e.g., ceftriaxone) are preferred for severe infection.

Salmonella		
	Nontyphoidal	**Typhoidal**
Epidemiology	• Major cause of gastroenteritis worldwide (including US) • Associated with undercooked poultry/eggs	• Most common in developing countries with poor sanitation (eg, unvaccinated travelers) • Associated with contaminated food or water
Clinical	• Vomiting • Diarrhea ± blood • Fever • Invasive disease rare	• Fever & bacteremia • Abdominal pain & rose spots • Late findings: HSM, intestinal perforation
Diagnosis	• Stool culture	• Blood culture
Outcome & treatment	• Usually self-limited • Antibiotics rarely needed	• Potentially fatal • Antibiotics (eg, ceftriaxone) • Drug resistance common

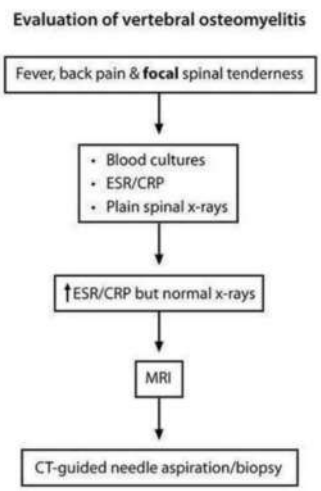
Clinical manifestations of typhoid fever	
Week 1	• Rising fever • Bacteremia • Relative bradycardia (pulse-temperature dissociation)
Week 2	• Abdominal pain • Rose spots on trunk & abdomen
Week 3	• Hepatosplenomegaly • Intestinal bleeding & perforation

3. Osteomyelitis

- Osteomyelitis: infection of the bone marrow
- Acute form: develops within days or weeks
- Chronic form: develops slowly (over months or years) and is associated with avascular bone necrosis and sequestrum formation (necrotic bone fragment that has become detached from the original bone)

Routes of infection

- Hematogenous osteomyelitis
  - Most commonly due to a single pathogen
- Exogenous osteomyelitis:
  - usually due to multiple pathogens
  - Posttraumatic: infection following deep injury (penetrating injury, open fractures, severe soft tissue injury)
  - Contiguous: spread of infection from adjacent tissue
- Secondary to infected foot ulcer in diabetic patients
- Iatrogenic (e.g., postoperative infection of a prosthetic joint implant)



Osteomyelitis in children	
Pathogenesis	• Hematogenous spread • **S *aureus*** MCC
Clinical features	• Fever, irritability • Limited function (eg, limp) • Bony tenderness, swelling
Diagnosis	• Elevated ESR, CRP, WBC count • Blood culture • X-ray (often normal), MRI • Definitive: Bone biopsy/culture
Treatment	• Antistaphylococcal antibiotic (eg, vancomycin)

Most common pathogens causing osteomyelitis		
Pathogens		**Commonly affected groups**
Staphylococcus aureus (most common cause)		• Children and adults • Individuals that recreationally use IV drugs [4] • Patients with vertebral lesions • Patients with prosthetics [5] • Diabetic patients with foot ulcers and pressure ulcers
Staphylococcus epidermidis		• Patients with prosthetics
Streptococci		• Diabetic patients with foot ulcers and pressure ulcers • Neonates and infants
Pseudomonas aeruginosa		• IV drug users [6] • Plantar puncture wounds (especially if wearing rubber-soled footwear)
Enterobacteriaceae	Salmonella	• Patients with sickle cell anemia
	Klebsiella	• Patients with UTIs
Mycobacterium tuberculosis		• See "Tuberculous spondylitis" (Pott disease).
Pasteurella multocida		• Bites from dogs and cats
Fungi (e.g., Candida)		• Immunocompromised patients • Individuals that recreationally use IV drugs

1. Acute osteomyelitis

- **Onset:** usually gradual, over several days
- **Chief complaint:** pain at the site of infection, possibly related to movement
- **Possible localized findings:** point tenderness, swelling, redness, warmth
- **Possible systemic findings:** malaise, fever, chills
- Common localization of hematogenous osteomyelitis
    - Infants: long bone metaphysis, joints
    - Children: long bone metaphysis (joint infection is very rare)
    - Adults: vertebral involvement is most common

2. Chronic osteomyelitis

- **Onset:** Usually following a prior episode of osteomyelitis! May last for months
- **Chief complaint:** recurrent pain
- **Possible findings:** Swelling, redness, Local sinus tract formation, perhaps draining pus

❖ Diagnostics

Clinical approach

- Suspect osteomyelitis in patients with focal symptoms (point tenderness) accompanied by nonspecific signs and symptoms of inflammation.
- Initial work-up includes blood cultures, inflammatory markers, and x-ray imaging.
- Rule out possible primary sources of infection and/or sites of dissemination (e.g., dental infection, furuncle, urinary tract infections).

❖ Treatment:

- Conservative
    - Bed rest and immobilization of the affected extremity
    - Antibiotic treatment
- Surgical Indications:
    - Osteomyelitis refractory to antibiotic treatment: debridement of necrotic bone and tissue
    - Abscess: drainage
    - Post-traumatic osteomyelitis: debridement and fracture management (e.g., external fixator)
    - Infected prosthetic joint or foreign body: removal
    - Revascularization in case of poor wound healing due to peripheral artery disease

Initial empiric antibiotic treatment		
Patient group		**Regimen**
In adults		• IV Vancomycin **PLUS** either antipseudomonal cephalosporins (ceftazidime, cefepime) OR antipseudomonal fluoroquinolones (ciprofloxacin, levofloxacin)
In children	< 3 months of age	• IV 3rd generation cephalosporin (cefotaxime) PLUS ◦ An antistaphylococcal agent (nafcillin, oxacillin) ◦ OR vancomycin or clindamycin if MRSA is likely
	> 3 months of age	• IV Nafcillin/oxacillin OR cefazolin • Vancomycin OR clindamycin if MRSA is likely
Pathogen-directed IV antibiotics (according to bone biopsy findings)		
Pathogen		**Regimen**
Methicillin-susceptible S. aureus (MSSA)		• IV Nafcillin/oxacillin OR 1st or 2nd generation cephalosporin (cefazolin, cefuroxime)
MRSA or S. epidermidis		• IV Vancomycin
Gram-negative pathogens (including Pseudomonas)		• Antipseudomonal cephalosporins (ceftazidime, cefepime) OR antipseudomonal fluoroquinolones (ciprofloxacin, levofloxacin)
Special cases		
Secondary osteomyelitis (e.g., prosthetic joints or foreign bodies)		Rifampicin in addition to the antibiotic regimen

Urinary tract infection & sexual transmitted diseases

- To be able to differentiate between asymptomatic bacteriuria, simple and complicated urinary tract infections.

Classification of urinary tract infections [7]		
		Details
By clinical presentation [8]	Asymptomatic bacteriuria (ASB)	• Significant bacteriuria without clinical features of UTI
	Urinary tract infection (UTI)	• Bacteriuria and clinical features of UTI
By location [9]	Lower UTI	• Infection of the bladder (**cystitis**), the most common location of UTIs, and/or urethra (urethritis) • Commonly associated with infection of the prostate (prostatitis) in men
	Upper UTI	• Infection of the kidneys and ureter (pyelonephritis)
By severity [10] [11][12]	Uncomplicated UTI	• Infection in nonpregnant, premenopausal women without further risk factors for infection, treatment failure, or serious outcomes
	Complicated UTI (cUTI)	• Infection in patients with risk factors for infection, treatment failure, or serious outcomes, including: ◦ Male sex ◦ Pregnancy ◦ Postmenopause ◦ Childhood and preadolescence ◦ Significant anatomical or functional abnormalities ◦ Immunosuppression ◦ Renal failure ◦ Metabolic disorders (e.g., diabetes) ◦ History of UTIs in childhood • Infection associated with recent instrumentation or medical devices, e.g.: ◦ Cystoscopy ◦ Indwelling catheters ◦ Drainage devices (e.g., ureteral stents, nephrostomy tubes) • Healthcare-associated UTIs (see below)

*Asymptomatic bacteriuria: Presence of ≥ 100,000 CFU/mL in at least two voided urine samples in patients with no symptoms of UTI (e.g., dysuria, frequency, urgency, suprapubic pain)

- Recite common organisms causes of urinary tract infection and sexual transmitted disease

❖ **UTI causes:**

- Escherichia coli: leading cause of UTI
- Staphylococcus saprophyticus: 2nd leading cause of UTI in sexually active women
- Klebsiella pneumoniae: 3rd leading cause of UTI

SEEK PP = S - S. saprophyticus, E - E. coli, E - Enterococcus, K - Klebsiella, P - Proteus, P - Pseudomonas are the bacteria commonly associated with UTIs.

❖ **STDs causes:**

- Viral:
  - HPV
  - HSV
  - HIV
  - HBV
- Bacterial:
  - Chlamydia
  - Neisseria gonorrhoeae
  - Klebsiella granulomatis
  - Haemophilus ducreyi
  - Treponema pallidum
- Parasite:
  - Trichomonas vaginalis
  - Phthirus pubis

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

- Identify patients with pyelonephritis based on history and examination.

- Fever, chills
- Flank pain
- Costovertebral angle tenderness: pain upon percussion of the flank (usually unilateral, may be bilateral)
- Dysuria as well as other symptoms of cystitis (e.g., frequency, urgency)
- Weakness, nausea, vomiting (diarrhea may also be present)
- Possible abdominal or pelvic pain

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

- Recall the key points in the management of UTIs and STDs.

1. Urethritis:
The cause Usually STDs. Treat Gonorrhea with **Ceftriaxone** and treat Chlamydia with **Doxycycline** or **Azithromycin**. Treat both, even if you only find one.

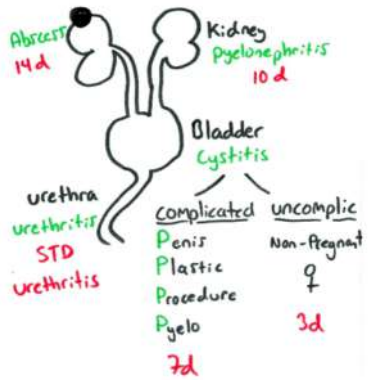
2. Asymptomatic bacteriuria:
If you screen AND there's a reason to treat (pregnancy or procedure) then yes, treat. But all other permutations are **NOT treated**. In pregnancy, it's treated to prevent progression to pyelo and to clear GBS. Use **amoxicillin** as the front line agent and **nitrofurantoin** if penicillin allergic.

3. Cystitis:
If it's an uncomplicated UTI, treat for 3 days. If it's a complicated UTI, treat for 7 days. The antibiotics of choice are **TMP-SMX (Bactrim)**, **Nitrofurantoin**, or **Fosfomycin**.

4. Pyelonephritis:
admitte and give **IV Ceftriaxone or IV Amp + Sulbactam.** Bonus - There's the condition called "ambulatory pyelo" where a young healthy woman can tolerate po, so she gets PO Cipro. This is the only indication for PO Cipro on the board exams.

Disease	*Symptoms*	*Test*	*Treatment*
Asx Bacteriuria	Asx screen Procedure, pregnant	U/A U_{Cx}	Pregnant: Amoxicillin Nitrofurantoin
Urethritis	Frequency Urgency Dysuria + Discharge	U/A U_{Cx} + DNA	Ceftriaxone 125mg IM + Doxy 100 x 7 days or Azithro 250 x 1 po
Cystitis	Frequency Urgency Dysuria	Clinical	TMP-SMX or Nitrofurantoin or Fosfomycin
Pyelo	Frequency Urgency Dysuria + Fever + CVA Tender	U/A U_{Cx} B_{Cx}	IV Cephalosporin (inpt) or PO FQ (outpt)
Abscess	Pyelo that does not improve	CT or U/S	Drainage + Abx (same as Pyelo)

Pregnant Side Note
Confirmation of eradication is required only in pregnancy. It's justified by being "another screen," ≥ 2 infections means PPx Abx in pregnancies thereafter.



Overview of sexually transmitted infections		
Pathogens	**Associated disease**	**Management**
Viral pathogens		
Human papillomavirus type 6 and 11	• Condylomata acuminata • Bowenoid papulosis (condylomata plana)	• Local cytotoxic therapy (e.g., with **5-fluorouracil**) • Cryotherapy • Operative management: curettage (surgical excision), laser surgery, or electrosurgery
Herpes simplex virus type 2 (HSV-2)	• Genital herpes	• Acyclovir PO for episodic or suppressive treatment
HIV	• Opportunistic infections • Lymphoma • Kaposi sarcoma	• Systemic antiretroviral therapy: HAART/cART
Hepatitis B virus (HBV)	• Hepatitis B	• Systemic antiviral therapy PO (e.g., **entecavir**) • **Interferon** (immune-modulating, antiviral, and antiproliferative agent) injected SC or IM
Bacterial pathogens		
Chlamydia trachomatis D–K	• Urogenital chlamydia infections ◦ ♀ : Urethritis, vulvovaginitis, cervicitis, salpingitis, tuboovarian abscess, pelvic inflammatory disease (PID), reactive arthritis ◦ ♂ : Urethritis, epididymitis, reactive arthritis, prostatitis	• Drug of choice: **doxycycline** OR **azithromycin** PO • Alternative: fluoroquinolone (e.g., ciprofloxacin, moxifloxacin)
Chlamydia trachomatis L1–L3	• Lymphogranuloma venereum	
Klebsiella granulomatis	• Granuloma inguinale	
Haemophilus ducreyi	• Chancroid	• **Ceftriaxone** IM single dose • Plus **azithromycin** PO single dose [1] • Expedited partner therapy ◦ Cefixime PO (if chlamydia has been excluded in the patient) ◦ Cefixime PO PLUS doxycycline [2]
Neisseria gonorrhea	• Gonorrhea ◦ ♀ : Urethritis, salpingitis, tuboovarian abscess, pelvic inflammatory disease, cervicitis, Bartholin gland cyst ◦ ♂ : Urethritis, epididymitis ◦ Viscous and purulent discharge ◦ Arthritis	
Treponema pallidum	• Syphilis	• **Penicillin G** IM • Alternatives if allergic to penicillin: tetracycline, macrolides, or cephalosporin
Parasitic pathogens		
Trichomonas vaginalis	• Trichomoniasis (cervicitis)	• Metronidazole PO
Phthirus pubis	• Pediculosis pubis (pubic lice, crab louse) ◦ Irritated skin in the pubic hair region ◦ Tiny brown lice droppings detectable	• **Permethrin** 1% lotion (insecticide)

Emerging infections and Bioterrorism

- Understand the pathophysiology, clinical presentation and complication of MERS-CoV and outline the essential key points in the management.

Middle East respiratory syndrome coronavirus (MERS-CoV)

is a virus transferred to humans from infected dromedary camels. It is a zoonotic virus, meaning it is transmitted between animals and people, and it is contractable through direct or indirect contact with infected animals. MERS-CoV has been identified in dromedaries in several countries in the Middle East, Africa and South Asia. In total, 27 countries have reported cases since 2012, leading to 858 known deaths due to the infection and related complications.

The origins of the virus are not fully understood but according to the analysis of different virus genomes it is believed that it may have originated in bats and later transmitted to camels at some point in the distant past.

Human-to-human transmission is possible, but only a few such transmissions have been found among family members living in the same household. In health care settings, however, human-to-human transmission appears to be more frequent.

MERS-CoV infections range from showing no symptoms (asymptomatic) or mild respiratory symptoms to severe acute respiratory disease and death.

❖ Pathophysiology

One of the most important cells of the innate immune system is the macrophage. Its function is to eliminate pathogens, to present antigens to T cells, to produce cytokines and chemokines to maintain homeostasis, and to modulate the immune response in tissues.

Compared with severe acute respiratory syndrome coronavirus (SARS-Cov), MERS-CoV can establish infection in monocyte-derived macrophages (MDMs) and macrophages. The virus induces release of proinflammatory cytokines, leading to severe inflammation and tissue damage, which may manifest clinically as severe pneumonia and respiratory failure. Vascular endothelial cells located in the pulmonary interstitium may also be infected by MERS-CoV, and, because MERS-CoV receptor DPP4 is expressed in different human cells and tissues, dissemination of the infection may occur. This may explain the increased severity and higher fatality rate compared with SARS-CoV infection

Interestingly, lymphopenia has been noted in most patients infected with MERS-CoV, as was noted in SARS infections. This is due to cytokine-induced immune cell sequestration and release and induction of monocyte chemotactic protein-1 (MCP-1) and interferon-gamma-inducible protein-10 (IP-10), which suppresses proliferation of human myeloid progenitor cells.

❖ Symptoms

A typical presentation of MERS-CoV disease is fever, cough and shortness of breath. Pneumonia is a common finding, but not always present. Gastrointestinal symptoms, including diarrhoea, have also been reported. Severe illness can cause respiratory failure that requires mechanical ventilation and support in an intensive care unit. The virus appears to cause more severe disease in older people, people with weakened immune systems and those with chronic diseases such as renal disease, cancer, chronic lung disease, and diabetes.

Approximately 35% of patients with MERS-CoV have died, but this may be an overestimate of the true mortality rate, as mild cases of MERS may be missed by existing surveillance systems. The case fatality rates are currently counted only amongst the laboratory-confirmed cases.

Until more is understood about MERS-CoV, people with diabetes, renal failure, chronic lung disease and immunocompromised persons are considered at high risk of severe disease from MERS-CoV infection. These people should avoid contact with camels, drinking raw camel milk or camel urine, or eating meat that has not been properly cooked

❖ Treatment

No vaccine or specific treatment is currently available, although several MERS-CoV specific vaccines and treatments are in development. Treatment is supportive and based on the patient's clinical condition.

As a general precaution, anyone visiting farms, markets, barns, or other places where dromedary camels and other animals are present should practice general hygiene measures, including regular hand washing before and after touching animals and avoiding contact with sick animals.

The consumption of raw or undercooked animal products, including milk and meat, carries a high risk of infection that can cause disease in humans. Animal products that are processed appropriately through cooking or pasteurization are safe for consumption but should also be handled with care to avoid cross contamination with uncooked foods. Camel meat and camel milk are nutritious products that can continue to be consumed after pasteurization, cooking or other heat treatments.

Transmission of the virus has occurred in health care facilities in several countries, including transmission from patients to health care providers and transmission between patients before MERS-CoV was diagnosed. It is not always possible to identify patients with MERS-CoV early or without testing because symptoms and other clinical features may be non-specific.

- Understand the pathophysiology, clinical presentation and complication of SARS-COV 2 and outline the essential key points in the management.

COVID-19 is a pandemic acute infectious respiratory disease caused by infection with the coronavirus subtype SARS-CoV-2, first detected in Wuhan, China, in December 2019. Transmission occurs primarily via respiratory droplets. Following an incubation period of 2–14 days (average ~ 5 days), COVID-19 usually presents with fever and upper respiratory symptoms, especially dry cough and often dyspnea; asymptomatic courses and other symptoms can also occur.

Clinical courses range from very mild to severe with pneumonia and life-threatening complications such as ARDS, shock, and organ dysfunction.

Recommendations for infection control and preventive measures vary but generally involve personal hygiene (e.g., washing hands), avoiding exposure/public places, quarantine/isolation, and wearing suitable personal protective equipment (PPE).

Diagnosis is confirmed by RT-qPCR of SARS-CoV-2 RNA isolated from a nasopharyngeal swab.
In mild clinical cases, patients should self-isolate with supportive care and monitoring at home.

Patients with severe disease (i.e., dyspnea, cyanosis, chest discomfort, or mental status change), signs of respiratory distress (SpO2 ≤ 93%, respiratory rate > 22/min), or at high risk of severe disease (≥ 65 years, presence of certain comorbidities) should be admitted.
Hospitalized patients should receive supportive and oxygen therapy and be regularly monitored with supporting laboratory and imaging studies (Chest x-ray, Chest CT, possibly POCUS).

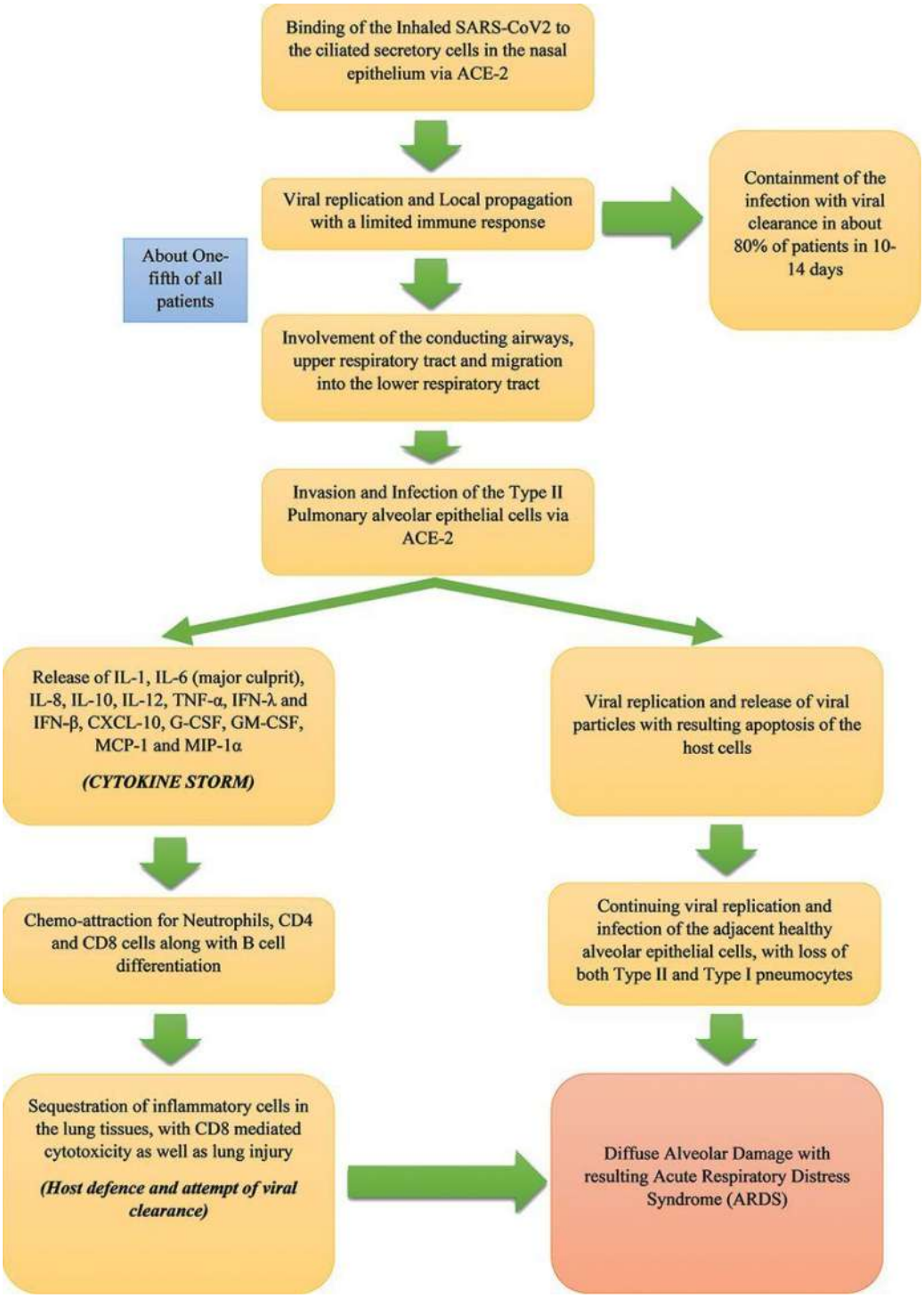
Notable findings indicative of progression to pneumonia include lymphocytopenia, elevated CRP, and CT scans showing ground-glass opacities (can progress to solid white consolidation) and inter- and/or intralobular septal thickening (indicating swelling of the interstitial space).

POCUS can assist in monitoring pneumonia and possibly screening for cardiomyopathy.

Intensive care and airway management are indicated for patients displaying signs of respiratory failure (e.g., dyspnea with hypoxemia, respiratory rate > 30/min).
Endotracheal intubation should be initiated early, preferably by rapid-sequence induction.
Mechanical ventilation should be according to ARDS protocols (e.g., ARDSnet protocol).

The overall mortality rate ranges from ~ 0.5–3%, and greatly increases for elderly (~ 15% for > 80 years) as well as those with certain underlying conditions (e.g., cardiac, pulmonary, diabetes mellitus).

❖ Pathophysiology



❖ **Management**

asymptomatic or mild courses:

Management of asymptomatic or mild courses consists primarily of supportive self-care at home (home care) and isolation in accordance with health department regulations. Antiviral treatment should be administered to patients at high risk of disease progression.

- Pharmacological treatment
- Antipyretic and anti-inflammatory therapy for controlling fever and pain (if required)
- Acetaminophen (paracetamol): drug of choice in most patients, unless contraindications are present (e.g., liver disease)

Alternative: ibuprofen or other NSAIDS, but limit use in elderly patients and those with cardiovascular or renal disease

hospitalized patients:

General approach

- Administer O2 therapy via nasal canula: 1–6 L O2/min if SpO2 ≤ 93%

Careful with patients with COPD: a SpO2 of 90–93% is appropriate

- Provide supportive care:

Adequate hydration, nutrition, and rest

Fever management

Fluid-sparing resuscitation and electrolyte balance as needed

- Evaluate and monitor: Vital signs, SpO2, laboratory studies, and imaging should regularly be conducted to help guide management and monitor progression.
- Administer medical therapy as needed.

Recommended therapies may include remdesivir, dexamethasone, empiric antibiotic therapy, and/or anticoagulation

Consider experimental drugs in the context of compassionate use programs, research studies, and individual cases after weighing the risks and benefits

- Admit to ICU and administer ventilation if any of the following:

Signs of respiratory failure

Dyspnea with hypoxemia

Tachypnea (RR > 30/min)

Discontinuation of isolation

CDC recommends to end home isolation according to a strategy based on clinical criteria (December 2020)

- For patients with symptomatic COVID-19:
- 10 days after the onset of symptoms AND
- No fever for at least 24 hours without antipyretics AND
- Respiratory symptoms have improved
- For patients with asymptomatic COVID-19: 10 days have passed without illness since the date of the positive COVID-19 test.

- Recite organisms with the potential for use in bioterrorism.
- Identify features (clinical, situation, population) that may suggest a possible act of bioterrorism

CDC Bioterrorism Agents

Category A
Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (variola major)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

Category B
Brucellosis (*Brucella species*)
Epsilon toxin of Clostridium perfringens
Food safety threats (*e.g., Salmonella species, Escherichia coli O157:H7, Shigella*)
Glanders (*Burkholderia mallei*)
Melioidosis (*Burkholderia pseudomallei*)
Psittacosis (*Chlamydia psittaci*)
Q fever (*Coxiella burnetii*)
Ricin toxin from *Ricinus communis* (castor beans)
Staphylococcal enterotoxin B
Typhus fever (*Rickettsia prowazekii*)
Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
Water safety threats (e.g., *Vibrio cholerae, Cryptosporidium parvum*)

Category C
Emerging infectious diseases such as Nipah virus and hantavirus

Category A Diseases/Agents

For more info:

https://emergency.cdc.gov/agent/agentlist-category.asp

https://www.statpearls.com/ArticleLibrary/viewarticle/131243

Endocrine Disorders

Lectures List

Endocrine disorders	
1	Pituitary disorders - Understand the hypothalamic and pituitary axis. - Recognize pituitary hormone deficiency/excess in the hormonal panel. - Recognize presenting problems in pituitary diseases like Diabetes insipidus, hyperprolactinemia, Acromegaly, and anterior pituitary hormones deficiency. - Understand the basics of management pituitary hormones deficiency
2	Thyroid Disorders - Identify common presentation of hypo/hyperthyroidism. - To be able to interpretive thyroid function tests and initiate treatment. - Outline the treatment of myxedema coma and thyroid storm.
3	Adrenal glands disorders - Recognize the clinical features findings of patients with adrenal insufficiency and crisis. - Recall the fundamental investigations and management of adrenal insufficiency. - To understand the pathophysiology of Cushing's syndrome and to apply diagnostic approach and basics of management. - To understand clinical presentation of Pheochromocytoma and to apply diagnostic approach and basics of management.
4	Diabetes and DKA - Understand different types of diabetes and modalities of diagnosis and treatment. - Understand the pathophysiology of diabetic ketoacidosis. - Know the key points in the treatment of diabetic ketoacidosis. - Recall long-term complication of diabetes, rule of screenings and basic of management.
5	Parathyroid and Bone diseases - Understand the calcium homeostasis in relation to parathyroid hormone and vitamin D. - Recognize the clinical features findings of patients with hypercalcemia, recall common causes and apply diagnostic approach - Understand Pathogenesis of Osteoporosis, key investigations and basics of management.
6	Dyslipidemia - Recognize causes of secondary dyslipidemia and rule of screening in high risk individuals. - Recognize and understand lipid profile panel and identify abnormalities. - To apply lifestyle modifications and drug therapy for patients with dyslipidemia. - Identify parameters for the key characteristics for metabolic syndrome and understand basics of management.

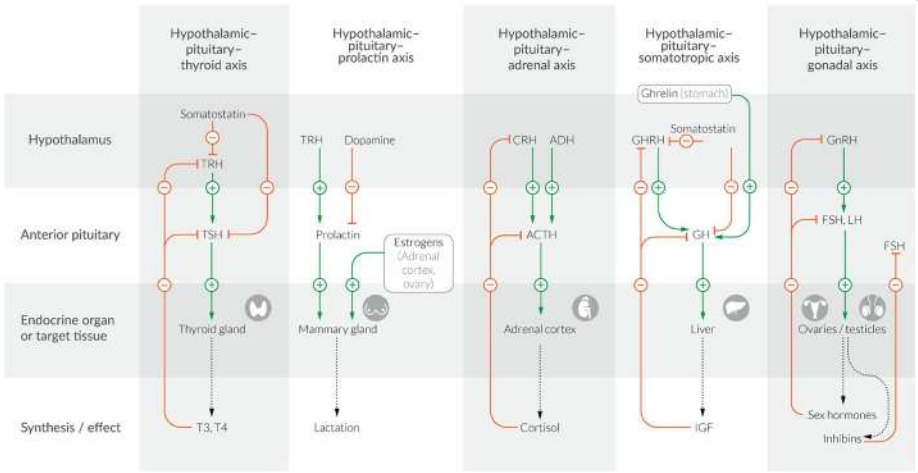
Pituitary disorders

- Understand the hypothalamic and pituitary axis

1- Hypothalamus and anterior pituitary

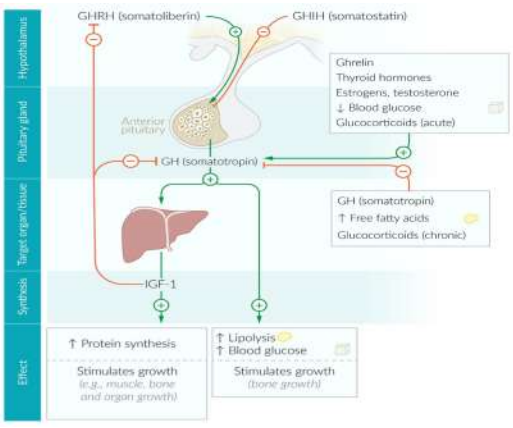
Tropic hypothalamic hormones and their effects

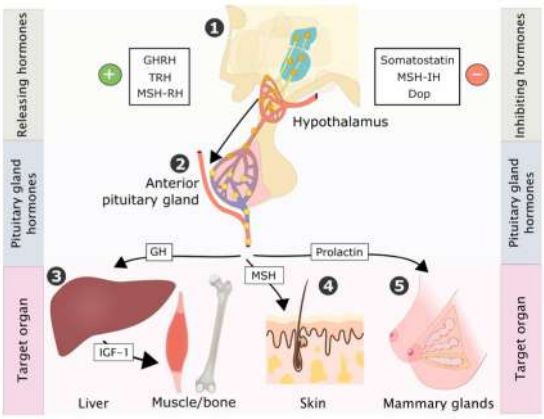
Axis	Hypothalamus	Pituitary gland	Endocrine target organ
Hypothalamic-pituitary-adrenal axis	• CRH ◦ Stimulates ACTH, MSH, and β-endorphin secretion from proopiomelanocortin (POMC) precursor ◦ CRH levels decrease after long-term steroid treatment via negative feedback.	• ACTH ◦ Stimulates adrenal glucocorticoid and androgen production ◦ Cleaved in the corticotropic cells of the anterior pituitary ◦ ACTH and MSH share the common precursor POMC, which explains the hyperpigmentation seen in Cushing disease.	Adrenal • cortex
Hypothalamic-pituitary-thyroid axis	• TRH ◦ Stimulates TSH and prolactin secretion ◦ An increase in TRH levels (e.g., in primary/secondary hypothyroidism) may result in the development of galactorrhea because it stimulates prolactin secretion.	• TSH ◦ Stimulates thyroid hormone production ◦ TSH secretion is inhibited by dopamine, somatostatin, and glucocorticoids. [4] ◦ TSH levels are the best initial test in the workup of hypothyroidism.	• Thyroid gland
Hypothalamic-pituitary-gonadal axis	• GnRH ◦ Stimulates FSH and LH secretion ◦ During breastfeeding, high prolactin levels cause supressed GnRH secretion, which results in the development of lactational amenorrhea. ◦ Pulsatile GnRH secretion is responsible for puberty and reproductive function.	• Gonadotropins ◦ LH ▪ Female individuals: triggers ovulation ▪ Male individuals: stimulates testosterone synthesis in Leydig cells ◦ FSH: stimulates the maturation of germ cells in both male and female individuals	• Gonads ◦ Female individuals: ovaries ◦ Male individuals: testicles



Nontropic hypothalamic hormones and their effects

Axis	Hypothalamus	Pituitary gland
Hypothalamic-pituitary-somatotropic axis	• GHRH ◦ Stimulates GH secretion ◦ Synthetic forms of GHRH (tesamorelin) can be used for abdominal fat reduction in HIV-associated lipodystrophy. • Somatostatin ◦ Inhibits GH and TSH secretion ◦ Synthetic forms of somatostatin are used in the treatment of acromegaly (e.g., octreotide).	• GH (growth hormone, somatotropin) ◦ Direct effects ▪ ↓ Glucose uptake into cells (↑ **insulin resistance**) ▪ ↑ Lipolysis ▪ ↑ Protein synthesis in muscle ▪ ↑ Amino acid uptake ◦ Indirect effects: mediated by IGF-1 (insulin-like growth factor 1; originally called somatomedin C) ▪ **Growth stimulation** ▪ Anabolic effect on body ◦ GH regulation [5][6] ▪ ↑ GH secretion: exercise, deep sleep, puberty, hypoglycemia, CKD, thyroid hormone, estrogen, testosterone, and short-term glucocorticoid exposure ▪ ↓ GH secretion: glucose, somatostatin, somatomedin, free fatty acids, and chronic glucocorticoid therapy [6][7]
Hypothalamic-pituitary-prolactin axis	• Dopamine (prolactin-inhibiting hormone): inhibits secretion of prolactin in the pituitary gland • TRH: stimulates the secretion of prolactin (but is not part of the hypothalamic-pituitary-prolactin axis)	• Prolactin (secreted by lactotropic cells) ◦ ↑ Breast tissue growth and lactation ◦ Inhibits GnRH secretion ▪ Female individuals ▪ Inhibition of ovulation ▪ Amenorrhea ▪ Galactorrhea ▪ Decreased libido ▪ Male individuals ▪ Inhibition of spermatogenesis ▪ Decreased libido
Hypothalamic-melanocortin system	• Melanocyte-inhibiting hormone: inhibits release of MSH	• α-MSH ◦ Cleaved in the arcuate nucleus ◦ Regulation of appetite and metabolism: promotes satiety [8] ◦ Stimulates melanogenesis → melanocyte stimulation → hyperpigmentation • β-MSH



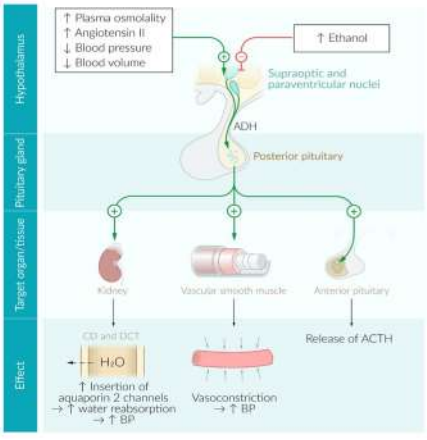


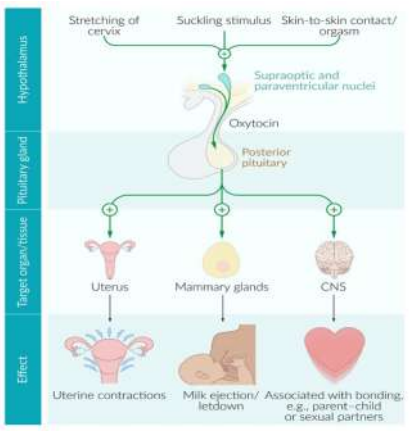
2- Hypothalamus and posterior pituitary

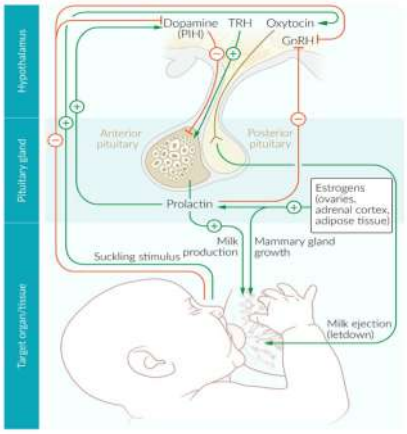
Hormones of the posterior pituitary gland			
Hormone	**Regulation** [9]	**Main effects**	**Clinical relevance**

Antidiuretic hormone	• Plasma osmolality: sensed by hypothalamic osmoreceptors
	• Hypovolemia: sensed by the atrial stretch receptors
	• Hypotension: sensed by the peripheral baroreceptors
	• Angiotensin II: sensed by hypothalamic receptors
		• Regulation of plasma osmolality
		  ◦ Mediated by V2 receptors
		  ◦ Insertion of aquaporin channels in the principal cells of the renal collecting duct and DCT [10]
		  ◦ Results in increased water reabsorption
		• Regulation of blood pressure
		  ◦ Mediated by V1 receptors
		  ◦ Vasoconstrictive effects at higher levels
		• Increase of urea reabsorption in the collecting duct: increases the corticomedullary gradient and facilitates urine concentration
		• ACTH release [11]
			• Elevated in SIADH despite plasma hypoosmolality
			• ADH deficiency or resistance can lead to diabetes insipidus.
			• Alcohol inhibits ADH release and causes diuresis. [12]

Oxytocin	• Nipple stimulation • Stretching of the vagina or cervix	• Promotes uterine contractions during labor • Facilitates milk ejection reflex via myoepithelial cell contraction	• Involved in the neuromodulation of social and reproductive behavior, fear, anxiety, and depression







- Recognize pituitary hormone deficiency/excess in the hormonal panel.

10.17 Investigation of pituitary and hypothalamic disease

Identify pituitary hormone deficiency

- ACTH deficiency: short ACTH stimulation test; insulin tolerance test (if uncertainty in interpretation of short ACTH stimulation test)
- LH/FSH deficiency: male – random serum testosterone, LH, FSH; pre-menopausal female – ask if menses are regular; post-menopausal female – random serum LH, FSH (usually >30 mU/L)
- TSH deficiency: serum T_4; TSH often detectable in secondary hypothyroidism (inactive circulating TSH isoforms)
- Growth hormone deficiency (only investigate if GH replacement contemplated): measure immediately after exercise; consider other stimulatory tests
- Cranial diabetes insipidus (may be masked by ACTH/TSH deficiency): exclude other causes of polyuria (blood glucose, potassium and calcium measurements); water deprivation test or 5% saline infusion test

Identify hormone excess

- Measure serum prolactin; investigate for acromegaly (glucose tolerance test) or Cushing's syndrome if indicated

Establish the anatomy and diagnosis

- Visual field testing; image pituitary/hypothalamus by MRI/CT

- Recognize presenting problems in pituitary diseases like Diabetes insipidus, hyperprolactinemia, Acromegaly, and anterior pituitary hormones deficiency.

1. Diabetes insipidus

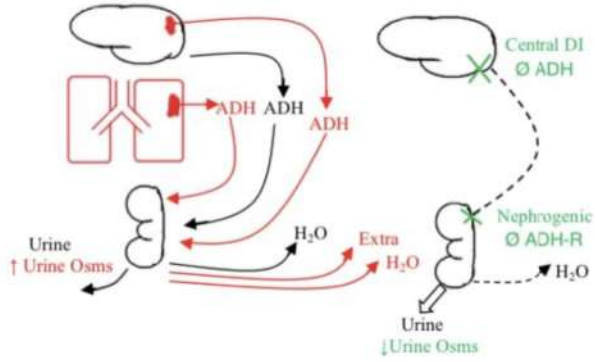
❖ general characteristics

1. Two forms
    a. **Central DI** is the most common form—due to low ADH secretion by posterior pituitary
    b. **Nephrogenic** DI—ADH secretion is normal but tubules cannot respond to ADH
2. Causes
    a. Central DI
        • Idiopathic—50% of all cases
        • Trauma—surgery, head trauma
        • Other destructive processes involving the hypothalamus, including tumors, sarcoidosis, tuberculosis, syphilis, Hand–Schüller–Christian disease, eosinophilic granuloma, and encephalitis
    b. Nephrogenic DI—the most common cause in adults is chronic lithium use. Other causes include hypercalcemia, pyelonephritis, and demeclocycline use. It may also be congenital—caused by mutations in the ADH receptor gene or the aquaporin-2 gene

❖ Clinical features

1. Polyuria is a hallmark finding: 5 to 15 L daily; urine is colorless (because it is so dilute).
2. Thirst and polydipsia—hydration is maintained if the patient is conscious and has access to water.
3. Hypernatremia is usually mild unless the patient has an impaired thirst drive.

If a patient presents with polyuria and polydipsia, consider the following first in the differential diagnosis:
• Diabetes Mellitus
• Diuretic Use
• Diabetes Insipidus
• Primary Polydipsia: is usually seen in patients with psychiatric disturbances.
If The Patient Is Deprived Of water, urine osmolarity will increase appropriately.



❖ Diagnosis

1. Urine—low specific gravity and low osmolality indicate DI
2. Plasma osmolality
    a. Normal: 250 to 290 mOsm/kg
    b. Primary polydipsia: 255 to 280 mOsm/kg
    c. DI: 280 to 310 mOsm/kg
3. A water deprivation test (dehydration test) is required to make the diagnosis (see Table)
    a. Procedure
    • Withhold fluids, and measure urine osmolality every hour
    • When urine osmolality is stable (<30 mOsm/kg hourly increase for 3 hours), inject 2g desmopressin subcutaneously. Measure urine osmolality 1 hour later
    b. Response—see Table
4. ADH level (not the test of choice; takes a long time to get results)
    a. Low in central DI
    b. Normal or elevated in nephrogenic DI

TABLE 4-1 Response to the Water Deprivation Test

	Increase in Urine Osmolality Above 280 mOsm/kg with Dehydration	Further Response to ADH
Normal Patients	+	–
Diabetes Insipidus Patients	–	+
Nephrogenic Diabetes Insipidus Patients	–	–

❖ Treatment

1. Central DI
    a. Desmopressin (DDAVP) is the primary therapy and can be given by nasal spray, orally, or by injection.
    b. Chlorpropamide increases ADH secretion and enhances the effect of ADH.
    c. Treat the underlying cause.
2. Nephrogenic DI—treat with sodium restriction and thiazide diuretics.
    a. These deplete the body of sodium, which leads to increased reabsorption of sodium and water in the proximal tubules.
    b. The reabsorption of sodium and water in the proximal tubules means that less water reaches the distal tubules, leading to decreased urine volume.

Dz	*Pt*	*U/A*	*Water Deprivation Test*	*Tx*	*Cause*
Diabetes Mellitus	Polydipsia Polyuria Weight Loss	Hypertonic Urine with Glucose	N/A	Insulin	Autoimmune Obesity
Central DI	Polydipsia Polyuria ⊕ Nocturnal Sx	Hypotonic Urine	Corrects with ADH	Desmopressin	Trauma, Stroke, Tumor Granulomas
Nephro DI	Polydipsia Polyuria ⊕ Nocturnal Sx	Hypotonic Urine	Does Ø Correct	Diuretics	Lithium Demeclocycline
Psychogenic Polydipsia	Polydipsia Polyuria Ø Nocturnal Sx	Hypotonic Urine	Corrects with Water Restriction	Stop drinking so much water	Psychiatric Disease

2. Hyperprolactinemia

❖ Causes

1. Prolactinoma is the most common cause & the most common type of pituitary adenoma (up to 40%)
2. Medications (e.g., psychiatric medications, H2 blockers, metoclopramide, verapamil, estrogen)
3. Pregnancy
4. Renal failure
5. Suprasellar mass lesions (can compress hypothalamus or pituitary stalk)
6. Hypothyroidism
7. Idiopathic

❖ Clinical features

1. Men:
    a. Hypogonadism, decreased libido, infertility, impotence
    b. Galactorrhea or gynecomastia (uncommon)
    c. Parasellar signs and symptoms (visual field defects and headaches)
2. Women
    a. Premenopausal: menstrual irregularities, oligomenorrhea or amenorrhea, anovulation and infertility, decreased libido, dyspareunia, vaginal dryness, risk of osteoporosis, galactorrhea
    b. Postmenopausal: parasellar signs and symptoms (less common than in men)

❖ Diagnosis

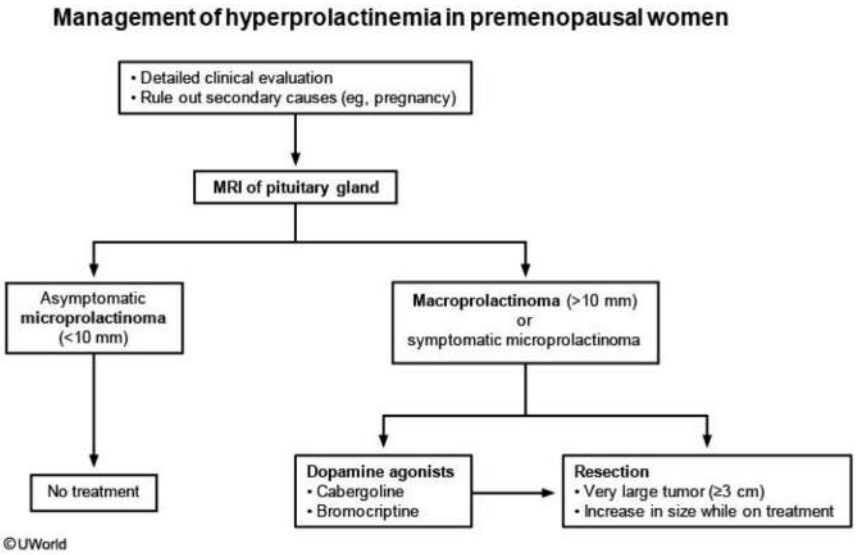
1. Elevated serum prolactin level.
2. Order a pregnancy test and TSH level, because both pregnancy and primary hypothyroidism are on the differential diagnosis for hyperprolactinemia.
3. CT scan or MRI to identify any mass lesions.

High levels of prolactin inhibit secretion of GnRH. This leads to decreased secretion of LH and FSH, which in turn leads to decreased production of estrogen and testosterone

Parasellar signs and symptoms (mass effects of the tumor) are more prevalent in men than in women. This is largely because the early symptoms in men (e.g., impotence) are often attributed to psychological causes and medical evaluation is delayed, allowing for larger tumor growth.

❖ **Treatment**

1. Treat the underlying cause (e.g., stop medication, treat hypothyroidism).
2. If prolactinoma is the cause and the patient is symptomatic, treat with **bromocriptine**, a dopamine agonist that secondarily diminishes the production and release of prolactin. Continue treatment for approximately 2 years before attempting cessation. **Cabergoline** (another dopamine agonist) may be better tolerated than bromocriptine and is often chosen as first-line therapy.
3. Consider surgical intervention if symptoms progress despite appropriate medical therapy. However, the recurrence rate after surgery is high.



3. Acromegaly

❖ **general characteristics**

1. Acromegaly is broadening of the skeleton, which results from excess secretion of pituitary GH after epiphyseal closure (if before epiphyseal closure, gigantism [excessive height] results).
2. It is almost always caused by a GH-secreting pituitary adenoma (represents 10% of pituitary adenomas).

❖ Clinical features

1. Growth promotion
   - Soft tissue and skeleton overgrowth, Coarsening of facial features
   - Abnormally large hand and foot size (ask about increasing glove/ring size)
   - Organomegaly, Arthralgia due to joint tissue overgrowth
   - Hypertrophic cardiomyopathy, Enlarged jaw (macrognathia)
2. Metabolic disturbances
   - Glucose intolerance and DM in 10% to 25% of patients, Hyperhidrosis
3. Parasellar manifestations (mass effect)
   - a. Headache
   - b. Superior growth leads to compression of the optic chiasm, which results in visual loss (bitemporal hemianopsia)
   - c. Lateral growth leads to cavernous sinus compression
   - d. Inferior growth leads to sphenoid sinus invasion
   - e. HTN, sleep apnea

❖ Diagnosis

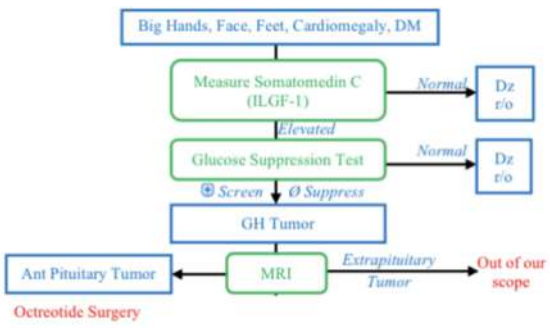
1. IGF-1, also known as somatomedin C, should be significantly elevated in acromegaly.
2. Oral glucose suppression test—glucose load fails to suppress GH (as it should in healthy individuals). This confirms the diagnosis if the IGF-1 level is equivocal.
3. MRI of the pituitary.
4. A random GH level is not useful because there is wide physiologic fluctuation of GH levels.

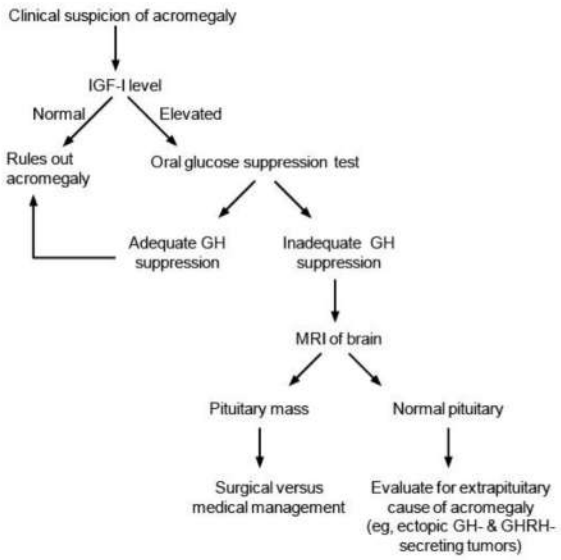
❖ Treatment

1. Transsphenoidal resection of pituitary adenoma—treatment of choice
2. Radiation therapy if IGF-1 levels stay elevated after surgery
3. Octreotide or other somatostatin analog to suppress GH secretion

Other laboratory abnormalities in Patients with acromegaly
- Hyperprolactinemia (tumor secretes prolactin and growth hormone)—30% of patients
- Elevations In Serum Glucose, triglycerides, and phosphate levels

Cardiovascular disease (cardiomyopathy) is the most common cause of death in patients with acromegaly.





4. Anterior pituitary hormones deficiency

❖ general characteristics

1. All or some of the hormones released from the anterior pituitary may be absent.
2. Loss of hormones is unpredictable, but LH, FSH, and GH are usually lost before TSH and ACTH.
3. Clinical manifestations depend on which hormones are lost.

❖ Causes

1. Hypothalamic or pituitary tumor is the most common cause.
2. Other causes: radiation therapy, Sheehan syndrome, infiltrative processes (e.g., sarcoidosis, hemochromatosis), head trauma, cavernous sinus thrombosis, surgery.

❖ Clinical features

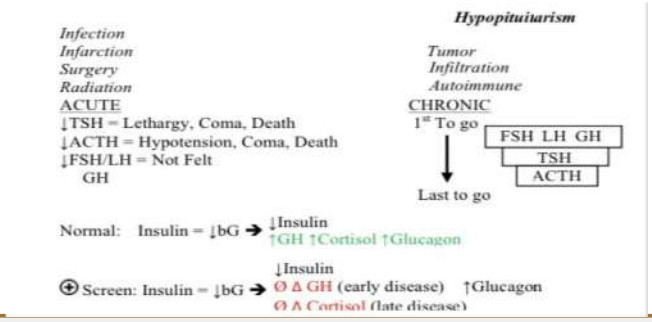
1. Reduced GH: growth failure (decreased muscle mass in adults), increased LDL, increased risk of heart disease
2. Reduced prolactin: failure to lactate
3. Reduced ACTH: adrenal insufficiency
4. Reduced TSH: hypothyroidism
5. Reduced gonadotropins (LH and FSH): infertility, amenorrhea, loss of secondary sex characteristics, diminished libido
6. Reduced antidiuretic hormone (ADH) (if hypothalamic lesion): diabetes insipidus
7. Reduced melanocyte-stimulating hormone (MSH): decreased skin and hair pigmentation

❖ Diagnosis

1. Low levels of target hormones with low or normal levels of trophic hormones (it is the suppression of the trophic hormone that is important, although the absolute level may be in the normal reference range)
2. MRI of the brain (may miss microadenomas)

❖ Treatment

1. Replacement of appropriate hormones
2. Women who want to conceive should be referred to an endocrinologist



- Understand the basics of management pituitary hormones deficiency

Hormone replacement in hypopituitarism [6]	
Secondary adrenal insufficiency	• Routine management: **glucocorticoids** with dose increases during periods of stress
Secondary hypothyroidism	• New diagnosis: Rule out ACTH deficiency before starting treatment, as levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis. [14] • Routine management: **levothyroxine** • Monitor treatment efficacy with free T4 levels (not TSH).

Secondary hypogonadism	• Men
	  ◦ **Testosterone** replacement [15]
	  ◦ If fertility is desired, exogenous gonadotropins (e.g., hCG) [16]
	• Females: **estrogen** replacement with **progesterone**

Growth hormone deficiency [8]	• Children: **growth hormone** replacement [17] • Adults: GH replacement may be offered but is not usually required.
Central diabetes insipidus	• Routine management: **desmopressin**

Emergency management:

Acute loss of pituitary function, e.g., via pituitary apoplexy (including Sheehan syndrome), iatrogenic (hypophysectomy), or traumatic brain injury, can lead to life-threatening complications.

- Adrenal crisis: Give immediate IV hydrocortisone without waiting for diagnostic confirmation.
- Myxedema coma:
  Give IV hydrocortisone because of the risk of levothyroxine precipitating an adrenal crisis through enhanced clearance of cortisol.
  Replace thyroid hormones via IV levothyroxine and liothyronine.
- Hypernatremia
  Start desmopressin
  Replace free water deficit

Once stabilized, patients should be started on maintenance pituitary hormone replacement.

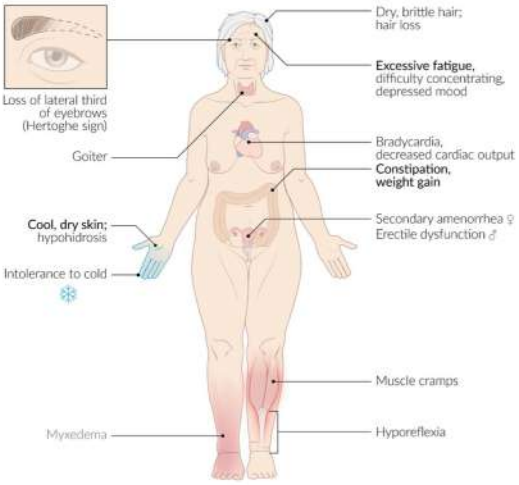
Hypopituitarism patients with TSH deficiency should not be treated with levothyroxine until ACTH deficiency has been ruled out and/or treated because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis.

	Patient Presentation	*Pathology*	*Dx*	*Tx*
Prolactinoma	F: Amenorrhea, Galactorrhea, Ø Vision Δs, Microadenoma M: Vision Δs, Macroadenoma	Dopamine Antagonists Hypothyroid Pituitary Tumor ↑Prolactin	1st: Prolactin Then: TSH/T4 Best: MRI	Start: Bromocriptine Best: Surgery when pregnancy, field cuts, medication failure
Acromegaly	Children: Gigantism Adults: Big hands, Big Feet, Big Heart and DM	↑GH	1st: Glucose Suppression Test Best: MRI	Start: Octreotide Best: Surgery
Hypopituitary	Acute: Coma, Lethargy, Hypotension Chronic: Less important go first	Infection, Infarction, Surgery, Radiation	1st: Glucose Stimulation Test Best: MRI	Start: Replace Missing Hormones
Sheehan's Apoplexy	Post-partum after a long labor Previous Tumor Bleeds, Stupor Nuchal Rigidity, Nausea/Vomiting	Tumor, Infiltration, Autoimmune		Best: Treat underlying disease if possible
Empty Sella Syndrome	Asx	Not pathological	1st and Best: MRI	Ø: Needs no treatment

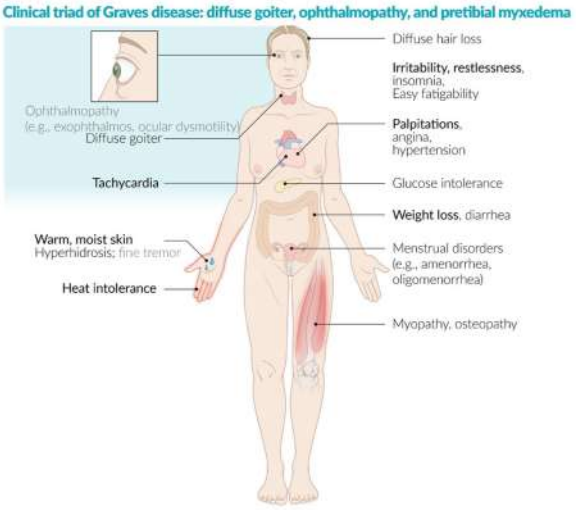
Thyroid disorders

- Identify common presentation of hypo/hyperthyroidism.

Hypothyroidism



Hyperthyroidism

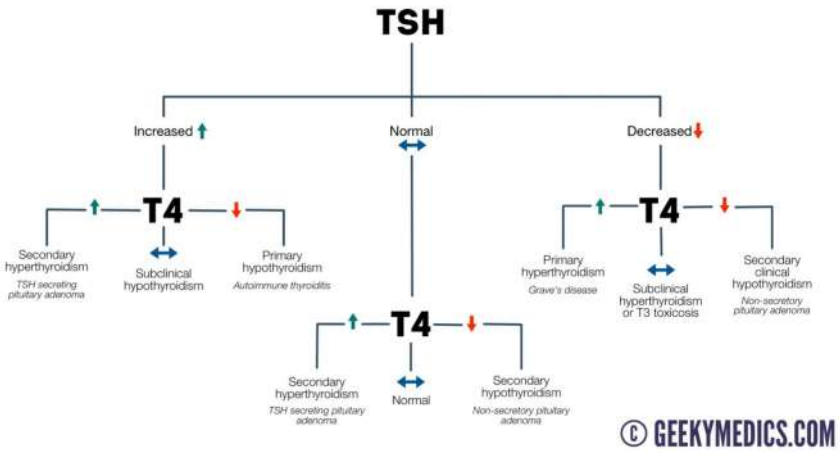


- To be able to interpretive thyroid function tests and initiate treatment.

Overview of thyroid function tests in thyroid disorders

		Etiology	Thyroid function tests		
			TSH level	Free T_4	Free T_3
Overt hypothyroidism	Primary hypothyroidism	• **Hashimoto thyroiditis** (most common cause) • Iatrogenic (e.g., following thyroidectomy or radioiodine therapy) • Antithyroid medication (e.g., amiodarone, lithium) • Transient hypothyroidism (e.g., silent thyroiditis, subacute granulomatous thyroiditis, postpartum thyroiditis)	• ↑	• ↓	
	Secondary hypothyroidism	• Pituitary disorders (e.g., pituitary adenoma) • Infiltrative diseases • Iatrogenic (e.g., following pituitary surgery)	• ↓		
	Tertiary hypothyroidism	• Hypothalamic disorders			
Subclinical hypothyroidism		• Asymptomatic • Same etiology as primary hypothyroidism	• Mildly ↑	• **Normal**	
Euthyroid sick syndrome	Low T_3 syndrome	• Occurs in severe illness or severe physical stress (most common in intensive care patients)	• Normal	• **Normal**	• ↓
	Low T_3 low T_4 syndrome			• ↓	
Primary hyperthyroidism		• **Graves disease** • Toxic MNG • Toxic adenoma (see "Thyroid nodules" and "Thyroid cancer") • Postpartum thyroiditis • Subacute granulomatous thyroiditis (de Quervain thyroiditis)	• ↓	• ↑	
Secondary hyperthyroidism		• Thyrotropic adenoma	• Normal/ ↑		
Subclinical hyperthyroidism		• Same etiology as primary hyperthyroidism	• ↓	• Normal	

https://geekymedics.com/thyroid-function-test-tft-interpretation/



Management of hypothyroidism

Frank hypothyroidism (Raised TSH, low FT4)

Replace with LT4

No evidence for additional benefit of T3 replacement

Aim to normalise TSH

Dose adjustment of LT4:
Pregnancy
Weight gain/loss
Concomitant medications (ferrous sulphate, antacids...etc...)

Subclinical hypothyroidism (TSH 4-10 mIU/l & normal FT4)

LT4 therapy recommended:
Detectable TPOAb
Undetectable TPOAb but patient symptomatic (trial of therapy)

Observe without treatment
Negative TPOAb and asymptomatic

Hypothyroid coma

Transfer patient to ICU setting

LT4 using NG tube or intravenously
No consensus regarding FT3 therapy

Supportive therapy
Steroid cover
Electrolytes/fluid
Antibiotics
Warming
Respiratory support

Management of hyperthyroidism

Medical

Control of symptoms

BB, CCB
Caution: asthma (BB)

Discontinue once euthyroid

Control of hyperthyroidism

Thionamides: Carbimazole, methimazole, propylthiouracil

Treatment can be given as titration or block & replace

Caution: AGRANULOCYTOSIS

Rarely: potassium iodide, potassium perchlorate, lithium

Outcome
Remission of GD in 50% of cases after 6-18 months treatment

RAI

Indicated for:
TMNG
GD (particularly relapsed disease)

Caution: pregnancy, TED, incontinence, breast feeding

Outcome
Euthyroid/hypothyroid in 90% after 1st dose

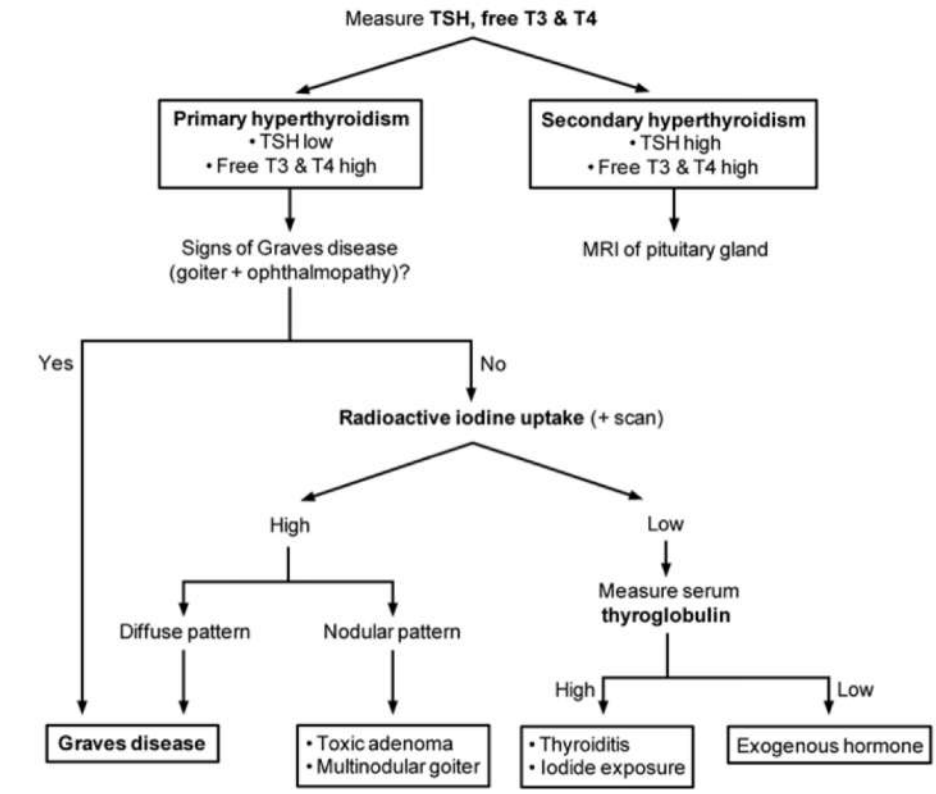
Surgery

Indicated for:
CI to medical therapy
Relapsed GD & TED
Large disfiguring goitre
Suspicious thyroid nodules
Patient preference

Caution: laryngeal nerve palsy, hypoparathyroidism bleeding

Outcome
Hypothyroidism
Possible hypocalcaemia (transient or permanent)

Evaluation of hyperthyroidism



©UWorld

Choice of treatment in Graves hyperthyroidism

Antithyroid drugs

- Mild hyperthyroidism
- Older age with limited life expectancy
- Preparation for radioactive iodine or thyroidectomy
- Pregnancy (PTU in 1st trimester)

Radioactive iodine

- Moderate to severe hyperthyroidism with/without mild ophthalmopathy
- Patient preference in mild hyperthyroidism

Thyroidectomy

- Very large goiter
- Suspicion of thyroid cancer
- Coexisting primary hyperparathyroidism
- Pregnant patients who cannot tolerate thionamides
- Severe ophthalmopathy
- Retrosternal goiter with obstructive symptoms

PTU = propylthiouracil.

©UWorld

- Outline the treatment of myxedema coma and thyroid storm.

1. Myxedema Coma

- A rare condition that presents with:
  - depressed state of consciousness
  - profound hypothermia
  - respiratory depression
- May develop after years of severe untreated **hypothyroidism**
- Precipitating factors are trauma, infection, cold exposure, and narcotics.
- a medical emergency, with a high mortality rate (50% to 75%) even with treatment
- Provide supportive therapy to maintain BP and respiration. Give **IV thyroxine** and **hydrocortisone** while carefully monitoring the hemodynamic state.

2. Thyroid Storm

- This is a rare, life-threatening complication of thyrotoxicosis characterized by an acute exacerbation of the manifestations of **hyperthyroidism**.
- There is usually a precipitating factor, such as infection, diabetic ketoacidosis (DKA), or stress (e.g., severe trauma, surgery, illness, childbirth).
- High mortality rate: up to 20% of patients enter a coma or die.
- Clinical manifestations include marked fever, tachycardia, agitation or psychosis, confusion, and GI symptoms (e.g., nausea, vomiting, diarrhea).
- Provide **supportive therapy** with IV fluids, cooling blankets, and glucose.
- Give **antithyroid agents** (PTU every 2 hours). Follow with iodine to inhibit thyroid hormone release.
- Administer **β-blockers** for control of heart rate.
- Give **dexamethasone** to impair peripheral generation of T3 from T4 and to provide adrenal support.

Give stress dose steroids prior to thyroid repletion to prevent causing adrenal crisis

Adrenal gland disorders

- Recognize the clinical features findings of patients with adrenal insufficiency and crisis.

Adrenal insufficiency

1. Lack of cortisol

a. GI symptoms—anorexia, nausea and vomiting, vague abdominal pain, weight loss
b. Mental symptoms—lethargy, confusion, psychosis.
c. Hypoglycemia—Cortisol is a gluconeogenic hormone.
d. Hyperpigmentation
• This is a common finding in primary adrenal insufficiency; not seen in secondary adrenal insufficiency because in secondary adrenal insufficiency ACTH levels are low, not high.
• Low cortisol stimulates ACTH and MSH secretion.
e. Intolerance to physiologic stress is a feared complication.

2. Low aldosterone (only seen in primary adrenal insufficiency because aldosterone depends on the renin–angiotensin system, not ACTH). Results in:

a. Sodium loss, causing hyponatremia and hypovolemia, which may lead to: • Hypotension, decreased cardiac output, and decreased renal perfusion. • Weakness, shock, and syncope.
b. Hyperkalemia (due to retention of potassium).

Hyperpigmentation and hyperkalemia appear in primary, not secondary, adrenal insufficiency.

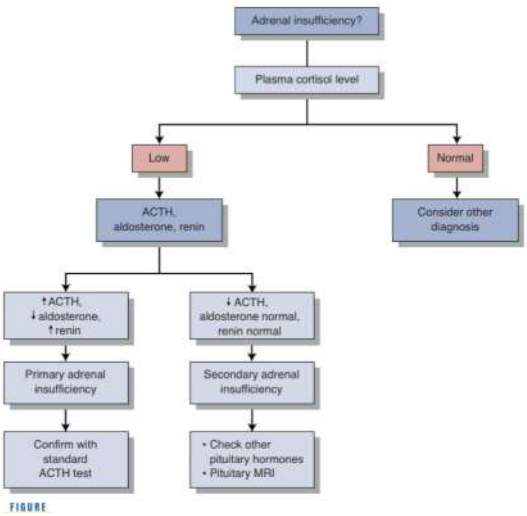
- Recall the fundamental investigations and management of adrenal insufficiency.

❖ **Diagnosis:**

1. Decreased plasma cortisol level
2. Plasma ACTH level—if low, this implies a secondary adrenal insufficiency (ACTH-dependent cause).
3. Standard ACTH test.
    a. This is a definitive test for primary adrenal insufficiency; give an IV infusion of synthetic ACTH, and measure plasma cortisol at the end of the infusion.
    b. In primary adrenal insufficiency, cortisol does not increase sufficiently.
    c. In secondary adrenal insufficiency, cortisol fails to respond to ACTH infusion,as in primary adrenal insufficiency (the adrenals are not used to being stimulated, so they do not respond right away). If the test is repeated for 4 or 5 days, the adrenals eventually respond normally.
4. Perform imaging tests (MRI of brain—pituitary/hypothalamus) if secondary or tertiary adrenal insufficiency is diagnosed.

❖ **Treatment:**

1. Primary adrenal insufficiency: daily oral glucocorticoid (hydrocortisone or prednisone) and daily fludrocortisone (mineralocorticoid).
2. Secondary adrenal insufficiency: same as in primary adrenal insufficiency, except that mineralocorticoid replacement is not necessary.



FIGURE

Primary adrenal insufficiency	
Etiology	• **Autoimmune adrenalitis** (most common) • Infection (eg, tuberculosis) • Metastatic infiltration
Clinical features	• Fatigue, weakness, anorexia/weight loss • Nausea, vomiting, abdominal pain • Salt craving, postural hypotension • Hyperpigmentation • **Acute adrenal crisis:** confusion, hypotension/shock
Laboratory findings	• Hyponatremia, hyperkalemia, eosinophilia • Low morning cortisol, high ACTH
Treatment	• Glucocorticoids (eg, hydrocortisone, prednisone) • Mineralocorticoids (eg, fludrocortisone)

Primary versus central adrenal insufficiency		
	Primary	**Central (secondary/pituitary; tertiary/hypothalamic)**
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

- To understand the pathophysiology of Cushing's syndrome and to apply diagnostic approach and basics of management.

❖ general characteristics

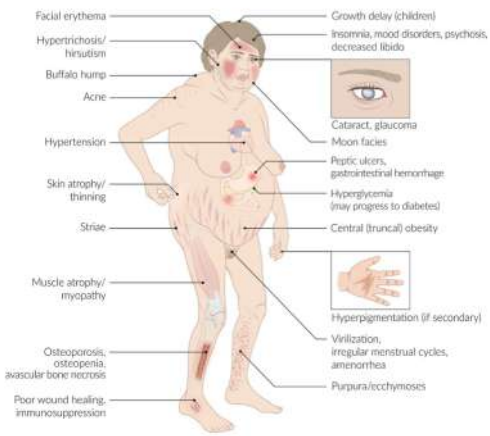
1. Cushing syndrome results from excessive levels of glucocorticoids (cortisol is the principal glucocorticoid) due to any cause.
2. Cushing disease results from pituitary Cushing syndrome (pituitary adenoma).

❖ Causes

1. Iatrogenic Cushing syndrome is the most common cause, and is due to prescribed prednisone or other steroids. Androgen excess is absent (because the exogenous steroid suppresses androgen production by the adrenals).
2. ACTH-secreting adenoma of the pituitary (Cushing disease) is the second most common cause and leads to bilateral adrenal hyperplasia. Androgen excess is common.
3. Adrenal adenomas and carcinomas (10% to 15%).
4. Ectopic ACTH production (10% to 15%).
    a. ACTH-secreting tumor stimulates the cortisol release from the adrenal glands without the normal negative feedback loop (because the source of the ACTH is outside the pituitary gland).
    b. More than two-thirds are small cell carcinomas of the lung. Bronchial carcinoid and thymoma may be the cause.

❖ Clinical features

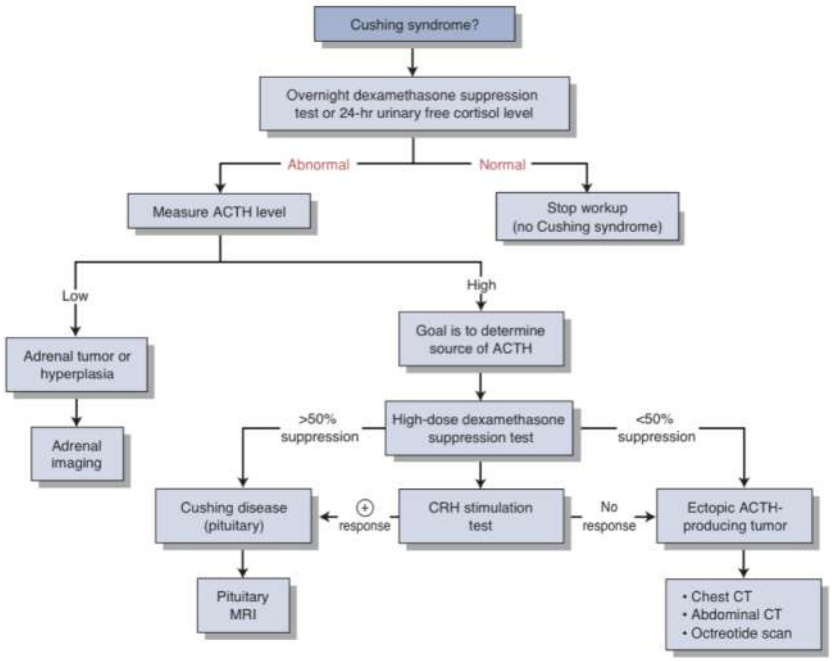
1. Changes in appearance: central obesity, hirsutism, moon facies, "buffalo hump," purple striae on abdomen, lanugo hair, acne, easy bruising
2. HTN
3. Decreased glucose tolerance (diabetes)
4. Hypogonadism—menstrual irregularity and infertility
5. Masculinization in females (androgen excess, see Figure 4-5)—only seen in ACTH-dependent forms
6. Musculoskeletal—proximal muscle wasting and weakness (due to protein catabolism), osteoporosis, aseptic necrosis of femoral head may occur (especially with exogenous steroid use)
7. Psychiatric disturbances—depression, mania
8. Increased likelihood of infections



Effects of cortisol (Generally catabolic)
- Impaired collagen production, enhanced protein catabolism
- Anti-insulin effects(leading to glucose intolerance)
- Impairedimmunity(has inhibitory effects on PMNs, T cells)
- Enhances catecholamine activity (HTN)

❖ **Diagnosis:**

1. Initial screening
    a. An overnight (low-dose) dexamethasone suppression test is the initial screening test. Give the patient 1 mg of dexamethasone at 11 pm. Measure the serum cortisol level at 8 am.
        • If the serum cortisol is <5, Cushing syndrome can be excluded (this test is very sensitive).
        • If the serum cortisol is >5 (and often >10), the patient has Cushing syndrome. Order a high-dose dexamethasone suppression test to determine the cause (Cushing disease vs. adrenal tumor vs. ectopic ACTH tumor).
    b. The 24-hour urinary free cortisol level is another excellent screening test; values greater than four times normal are rare except in Cushing syndrome.
2. ACTH level—Once you establish a diagnosis of Cushing syndrome, measure the ACTH level. If it is low, the cause of high cortisol levels is likely an adrenal tumor or hyperplasia, not a pituitary disease or an ectopic ACTH-producing tumor.
3. High-dose dexamethasone suppression test.
    a. In Cushing disease, the result is a decrease in cortisol levels (greater than 50% suppression occurs).
    b. If cortisol suppression does not occur and plasma ACTH levels are high, an ectopic ACTH-producing tumor is likely the diagnosis.
4. CRH stimulation test—CRH is administered intravenously.
    a. If ACTH/cortisol levels increase (deemed a "response"), then Cushing disease is the diagnosis.
    b. If ACTH/cortisol levels do not increase (deemed "no response"), then the patient has either ectopic ACTH secretion or an adrenal tumor.
5. Imaging tests (once hormonal studies have established the site of disease, e.g.,pituitary or adrenal)—CT scan or MRI of the appropriate area.



❖ **Treatment:**

Exogenous Cushing syndrome
Consider lowering the dose of glucocorticoids
Consider the use of alternatives to glucocorticoids (e.g., azathioprine)

Endogenous Cushing syndrome

- Inoperable disease: (e.g., inoperable adrenal carcinomas, advanced small cell carcinoma of the lung): drugs to suppress cortisol synthesis; (e.g., metyrapone, mitotane, ketoconazole)
- Operable disease: Surgical therapy is the treatment of choice.

- Adrenocortical tumor: laparoscopic or open adrenalectomy (a surgical procedure to remove one or both adrenal glands)
- Pituitary adenoma: transsphenoidal resection of the pituitary adenoma
- ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid)

Patients who develop severe hypokalemia due to the mineralocorticoid effect of cortisol may be treated with spironolactone (aldosterone antagonist).

Following surgical therapy, patients who develop adrenal insufficiency require lifelong glucocorticoid replacement therapy.

- To understand clinical presentation of Pheochromocytoma and to apply diagnostic approach and basics of management

❖ general characteristics

1. Pheochromocytomas are rare tumors that produce, store, and secrete catecholamines.
2. Ninety percent found in adrenal medulla (10% extra-adrenal).
3. Curable if diagnosed and treated, but may be fatal if undiagnosed.
4. Arise from the chromaffin cells of the adrenal medulla or from the sympathetic ganglia if extra-adrenal.

❖ Clinical features

1. HTN—BP is persistently high, with episodes of severe HTN (paroxysmal).
2. Severe pounding headache
3. Inappropriate severe sweating
4. Tachycardia
5. Palpitations, with sudden severe HTN
6. Anxiety
7. Feeling of impending doom

Laboratory findings: hyperglycemia, hyperlipidemia, hypokalemia

❖ Diagnosis

1. Urine screen—test for the presence of the following breakdown products of catecholamines:
    a. Metanephrine
    b. Vanillylmandelic acid, homovanillic acid, normetanephrine
2. Plasma metanephrines have been proposed by some investigators as a superior test to urine metanephrines, especially when clinical suspicion is high
3. Urine/serum epinephrine and norepinephrine levels—if the epinephrine level is elevated, the tumor must be adrenal or near the adrenal gland (organ of Zuckerkandl) because nonadrenal tumors cannot methylate norepinephrine to epinephrine
4. Tumor localization tests—CT, MRI

❖ Treatment

Surgical tumor resection with early ligation of venous drainage is the treatment of choice.
Ligation lowers the possibility of catecholamine release/crisis by tying off drainage. Patients should be treated with α-blockade (typically phenoxybenzamine) for 10 to 14 days prior to surgery as well as β-blockade (i.e., propranolol) for 2 to 3 days prior to surgery. The α-blockade is used to control BP, and the β-blockade is used to decrease tachycardia. Laparoscopic adrenalectomy can be safely performed for most small- to medium-sized pheochromocytomas.

Pheochromocytoma	
Indications for testing	• Classic triad: episodic headache, sweating & tachycardia • Resistant HTN or HTN accompanied by unexplained ↑ glucose • Family history or familial syndrome (eg, MEN2, NF1, VHL)
Diagnostic approach	• Urine or plasma metanephrine levels • Confirmatory abdominal imaging for ↑ metanephrines
Notable features	• 10% bilateral, 10% extraadrenal, 10% malignant
Management	• Preoperative alpha blockade prior to beta blockade • Laparoscopic or open surgical resection

Diabetes and DKA

- Understand different types of diabetes and modalities of diagnosis and treatment.

❖ general characteristics

1. Classification
    a. Type I IDDM—approximately 5% of all diabetic patients.
        • This is characterized by a severe deficiency of insulin. Patients require insulin to live.
        • The onset is typically in youth (before age 20), but can occur at any age.
        • Not related to obesity.
    b. Type II NIDDM—90% or more of all diabetic patients.
        • Insulin levels are usually normal to high but may diminish over many years of having diabetes.
        • Insulin resistance (due to obesity) plays a major role.
        • It often goes undiagnosed for many years.

TABLE 4-3 Comparison of Type I and II Diabetes Mellitus

	Type I	Type II
Onset	Sudden	Gradual
Age at Onset	Any age (typically young)	Mostly in adults
Body Habitus	Usually thin	Frequently obese
Ketosis	Common	Rare
Autoantibodies	Present in most cases	Absent
Endogenous Insulin	Low or absent	Can be normal, decreased, or increased
HLA Association	**Yes (HLA-DQ/DR)**	**No**
Genetic Factors	Concordance rate between identical twins is 50%	Concordance rate between identical twins is 90%. Therefore, type II demonstrates a much stronger genetic component than type I.

Screening and Diagnosing Diabetes

Random Glucose
Normal < 200
Diabetes ≥ 200
Must have symptoms of diabetes

Fasting Glucose
Normal < 100
Prediabetes 100-124
Diabetes ≥ 125
Must have two readings to confirm

2-Hour Glucose Tolerance Test
Normal < 140
Prediabetes 140-199
Diabetes ≥ 200
Indicated when prediabetes is found on fasting

A1c
Normal < 5.7
Prediabetes 5.7-6.4
Diabetes ≥ 6.5
May miss early disease, do not use in gestational

❖ Treatment

1. Diet and exercise should ideally be the only interventions in most type II diabetic patients.
    a. Diet and exercise are especially effective in obese and sedentary patients (who constitute the majority of type II diabetic patients).
    b. Most patients, however, do not lose enough weight to control glucose levels through diet and exercise alone, and will require pharmacologic treatment.
    c. Glycemic control minimizes risks for nephropathy, neuropathy, and retinopathy in both Type 1 and 2 DM, and decreases risk for cardiovascular disease for Type 1 DM.

2. Oral hypoglycemic drugs
    a. Use these in type II diabetic patients when conservative therapy (diet and exercise) fails.
    b. Start with one agent (metformin is best initial drug therapy). If monotherapy fails, use two agents from different classes in combination. Each agent has advantages and disadvantages, so clinical judgment is required in selecting the initial agent.
    c. Metformin blocks gluconeogenesis. It is contraindicated in patients with renal failure.
    Other oral hypoglycemics include:
        - Sulfonylureas
        - Thiazolidinediones (glitazones)
        - Alpha glucosidase inhibitors (acarbose, miglitol)
        - Incretins
        - Pramlintide
        - Repaglinide/nateglinide

Insulin Versus oral Hypoglycemic agents in type II diabetes:
- If The Patient Has Severe hyperglycemia (fasting glucose >240 mg/dL), insulin typically is the agent of choice (whether type I or type II disease).
- Oral Hypoglycemic agents are effective in type II disease with moderate hyperglycemia (fasting glucose between 140 and 240 mg/dL).

Aspects of treatment	Approach
Individual treatment targets	• Blood glucose control and regular glycemic monitoring: A1C values • Weight loss: Type 2 diabetic patients with a BMI of 27–35 benefit from a weight reduction of 5%; in patients with a BMI > 35 kg/m^2, weight reduction of > 10% is recommended. • Blood pressure control • Improved blood lipid profile with statin therapy • Low dose aspirin for men > 50 years and women > 60 years with cardiovascular risk factors

Lifestyle modification	• ↑ Physical activity → ↓ blood glucose and ↑ insulin sensitivity
	• Smoking cessation
	• Balanced diet and nutrition
	  ◦ Small, frequent meals
	  ◦ Diet: ~ 55% carbohydrates (replace simple carbohydrates such as glucose and sucrose with complex carbohydrates), 30% fat, 15% protein
	  ◦ High-fiber diet
	  ◦ Alcohol should (if possible) be consumed with carbohydrates to avoid hypoglycemia.

Self-management education	• DSME/S programs
Medical treatment	• Oral antidiabetic drugs (see below) • Insulin therapy (see below) • Patients with prediabetes usually do not require medical treatment but do benefit from a healthy diet, weight loss, and exercise.
Monitoring complications	• Regular monitoring of weight, abdominal circumference, blood pressure, blood lipids, renal retention parameters (creatinine, electrolytes), injection site in patients receiving insulin therapy • Yearly eye exam (type 1: after 5 years with diabetes mellitus or after the age of 11 years); more frequently in patients with abnormal findings or diagnosed retinopathy • Annual urine testing for **microalbuminuria** • Foot exam for neuropathy and ulcers; advise patients to wear appropriate footwear and avoid injury • Routine screening for psychosocial problems, including signs of depression and cognitive impairment • Pneumococcal vaccines

Antihyperglycemic therapy algorithm for type 2 diabetes

- **HbA1C target for adults: < 7%** (53 mmol/mol)
- The guidelines for the treatment of DM recommend an individualized treatment strategy.
- If the target A1C is not reached within 3 months with conservative measures (e.g., diet, exercise), the next step in the therapeutic algorithm should be initiated.

Treatment algorithm	Description
General measures	Weight reduction, exercise , medical nutrition therapy, self-management education
Monotherapy	The drug of choice is **metformin**.

Dual therapy	• Metformin +
	  ◦ A second oral antidiabetic drug: dipeptidyl peptidase-4 inhibitor, sulfonylureas, thiazolidinedione, meglitinides, SGLT-2 inhibitors, alpha-glucosidase inhibitors, amylin analogs
	  ◦ GLP-1 receptor agonists (incretin mimetics)
	  ◦ Basal insulin

Triple therapy	Add a third oral antidiabetic drug, nightly basal insulin, or injectable GLP-1 receptor agonist
Combination injectable therapy	Metformin + basal insulin + mealtime insulin or GLP-1 receptor agonist
Only consider the substitution of drugs in cases in which the drug is not tolerated or side effects occur.	

❖ **Indications for insulin therapy**

- Newly diagnosed patients with significantly elevated A1C levels (> 8.5%) or symptomatic diabetes: Initiate insulin therapy with or without an antidiabetic drug.
- Patients with insufficient glycemic control (target A1C not reached) over a 3-month treatment period with metformin or another antidiabetic drug:

  Initiate basal insulin supported oral therapy (BOT).

Consider initiating insulin therapy.

- Pregestational and gestational diabetes
- Patients with end stage renal failure (oral antidiabetic drugs are contraindicated in this case)

Principles of insulin therapy

Total daily requirement of insulin	• On average, the body requires 40 USP units of insulin daily. • 20 units for basic metabolism → basal insulin • 20 units for calorie consumption → bolus insulin
Insulin correction factor	• 1 unit of insulin lowers the blood glucose level by 30–40 mg/dL (1.7–2.2 mmol/L)
Carbohydrate counting	• 10 g of carbohydrates increases the blood glucose level by 30–40 mg/dL (1.7–2.2 mmol/L).
Insulin-to-carbohydrate ratio	• On average, 1 unit of insulin is required for 15 g carbs = 1 carb serving (carb unit); however, this varies greatly from patient to patient. • Insulin sensitivity fluctuates over the course of a day → Insulin-to-carbohydrate ratio changes over the course of a day. ◦ Morning hours: 2 units insulin, lunchtime: 1 unit, evening hours: 1.5 units
Type 1 diabetes	• Insulin replacement therapy: The exogenous insulin requirement depends on the residual insulin production of the pancreas. • The initial total daily dose (TDD) of insulin should be 0.6–1.0 U/kg. • After beginning insulin treatment, there is often a temporary reduction in exogenous insulin demand.
Type 2 diabetes	• Residual endogenous insulin production is augmented with exogenous insulin, depending on the extent of insulin resistance (which in turn depends on the level of obesity). • The TDD of insulin should be 0.1–0.2 U/kg.

Drug	Mechanism	Side Effects	Contraindications
Metformin (first-line)	Inhibits hepatic gluconeogenesis and ↑ peripheral sensitivity to insulin	Weight loss, GI upset, and rarely, lactic acidosis	Contraindicated in the elderly (age > 80 years) and in renal insufficiency, hepatic failure, or heart failure
Sulfonylureas (glipizide, glyburide, glimepiride)	↑ Endogenous insulin secretion	Hypoglycemia and weight gain	
Thiazolidinediones (rosiglitazone, pioglitazone)[a]	↑ Insulin sensitivity	Weight gain, edema, hepatotoxicity, and bone loss	Contraindicated in patients with heart failure
DPP-4 inhibitors (sitagliptin, linagliptin, and other -liptins)	Inhibit degradation of GLP-1; ↑ insulin secretion and ↓ glucagon secretion	Weight neutral	
Incretins (exenatide, liraglutide, and other -tides)	GLP-1 agonists. Delay absorption of food; ↑ insulin secretion and ↓ glucagon secretion	Injected subcutaneously. Slow GI motility, nausea, and, rarely, pancreatitis. Can cause weight loss	
SGLT2 inhibitors (dapagliflozin and other -flozins)	Inhibit SGLT2 in proximal tubule to ↓ glucose reabsorption	UTIs, vulvovaginal candidiasis. Can cause weight loss and ↓ blood pressure	
α-glucosidase inhibitors (acarbose, miglitol)	↓ Intestinal absorption of carbohydrates	Flatulence, diarrhea, and hypoglycemia	
Insulin	Given alone or in conjunction with oral agents. Types of insulin include regular, short-acting (lispro, aspart, glulisine), NPH, long-acting (detemir, glargine), and combination preparations (longer + shorter-acting agents like 70 NPH/30 regular)	Weight gain and hypoglycemia	

Drug	*Class*	*Use*	*When*
Lantus **L**evemir	**L**ong Acting Insulin	**Basal insulin**	qPM
Huma**Log** Novo**Log**	**Rapid** acting Insulin Combo	**Prandial Insulin**	qAC
Humu**Lin** Novo**Lin**	**Medium** acting Insulin Combo (old school, easy)	**Idiot Insulin**	biD
NPH	Rapid Acting	Prandial	qAC
Regular	Rapid Acting	Generally useless	

Understand the pathophysiology of diabetic ketoacidosis.

Diabetic ketoacidosis (DKA)
DKA primarily affects patients with type 1 diabetes.

- **Osmotic diuresis and hypovolemia**

1. Insulin normally elevates cellular uptake of glucose from the blood.
2. In the insulin-deficient state of DKA, hyperglycemia occurs.
3. Hyperglycemia, in turn, leads to progressive volume depletion via osmotic diuresis.

Insulin deficiency → hyperglycemia → hyperosmolality → osmotic diuresis and loss of electrolytes → hypovolemia

- **Metabolic acidosis with increased anion gap**

1. Insulin deficiency also increases fat breakdown (lipolysis).
2. Metabolic acidosis develops as the free fatty acids generated by lipolysis become ketones, two of which are acidic (acetoacetic acid and beta-hydroxybutyric acid).
3. Serum bicarbonate is consumed as a buffer for the acidic ketones.
4. Metabolic acidosis with an elevated anion gap is therefore characteristic of DKA.

Insulin deficiency → ↑ lipolysis → ↑ free fatty acids → hepatic ketone production (ketogenesis) → ketosis → bicarbonate consumption (as a buffer) → anion gap metabolic acidosis
DKA is an important cause of anion gap metabolic acidosis with respiratory compensation.

- **Intracellular potassium deficit**

1. As a result of hyperglycemic hyperosmolality, potassium shifts along with water from inside cells to the extracellular space and is lost in the urine.
2. Insulin normally promotes cellular potassium uptake but is absent in DKA, compounding the problem.
3. A total body potassium deficit develops in the body, although serum potassium may be normal or even paradoxically elevated.

Insulin deficiency → hyperosmolality → K+ shift out of cells + lack of insulin to promote K+ uptake → intracellular K+depleted → total body K+ deficit despite normal or even elevated serum K+

There is a total body potassium deficit in DKA. This becomes important during treatment, when insulin replacement leads to rapid potassium uptake by depleted cells and patients may require potassium replacement.

Hypovolemia resulting from DKA can lead to acute kidney injury (AKI) due to decreased renal blood flow! Hypovolemic shock may also develop.

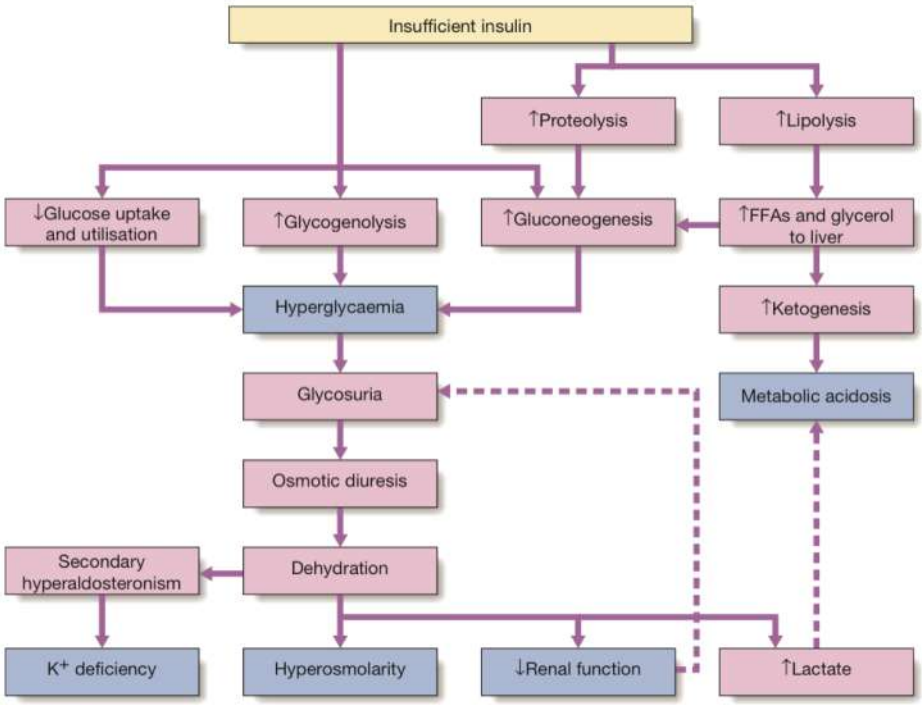


Fig. 11.1 Acute metabolic complications of insulin deficiency. (FFAs = free fatty acids)

- Know the key points in the treatment of diabetic ketoacidosis.

Emergency Box 15.1

Management of diabetic ketoacidosis

Phase I management

- Fluid replacement: 0.9% sodium chloride. An average regimen would be 1 L in 30 minutes, then 1 L in 1 hour, then 1 L in 2 hours, then 1 L in 4 hours, then 1 L in 6 hours.
- Insulin: soluble insulin by intravenous infusion. A typical starting dose would be 6 units/h (or 0.1 units/kg). Aim for fall in blood glucose of approx. 5 mmol/h.
- Add KCl to 0.9% sodium chloride depending on results of blood K measurement. Temporarily delay if serum potassium >5.0 mmol/L. Add 10 mmol/L if serum potassium is 3.5–5.0 mmol/l and 20 mmol if potassium is <3.5 mmol/L. Do not routinely administer at rate of >20 mmol/h.

IF:

- Blood pressure below 80 mmHg, give plasma expander (colloid, p. 331).
- If pH below 7.0, consider 500 mL of sodium bicarbonate 1.26% plus 10 mmol KCl over 1 hour. Bicarbonate should only be given under senior supervision and some guidelines do not advocate its use.

Phase 2 management

- When blood glucose falls to <14 mmol/L, reduce NaCl and add in 10% glucose with 20 mmol KCl at 100 mL/h. Continue insulin (necessary to switch off ketogenesis) with dose adjusted according to hourly blood glucose test results (e.g. i.v. 3 units/h glucose 15 mmol/L; 2 units/h when glucose 10 mmol/L).

Phase 3 management

- Once stable and able to eat and drink normally, transfer patient to four-times-daily s.c. insulin regimen (based on previous 24 hours insulin consumption, and trend in consumption). Overlap s.c. insulin with insulin infusion by 30 minutes.

Special measures

- Broad-spectrum antibiotic if infection likely
- Bladder catheter if no urine passed in 2 hours
- Nasogastric tube if drowsy or protracted vomiting
- Consider CVP monitoring if shocked or if previous cardiac or renal impairment.
- Consider s.c. prophylactic heparin in comatose, elderly or obese patients.

Monitoring

- Vital signs, volume of fluid given and urine output hourly
- Finger-prick glucose hourly for 8 hours
- Laboratory glucose and electrolytes 2-hourly for 8 hours, then 4–6 hourly, adjust K replacement according to results.

CVP, central venous pressure.

Note: The regimen of fluid replacement set out above is a guide for patients with severe ketoacidosis. Excessive fluid can precipitate pulmonary and cerebral oedema; adequate replacement must therefore be tailored to the individual and monitored carefully throughout treatment.

- Recall long-term complication of diabetes, rule of screenings and basic of management

Complication	Description
Retinopathy (nonproliferative, proliferative)	Appears when diabetes has been present for at least 3–5 years (see Figure 2.3-2). Preventive measures include control of hyperglycemia and hypertension, annual eye exams, anti-VEGF (nonproliferative), and laser photocoagulation therapy (focal for nonproliferative vs panretinal for proliferative)
Diabetic nephropathy	Characterized by glomerular hyperfiltration followed by microalbuminuria, macroproteinuria, and progression to CKD. Seen in patients with diabetes for > 10 years. Preventive measures include ACEIs or ARBs. BP control more effective than glucose control. Kimmelstiel-Wilson nodules seen on kidney biopsy
Neuropathy	Peripheral nerves: Most common neuropathy. Symmetric sensorimotor polyneuropathy leading to burning pain, foot trauma, infections, and ulcers Small fiber neuropathy: Pain and paresthesia Large fiber neuropathy: Absence of sensation Ischemic CN III damage: down-and-out eye, ptosis, diplopia, with preserved pupil response Treat with preventive foot care and analgesics (amitriptyline, gabapentin, NSAIDs). Monofilament testing predicts ulcer risk GI: Gastroparesis with delayed gastric emptying. Treat with metoclopramide or erythromycin. Can also get esophageal dysmotility, diarrhea/constipation GU: Neurogenic bladder with decreased sensation to void, overflow incontinence, high postvoid residuals. Can also have erectile dysfunction Cardiovascular: Orthostatic hypotension
Macrovascular complications	Cardiovascular, cerebrovascular, and peripheral vascular disease. Cardiovascular disease is the most common cause of death in diabetic patients. See Table 2.3-2 for risk modification guidelines

Complication	*Screen*	*Treatment*
Retinopathy	Retina Exam	Laser
Nephropathy	Microalb/Crea	Ace-inhibitor
Neuropathy	Monofilament	Gabapentin

- Screen for microalbuminuria at least once per year in diabetic patients with no evidence of nephropathy. Prescribe ACE inhibitor or ARB if urine test is positive for microalbuminuria.
- Check BUN and creatinine level at least once per year.
- Order eye screening yearly by an ophthalmologist to screen for diabetic retinopathy.
- Check the feet at every visit. Refer high-risk patients to a foot care specialist (e.g., podiatrist). Patients should check their feet regularly for ulcers and neuropathy.

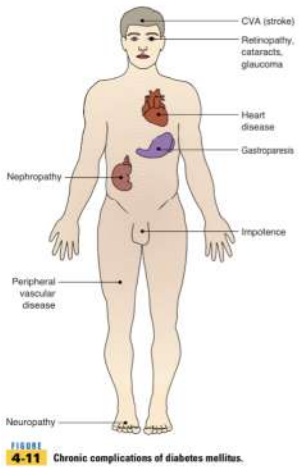
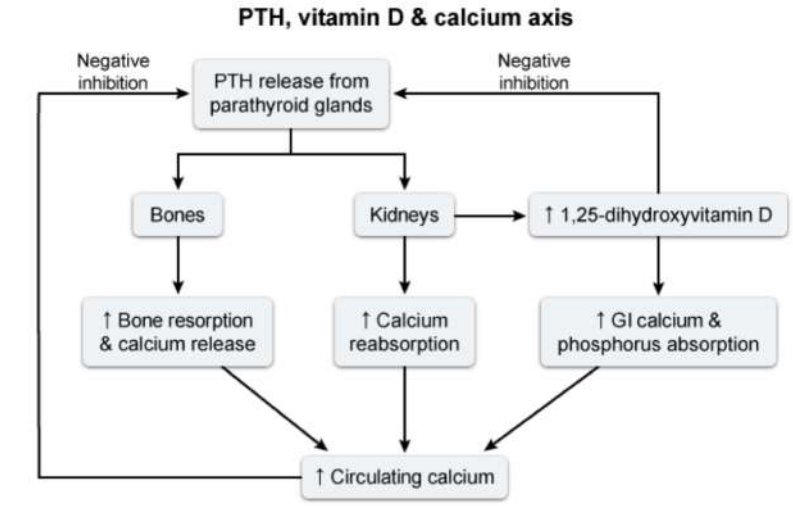


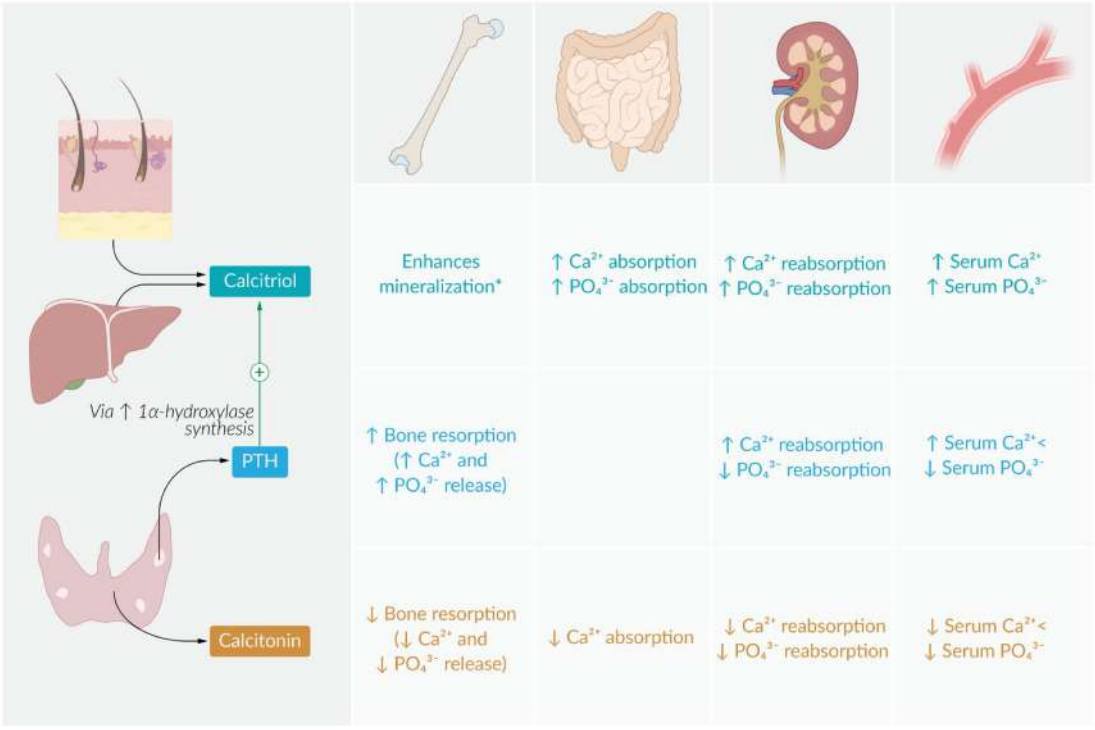
FIGURE 4-11 Chronic complications of diabetes mellitus.

Parathyroid bone disorders

- Understand the calcium homeostasis in relation to parathyroid hormone and vitamin D.



GI = gastrointestinal; PTH = parathyroid hormone.



- Recognize the clinical features findings of patients with hypercalcemia, recall common causes and apply diagnostic approach

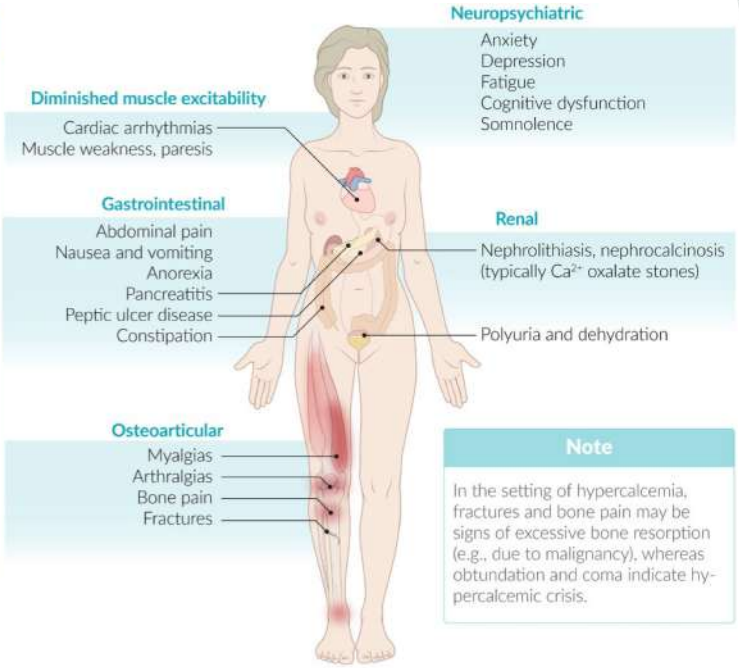
Hypercalcemia

Definition
Mild hypercalcemia: total serum Ca^{2+} > 10.5 mg/dL or ionized Ca^{2+} > 5.25 mg/dL
Severe hypercalcemia: total Ca^{2+} > 14 mg/dL or ionized Ca^{2+} > 10 mg/dL

Etiology
High PTH: hyperparathyroidism (1st–3rd degree), FHH
Low PTH: malignancies, granulomatous disorders
Other: medications (e.g., thiazide diuretics)

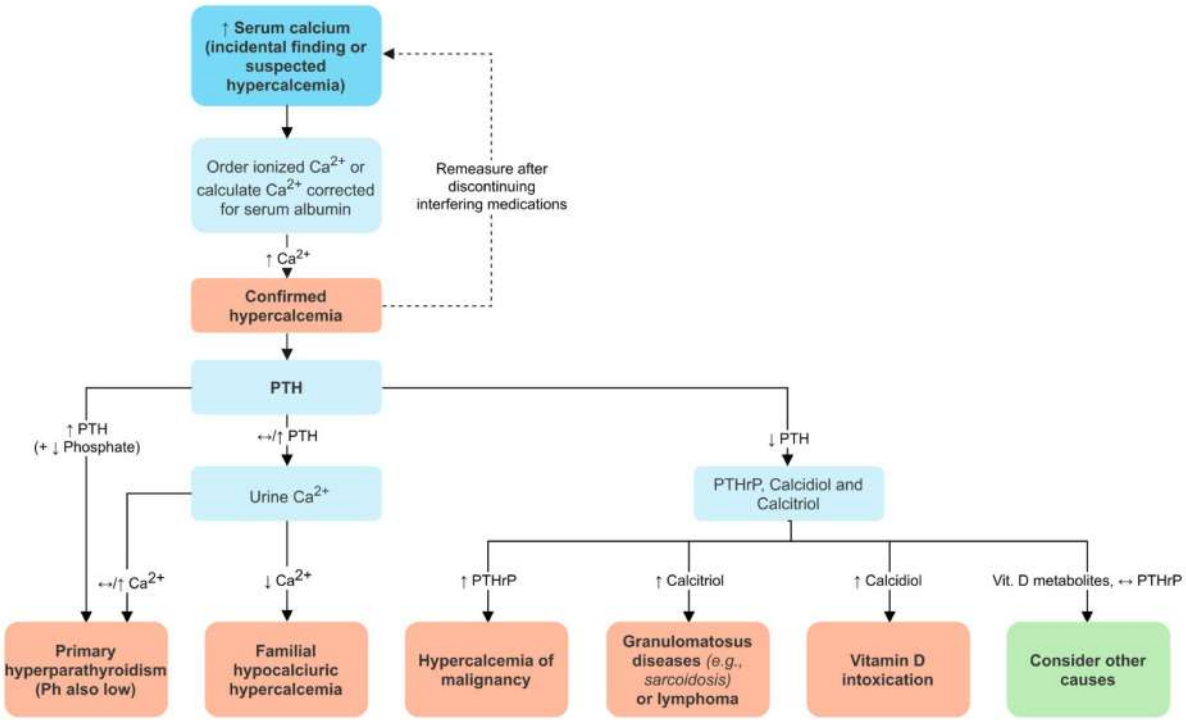
Diagnosis
Ionized Ca^{2+} or corrected serum Ca^{2+}
Serum intact PTH
ECG (e.g., QT interval shortening, J waves)
Bone evaluation

Treatment
Treat underlying conditions
Provide hydration, reduce calcium intake
Severe hypercalcemia: IV saline and/or calcitonin
Hypercalcemic crisis: forced diuresis after volume replacement



Note

In the setting of hypercalcemia, fractures and bone pain may be signs of excessive bone resorption (e.g., due to malignancy), whereas obtundation and coma indicate hypercalcemic crisis.



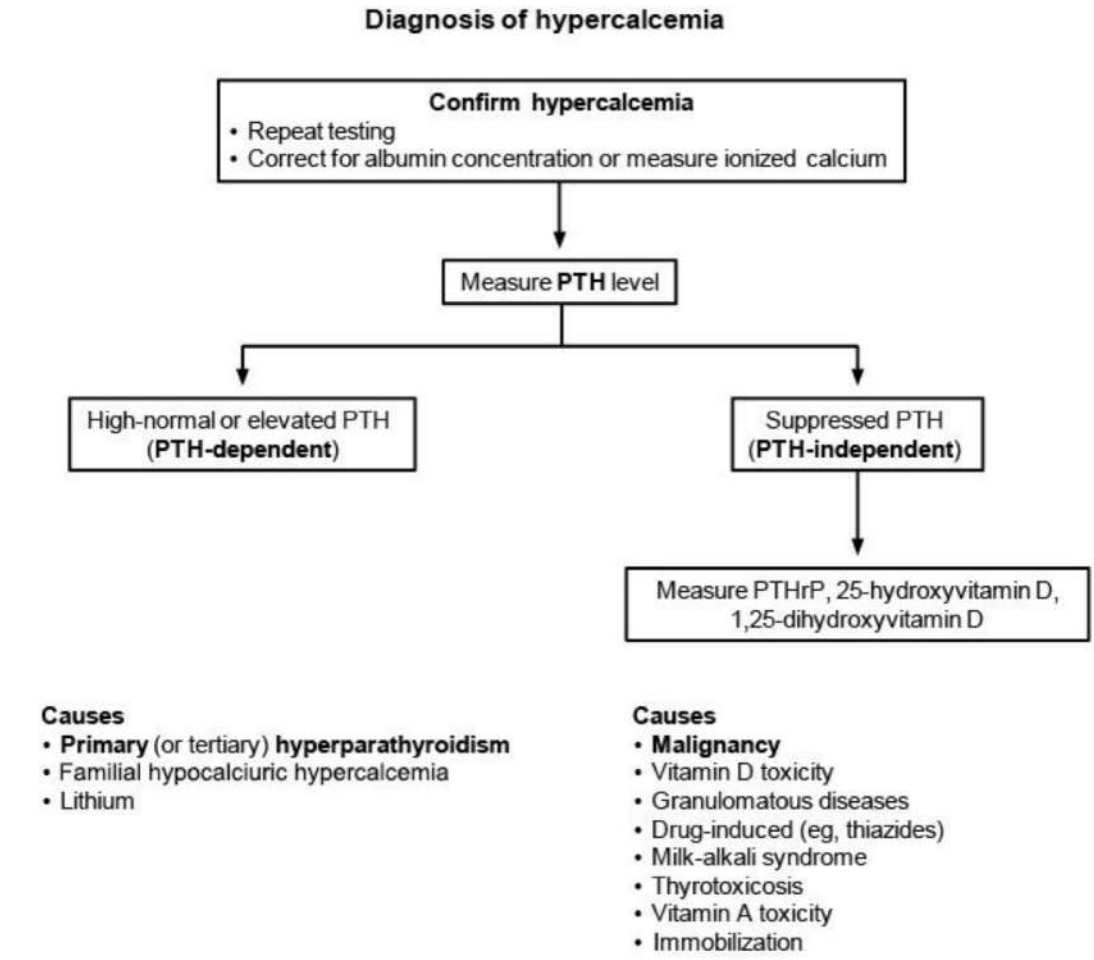
❖ **Causes:**

1. Endocrinopathies
    a. Hyperparathyroidism—increased Ca^{2+}, low PO_4^{3-}
    b. Renal failure—usually results in hypocalcemia, but sometimes secondary hyperparathyroidism elevates PTH levels high enough to cause hypercalcemia
    c. Paget disease of the bone—due to osteoclastic bone resorption
    d. Hyperparathyroidism, acromegaly, Addison disease
2. Malignancies
    a. Metastatic cancer—bony metastases result in bone destruction due to osteoclastic activity. Most tumors that metastasize to bone cause both osteolytic and osteoblastic activities (prostate cancer, mainly osteoblastic; kidney carcinoma, usually osteolytic)
    b. Multiple myeloma—secondary to two causes
        • Lysis of bone by tumor cells
        • Release of osteoclast-activating factor by myeloma cells
    c. Tumors that release PTH-like hormone (e.g., lung cancer)
3. Pharmacologic
    a. Vitamin D intoxication—increased GI absorption of calcium
    b. Milk-alkali syndrome—hypercalcemia, alkalosis, and renal impairment due to excessive intake of calcium and certain absorbable antacids (calcium carbonate, milk)
    c. Drugs—thiazide diuretics (inhibit renal excretion), lithium (increases PTH levels in some patients, e.g., squamous cell carcinoma)
4. Other
    a. Sarcoidosis—increased GI absorption of calcium
    b. Familial hypocalciuric hypercalcemia—distinguished from primary hyperparathyroidism by a low urine calcium excretion versus a normal or high urine calcium excretion in primary hyperparathyroidism

Hypercalcemia can cause pancreatitis. Hypocalcemia in patients with pancreatitis suggests pancreatic necrosis.

The presentation of hypercalcemia includes stones (nephrolithiasis), bones (bone pain, arthralgias), thrones (increased urinary frequency), groans (abdominal pain, nausea, vomiting), and psychiatric overtones (anxiety, depression, fatigue). Note that these are also the findings of vitamin D overdose!

❖ **Diagnosis:**



- Understand Pathogenesis of Osteoporosis, key investigations and basics of management

❖ **Pathogenesis:**

1. Decreased bone mass/quality causes increased bone fragility and fracture risk. In osteoporosis, the bone mineral density is at least 2.5 standard deviations below that of young, normal individuals.
2. Mechanism: failure to attain optimal (peak) bone mass before age 30, or rate of bone resorption exceeds rate of bone formation after peak bone mass is attained
3. Most osteoporotic patients are postmenopausal women and elderly men

❖ **Diagnosis:**

Diagnostic test: Dual-energy x-ray absorptiometry (DEXA).
Recommended as screening test for all women › 65 years of age and men › 70 years of age, and those with other risk factors for osteoporosis.

- Osteoporosis: Bone mineral density (T-score) is 2.5 standard deviations (SDs) less than normal.
- Osteopenia: T-score between 1 and 2.5 SDs below normal.

Lab tests: Look for secondary causes by measuring calcium, phosphate, parathyroid hormone (PTH), TSH, free T4, liver enzymes, creatinine, and electrolytes. If estrogen deficiency or hypogonadism is suspected, measure FSH, LH, estradiol, and testosterone.

❖ **Treatment:**

- Lifestyle modifications: Adequate calcium and vitamin D intake (supplementation can be used for prevention), smoking cessation, avoiding heavy alcohol use, and weight-bearing exercises.
- Best initial treatment: Bisphosphonates (eg, alendronate, risedronate, ibandronate, zoledronic acid) are used in the treatment of osteoporosis, not osteopenia.
- Other drugs: Teriparatide (PTH analogue), denosumab (a monoclonal antibody to RANK-L), selective estrogen receptor modulators (eg, raloxifene).

Medications for osteoporosis	
Bisphosphonates (eg, alendronate, risedronate)	• First-line treatment for most patients • Taken with water on an empty stomach an hour before food & other medications • Not recommended for patients with renal impairment • Atypical fractures possible with prolonged use • Oral and parenteral options available
Denosumab	Risk of infection & skin reactions Close monitoring for hypocalcemia needed
Anabolic agents (eg, teriparatide)	• Useful in severe osteoporosis • Monitor serum calcium, uric acid & renal function
Nasal calcitonin	• Modest reduction in fracture risk • Reduces pain from fracture
Selective estrogen receptor modulators (SERMs) (eg, raloxifene)	• Less effective than bisphosphonates • May lower risk of breast cancer • Increased risk of DVT

Dyslipidemia

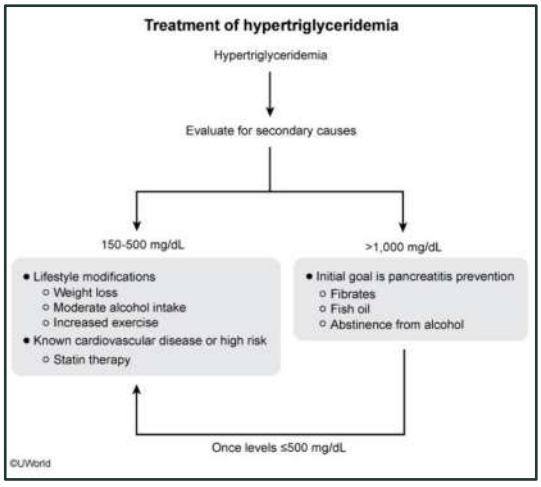
- Recognize causes of secondary dyslipidemia and rule of screening in high risk individuals.

Causes:

Acquired (more common)

- Obesity
- Diabetes mellitus
- Physical inactivity
- Heavy consumption of alcohol
- Hypothyroidism
- Nephrotic syndrome
- Cholestatic liver disease
- Cushing disease
- Drugs: antipsychotics, beta blockers (e.g., metoprolol), oral contraceptive pill, high-dose diuretic use

Inherited (less common)



Indications for statin therapy in prevention of ASCVD	
Secondary prevention	• Established ASCVD ○ Acute coronary syndrome ○ Stable angina ○ Arterial revascularization (eg, CABG) ○ Stroke, TIA, PAD
Primary prevention	• LDL ≥190 mg/dL • Age ≥40 with diabetes mellitus • Estimated 10-year risk of ASCVD >7.5%-10%

ASCVD = atherosclerotic cardiovascular disease; **CABG** = coronary artery bypass grafting; **PAD** = peripheral artery disease; **TIA** = transient ischemic attack.

Population	• Men age 35 years and older • Women age 45 years and older who are at increased risk for coronary heart disease (CHD)	• Men ages 20 to 35 years who are at increased risk for CHD • Women ages 20 to 45 years who are at increased risk for CHD	• Men ages 20 to 35 years • Women age 20 years and older who are not at increased risk for CHD
Recommendation	Screen for lipid disorders. Grade: A	Screen for lipid disorders. Grade: B	No recommendation for or against screening Grade: C
Risk Assessment	Consideration of lipid levels along with other risk factors allows for an accurate estimation of CHD risk. Risk factors for CHD include diabetes, history of previous CHD or atherosclerosis, family history of cardiovascular disease, tobacco use, hypertension, and obesity (body mass index ≥30 kg/m^2).		
Screening Tests	The preferred screening tests for dyslipidemia are measuring serum lipid (total cholesterol, high-density and low-density lipoprotein cholesterol) levels in non-fasting or fasting samples. Abnormal screening results should be confirmed by a repeated sample on a separate occasion, and the average of both results should be used for risk assessment.		
Timing of Screening	The optimal interval for screening is uncertain. Reasonable options include every 5 years, shorter intervals for people who have lipid levels close to those warranting therapy, and longer intervals for those not at increased risk who have had repeatedly normal lipid levels. An age at which to stop screening has not been established. Screening may be appropriate in older people who have never been screened; repeated screening is less important in older people because lipid levels are less likely to increase after age 65 years.		

- Recognize and understand lipid profile panel and identify abnormalities.

Lipid profile [11]

- Includes total cholesterol, HDL, LDL, and triglycerides
- LDL can be measured directly or estimated using the **Friedewald formula** (LDL = total cholesterol – HDL – (triglycerides/5) [16][11]

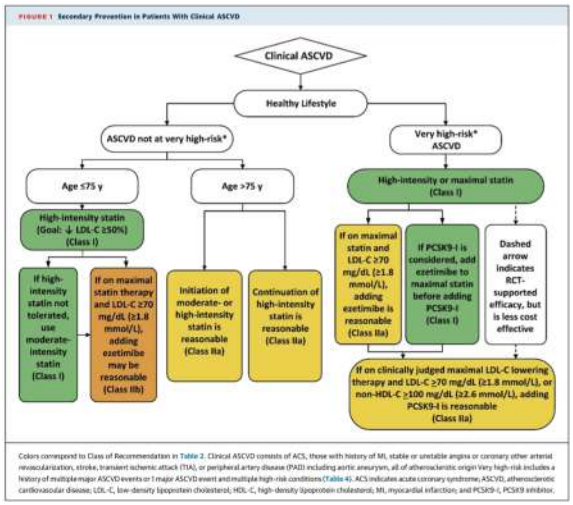
Parameters of fat metabolism [17]		
Laboratory parameter	**Optimal level**	**Abnormal levels**
Total cholesterol	• < 200 mg/dL	• Borderline: 200–239 mg/dL • High: ≥ 240 mg/dL
Triglycerides	• < 150 mg/dL	• Borderline: 150–199 mg/dL • High: 200–499 mg/dL • Very high: ≥ 500 mg/dL
LDL	• < 100 mg/dL	• Near optimal: 100–129 mg/dL • Borderline high: 130–159 mg/dL • High: 160–189 mg/dL • Very high: ≥ 190 mg/dL
HDL	• ≥ 60 mg/dL	• Low: < 40 mg/dL
LDL/HDL ratio [18]	• ♂ : < 3.5 • ♀ : < 3.0	• ♂ : > 3.5 • ♀ : > 3.0
Total cholesterol/HDL ratio [18]	• ♂ : < 5.0 • ♀ : < 4.5	• ♂ : > 5.0 • ♀ : > 4.5

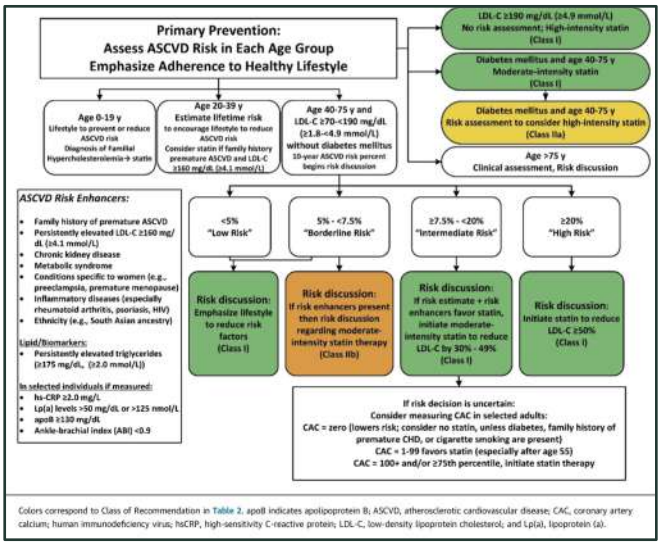
- To apply lifestyle modifications and drug therapy for patients with dyslipidemia.

Approach

- Encourage all patients to make lifestyle modifications
- Initiate pharmacologic therapy based on the patient's age, LDL level, and ASCVD risk.
  - Statins: first-line
  - Nonstatin lipid-lowering agents: may be added to statins if treatment goals are not met.
  - If treatment goals are not reached with maximally tolerated statin treatment, consider adding ezetimibe.
  - If goals are still not reached, a bile-acid sequestrant or PCSK9 inhibitor may be added.

- Patients with familial lipid disorders
  - Consider specialist referral.
  - Treatment should involve lifestyle modifications and pharmacologic therapy with individualized treatment goals.





- Identify parameters for the key characteristics for metabolic syndrome and understand basics of management

Definition:

Metabolic syndrome is defined by the Presence of ≥ 3 of the following conditions (or already receiving medical treatment for them)

- Insulin resistance: fasting glucose ≥ 100 mg/dL
- Elevated blood pressure: ≥ 130/85 mm Hg
- Elevated triglycerides: ≥ 150 mg/dL
- Low HDL-C: in men < 40 mg/dL; in women < 50 mg/dL
- Abdominal obesity: waist circumference ≥ 102 cm in men; ≥ 88 cm in women

Treatment:

- First-line: lifestyle modifications
  - Dietary changes: calorie restriction, healthy foods (e.g., fruit/vegetables, protein-rich, unsaturated fats, sodium-restricted)
  - Physical activity: minimum of 30 minutes moderate exercise per day (2.5 hours per week) , which increases insulin sensitivity, lowers blood pressure, and promotes weight loss
- Medical therapy: treat hypertension (e.g., ACE inhibitors), diabetes mellitus, and dyslipidemia (e.g., with statins)
- Bariatric surgery: if BMI ≥ 40 and no success with dietary and lifestyle changes
  - Sleeve gastrectomy (most common): large part of the greater curvature is removed, so that the remaining stomach resembles a sleeve
  - Roux-en-Y gastric bypass (2nd most common): Roux-en-Y

Complications:

Metabolic syndrome is associated with increased risk of:

- Cardiovascular disease
- Type 2 diabetes
- Non-alcoholic steatohepatitis → ↑ risk of developing liver cirrhosis and hepatocellular carcinoma
- Portal vein thrombosis

References