STUDY PDF

Internal Medicine Summary

Built from all Internal Medicine lecture slides and past paper questions, organized into eight rotation summaries for fast revision. Made by Ibrahim Al-Khatib

Contents

Respiratory

Rheumatology

Cardiology

Exam Map

PRIORITY TIER	CORE TOPICS	PAST-PAPER WEIGHT
Tier 1 (Crucial)	Ischemic Heart Disease, Acute Coronary Syndrome, Hypertension, Arrhythmias	~70% of questions
Tier 2 (Core)	Heart Failure, Valvular Heart Disease	~15% of questions
Tier 3 (Niche)	Pericardial Diseases, Cardiomyopathies, Infective Endocarditis	~15% of questions

Strongest Repeated Exam Themes & Revision Priorities:

- **Fatal Medication Contraindications:** The exam heavily tests what *not* to do. Memorize these absolute traps: AV-nodal blockers (adenosine, beta-blockers, CCBs, digoxin) are strictly contraindicated in WPW + Afib; nitrates in RV/Inferior MI; beta-blockers in acute decompensated HF and Prinzmetal angina; and short-acting oral nifedipine in hypertensive urgencies.
- **The Unstable Patient:** "Next best step" questions frequently pivot on hemodynamic stability. Pulseless VT/VFib = Immediate Defibrillation. Unstable but pulsing tachyarrhythmias (SVT/VT/Afib) = Synchronized Cardioversion.
- **Arrhythmia Pairings:** Link Multifocal Atrial Tachycardia (MAT) to severe pulmonary disease/COPD and treat with CCBs (never beta-blockers). Link SVT to structurally healthy hearts and treat with IV Adenosine.
- **Re-infarction Detection:** Troponin stays elevated for 10–14 days. You must select **CK-MB** (or its isoform assay) for detecting early re-infarction because it normalizes within 72 hours.
- **Valvular Intervention Rules:** Surgery is indicated *before* irreversible failure. Cutoffs are heavily tested: LVEF drops below **60%** for Mitral Regurgitation and below **50%** for Aortic Regurgitation. Remember that advanced age is *never* a contraindication for severe Aortic Stenosis intervention (TAVR/AVR).
- **Heart Failure Mortality:** You must differentiate between drugs that improve survival ("BAAS": Beta-blockers, ACEi/ARB/ARNI, Aldosterone Antagonists, SGLT2i) and those purely for symptom control (Furosemide, Digoxin).
- **Aortic Dissection Paradigm:** Medical management requires immediate reduction of shear stress. You must administer beta-blockers *before* vasodilators like nitroprusside to avoid a fatal reflex tachycardia that propagates the tear.
- **Endocarditis Prophylaxis Traps:** Prophylaxis is reserved *only* for highest-risk patients (prosthetic valves, prior IE) undergoing highest-risk procedures (dental/respiratory mucosa). Routine GI/GU procedures (e.g., colonoscopy) require no prophylaxis, even with a mechanical valve.
- **Post-MI Complications:** Differentiate by timing and presentation. A Ventricular Septal Defect (VSD) presents on days 3–5 with a new loud murmur, thrill, and right heart failure. Early post-MI

pericarditis is treated with **Aspirin only** (standard NSAIDs and steroids are contraindicated to avoid myocardial rupture).

- **Stroke & Permissive Hypertension:** Do not lower BP in an acute ischemic stroke unless it exceeds 220/120 mmHg. However, if the patient is a candidate for thrombolytics (tPA), the strict threshold changes to **< 185/110 mmHg**.

Ischemic Heart Disease

Core Concepts

Coronary Physiology & Ischemia Myocardial ischemia occurs when oxygen demand exceeds oxygen supply.

- **Myocardial Oxygen Supply Determinants:**
  - Coronary blood flow (determined by vessel patency). Note: **80% of coronary flow occurs in diastole**.
  - Hemoglobin level.
  - Arterial oxygen saturation.
  - Myocardial oxygen extraction (Note: This is **fixed at 65%-75%** even at rest, so the heart relies heavily on increasing *flow* to meet higher demands).
- **Myocardial Oxygen Demand Determinants:**
  - Heart rate.
  - Contractility.
  - Wall tension (ventricular pressure and radius).
  - Muscle mass (e.g., LVH).

Pathogenesis of Atherosclerosis

- **Endothelial Dysfunction:** Initiated by mechanical stress/inflammation. Upregulation of adhesion molecules attracts monocytes/T-lymphocytes.
- **Fatty Streak:** Macrophages consume oxidized LDL, becoming lipid-rich **foam cells**.
- **Plaque Types:**
  - **Stable Plaque:** Thick fibrous cap, lots of smooth muscle cells, intact endothelium, lack of inflammatory cells. (Causes stable angina).
  - **Unstable Plaque:** Thin fibrous cap, large necrotic lipid core, many inflammatory cells (activated macrophages), few smooth muscle cells, eroded endothelium. (Prone to rupture → ACS).

Diagnosis / Clinical Features

Coronary Syndromes

- **Stable Angina:** Typically arises with **>70% luminal stenosis**. Retrosternal pressure/heaviness lasting 2–10 mins. Precipitated by exertion/emotion; relieved by rest/nitrates.

- **Variant (Prinzmetal) Angina:** Vasospasm of epicardial coronary vessels. Frequently occurs **at rest/at night**. Presents with transient **ST-segment elevation** but **negative troponin**. Associated with females and other vasospastic conditions (migraine, Raynaud's).
- **Cardiac Syndrome X:** Exertional angina with a **positive stress test**, but **anatomically normal coronary arteries** on angiography. Caused by microvascular dysfunction. Excellent long-term prognosis.
- **Stress-Induced (Takotsubo) Cardiomyopathy:** Often triggered by severe emotional stress (e.g., fight with a spouse). Presents with chest pain and ST elevations resembling STEMI. Echo characteristically shows **apical dyskinesia with basilar preservation of contraction**.

Investigations

- **ECG Localization:**
  - *Inferior (RCA):* II, III, aVF
  - *Anterior/Septal (LAD):* V1 – V4
  - *Lateral (LCx):* I, aVL, V5, V6
- **Stress Testing:** Exercise tolerance test (ECG looking for ST depression), Stress Echo (looking for wall motion abnormalities), or Thallium/nuclear scan (shows decreased isotope uptake in ischemic areas during exercise).
- **Coronary Angiography:** Gold standard. Identifies anatomically significant occlusions.

Management

Stable Angina Management

- **Prognostic Therapy (Mortality Reduction):**
  - Aspirin.
  - Statins (Target LDL < 100 mg/dL, or < 70 mg/dL in high-risk).
  - ACE Inhibitors.
  - Revascularization (CABG/PCI) in specific anatomical variants (e.g., Left Main disease).
- **Symptomatic Therapy (Symptom Control):**
  - Beta-blockers (increase diastolic time, reduce HR/contractility).
  - Calcium channel blockers (decrease coronary tone, reduce HR).
  - Nitrates (decrease LV preload/wall tension by venodilation).
  - Metabolic modulators (e.g., Trimetazidine).

Management of Acute Chest Pain & STEMI

- **Primary PCI vs. Thrombolytics:** Primary PCI is superior to fibrinolysis. If a patient presents with a STEMI, **do not wait for cardiac biomarkers** (troponin) before initiating emergent management (PCI or thrombolytics).
- **Cardiac Arrest:** Sudden collapse with a provided monitor strip showing Ventricular Fibrillation (V-Fib) requires immediate **Defibrillation (unsynchronized cardioversion)**. If a patient is found unresponsive and gasping for air on the floor, the absolute first step is to **initiate CPR**.

Complications / Prognosis

- **Left Ventricular Function:** The single most important prognostic indicator in CAD. Normal EF is 50-75%; an EF <50% significantly increases mortality.
- **Extent of Ischemia:** Single vessel disease has ~2% annual mortality vs. Left Main Stem disease with ~12% annual mortality.

Past-Paper High Yield

Acute Coronary Syndrome & Medications

- **Thrombolytic Contraindications:** *Absolute* contraindications include ischemic stroke within 3 months, intracranial AV malformation, history of intracerebral bleed, and aortic dissection. **Active menstrual bleeding is NOT an absolute contraindication.**
- **Inferior MI & Hypotension:** In an inferior STEMI (II, III, aVF) presenting with hypotension (e.g., 90/50 mmHg), **use extreme caution with nitroglycerin** as it can drop preload and cause severe cardiovascular collapse.
- **TIMI Score Criteria:** Used in ACS. Includes: Age ≥65, Aspirin use in the past 7 days, elevated cardiac biomarkers (troponin), ≥3 CAD risk factors, and ST depression on ECG.
- **Beta-Blockers in Decompensated HF:** While standard therapy for stable CHF, beta-blockers (e.g., metoprolol) are strictly **contraindicated in ACUTE decompensated heart failure**.

Differential Diagnosis of Chest Pain

- **Pericarditis:** Young patient, sharp pleuritic pain, worsened by lying flat and breathing, improved by sitting up. Often follows a URTI.
  - *ECG:* Diffuse **concave** ST elevation and PR depression.
  - *Management:* NSAIDs and Colchicine. (Colchicine specifically decreases recurrence).
  - *Complication:* Cardiac tamponade. Steroids are *not* first-line.
- **Pulmonary Embolism (Massive):** Presents with severe pleuritic chest pain, dyspnea, and right heart strain. Expected findings include tachycardia, parasternal heave, S3, and loud P2. **Reversed splitting of S2 is UNEXPECTED** (reversed splitting is seen in left-sided issues like severe aortic stenosis or LBBB).
- **Constrictive Pericarditis / Right Heart Failure:** Elevated JVP that *increases* with inspiration (Kussmaul sign). Best next diagnostic step is a **Transthoracic Echocardiogram**.

Systemic Pathology & Cardiology Intersections

- **Cholesterol Crystal Embolization (Atheroembolism):** Occurs after vascular procedures. Features include **eosinophilia**, elevated CRP, progressive decline in eGFR over weeks, and peripheral atherosclerosis (e.g., blue toe syndrome). A positive ANA is **not** a typical feature.
- **Hypertrophic Obstructive Cardiomyopathy (HOCM):** Young patient with dyspnea/chest pain on exertion. Beta-blockers (metoprolol), non-dihydropyridine CCBs (verapamil), and disopyramide are indicated. **Digoxin is strictly contraindicated** as its positive inotropic effect worsens LV outflow tract obstruction.

- **Heterozygous Familial Hypercholesterolemia:** Expected lipid profile will show drastically elevated Total Cholesterol (e.g., ~320 mg/dL) and LDL (e.g., ~265 mg/dL), with relatively normal HDL and Triglycerides.
- **Rivaroxaban Mechanism:** Exerts its anticoagulant effect via direct inhibition of **Factor Xa**.

Memory Pearls

- **Nitrates** are strictly contraindicated in Inferior MI with Right Ventricular involvement (watch for low BP + Leads II, III, aVF).
- **Beta-blockers** are strictly contraindicated in **Prinzmetal/Variant angina** (can worsen unopposed alpha-mediated vasospasm) and **Acute Decompensated HF**.
- **Increased Estrogen** is *not* a risk factor for CAD. Pre-menopausal women have a lower risk of CAD than men of the same age; the risk equalizes post-menopause.

Acute Coronary Syndrome

Core Concepts

- **Spectrum of Disease:** Stable Angina → Unstable Angina (UA) → NSTEMI → STEMI → Sudden Death.
- **Pathophysiology:** Characterized by a disrupted atherosclerotic plaque (rupture, erosion, or fissure).
  - **Primary hemostasis:** Platelet adhesion, activation, and aggregation (forms platelet plug).
  - **Secondary hemostasis:** Coagulation system activation (forms fibrin clot).
- **Plaque Characteristics:**
  - **Stable Plaque:** Thick fibrous cap, lots of smooth muscle cells, intact endothelium, foam cells, lack of inflammatory cells.
  - **Vulnerable/Unstable Plaque:** Thin fibrous cap, few smooth muscle cells, eroded endothelium, inflammatory cells (activated macrophages).
- **Coronary Occlusion & Thrombus Type:**
  - **UA / NSTEMI:** Incomplete (subtotal) occlusion. Prone to distal embolization.
  - **STEMI:** Complete (total) occlusion.
- **Evolution of Infarction:** Ischemic (but viable) myocardium begins necrotizing subendocardially within 30 minutes, extending transmurally over 6–12 hours. *"Time is Muscle"*.

Diagnosis / Clinical Features

- **Typical Presentation:** Sudden, severe retrosternal compressive chest pain radiating to the left shoulder and arm. Lasts >30 minutes. Often at rest or early morning.
- **Associated Symptoms:** Sweating, nausea, vomiting, severe anxiety.
- **Painless MI:** Occurs in 10–15% of patients (classic in diabetics and the elderly). May present solely as hypotension, heart failure (e.g., basal crepitations), or arrhythmia.

- **Physical Exam:** Patient appears anxious and sweaty. Auscultation may reveal S3, S4, new murmurs, or pericardial rubs.
- **Unstable Angina Definitions:**
  - New onset angina (within 8 weeks).
  - Angina occurring at rest or minimal exertion.
  - Crescendo angina (increasing frequency, duration, or intensity).
  - Post-MI or post-revascularization angina (within 2 weeks).
- **Differentials to always consider:** Aortic Dissection, Massive Pulmonary Embolism, Acute Pericarditis.

Investigations

- **12-Lead ECG:** Essential initial step (Normal ECG does not exclude MI).
  - **Ischemic Cascade:** Hyperacute T waves → ST-segment elevation → Q-waves → T-wave inversion.
  - **STEMI Criteria (in V2–V3):**
    - Men ≥40 years: ≥2 mm
    - Men <40 years: ≥2.5 mm
    - Women: ≥1.5 mm
    - ≥1 mm in at least two other adjacent chest or limb leads.
  - **New LBBB:** Treated as a STEMI. Use **Sgarbossa Criteria** to diagnose STEMI in the presence of old LBBB (a score ≥3 has 98% specificity).
  - **Localization:**
    - Inferior: II, III, aVF
    - Lateral: I, aVL, V5, V6
    - Anterior / Septal: V1–V4
- **Cardiac Biomarkers:**
  - **Troponin (T, I):** Highly sensitive and specific. Rises in 4–6 hours (high-sensitivity in 2–4 hours), remains elevated for **10–14 days**. (Cannot detect early re-infarction). Elevated in myocarditis, PE, renal failure, and sepsis—but normal in pure pericarditis.
  - **CK-MB:** Rises in 4–6 hours, peaks at 17–24 hours, and **normalizes by 72 hours**. (Excellent for detecting early re-infarction).
    - *Isoforms:* CK-MB isoform assay (MB2/MB1 >1.5) is more sensitive than the routine CK-MB assay.
  - **Myoglobin:** Rises early (2–4 hours), peaks fast (6–12 hours), but lacks cardiac specificity.

Management

- **Immediate General Treatment (MONAH):**
  - **M**orphine: Analgesia and anxiolysis (decreases sympathetic tone and O_2 demand). Caution if hypotensive.

    - **O**xygen: 2–4 L/min if hypoxemic (SaO_2 < 90%).
    - **N**itroglycerin (Sublingual/Spray): Reduces preload and systemic vascular resistance. *Contraindicated in hypotension, right ventricular (RV) infarction, or recent PDE-5 inhibitor use.*
    - **A**spirin: 150–325 mg chewed and swallowed.
    - **H**eparin: Unfractionated (5000 U IV) or LMWH.
- **STEMI Reperfusion Strategy (Goal = Myocardial Salvage):**
    - **Primary PCI (Preferred):** If door-to-balloon time <90 minutes (or within 120 mins of first medical contact).
    - **Thrombolysis / Fibrinolysis:** If <3 hours from symptom onset AND PCI is unavailable/delayed. Goal door-to-needle is <30 minutes.
        - *Absolute Contraindications:* Active internal bleeding, suspected aortic dissection, trauma or surgery <2 weeks, history of hemorrhagic stroke, BP >200/120 mmHg, prolonged CPR, recent head trauma / intracranial neoplasm, diabetic proliferative retinopathy, pregnancy.
- **UA / NSTEMI Management:**
    - **NO THROMBOLYTICS.**
    - Dual Antiplatelet Therapy (Aspirin + Clopidogrel/Ticagrelor).
    - Anticoagulation (LMWH is superior to unfractionated heparin in this setting).
    - Anti-ischemic therapies (Beta-blockers, Nitrates) and Statins.
    - Invasive PCI strategy for **High-Risk** patients (TIMI score factors: rest pain >20 min, pulmonary edema, hypotension, new MR/S3, transient ST changes, elevated troponins).

Complications / Prognosis

- **Arrhythmias:** Most common cause of pre-hospital death. Includes VT/VF, AF (15% in first 24h), and AV blocks.
- **Heart Failure & Cardiogenic Shock:** Classified by Killip I–IV.
- **Mechanical Ruptures (first 10 days):**
    - Ventricular Free Wall Rupture (causes tamponade).
    - Ventricular Septal Defect (VSD).
    - Papillary Muscle Rupture (causes acute severe MR).
- **Pericardial Complications:**
    - **Early Pericarditis:** Treat with Aspirin. *(NSAIDs and steroids are strictly contraindicated).*
    - **Dressler's Syndrome:** Autoimmune reaction 2–12 weeks post-MI. Treat with Aspirin or Ibuprofen.
- **Poor Prognostic Indicators:** High TIMI risk score, EF <40%, large infarct size, anterior MI, new BBB, re-infarction, advanced age (>70), or history of DM.

Past-Paper High Yield

- **Cardiac Markers & Re-infarction:** Troponin stays elevated for 10–14 days and cannot be used to detect a secondary ischemic event within the first week. **CK-MB normalizes in 72 hours**, making it

the marker of choice for detecting early re-infarction.

- **Isoform Sensitivity:** The CK-MB isoform assay (specifically an MB2/MB1 ratio >1.5) is *more* sensitive than the routine CK-MB assay for early detection.
- **Troponin Specificity Traps:** Troponin levels are distinctly **normal in acute pericarditis**, but will be elevated in myocarditis.
- **Mechanical Complications (VSD):** A sudden drop in blood pressure accompanied by right-sided heart failure (elevated JVP), bilateral crackles, and a **new loud systolic murmur with a palpable thrill** on days 3–5 post-STEMI strongly indicates a post-infarction Ventricular Septal Defect (VSD). The immediate definitive management is **surgical VSD repair**.

Memory Pearls

- **Time to Normalization:** Myoglobin (1 day) → CK-MB (3 days) → Troponin (10–14 days).
- **LBBB in ACS:** A *new* LBBB with typical chest pain = STEMI equivalent (Go to Cath/Thrombolysis).
- **Inferior MI Trap:** Never give nitrates to an inferior STEMI patient with suspected RV extension (look for hypotension, clear lungs, elevated JVP). They are completely preload-dependent.
- **Thrombolysis in NSTEMI:** Never. Fibrinolytics are reserved strictly for STEMI/New LBBB presentations.

Cardiac Arrhythmias

Core Concepts

- **Mechanisms of Arrhythmias:** Include increased automaticity, triggered activity (early and delayed afterdepolarizations), and re-entry circuits (macro and micro re-entry).
- **ECG Basics & Approach:**
  - **Rate Calculation:**
    - Regular rhythm: `300 / number of large boxes` or `1500 / number of small boxes`.
    - Irregular rhythm: `Number of R waves in a 10-second strip × 6`.
  - **Axis:**
    - Normal: Leads I (+) and II (+).
    - Left Axis Deviation (LAD): Lead I (+), Lead II (-), Lead III (-).
    - Right Axis Deviation (RAD): Lead I (-), Lead II (+), Lead III (+).
  - **Intervals:**
    - **PR:** 120–200 ms (3–5 small squares).
    - **QRS:** < 120 ms (< 3 small squares).
    - **QTc:** < 460–470 ms (Men); < 470–480 ms (Women). A short QT is notably caused by digitalis toxicity.
  - **Hypertrophy Criteria:**
    - **Right Atrial Enlargement (RAE):** P wave amplitude > 2.5 mm in Lead II or > 1.5 mm in V1.

        - **Left Atrial Enlargement (LAE):** P wave duration ≥ 0.12s (notched in limb leads) or terminal negative portion in V1 ≥ 1 mm wide and deep.
        - **Left Ventricular Hypertrophy (LVH):** Cornell Criteria (S in V3 + R in aVL > 24 mm in men, > 20 mm in women).
        - **Right Ventricular Hypertrophy (RVH):** R/S ratio > 1 with negative T wave in V1, or R > 6 mm in V1.

Diagnosis / Clinical Features

- **Bradyarrhythmias (Rate < 60 bpm):**
    - **Sinus Bradycardia:** Caused by high vagal tone, ischemia, structural disease, medications, or high athletic conditioning.
    - **Sick Sinus Syndrome (SSS):** SA node dysfunction common in advanced age. Features marked persistent bradycardia, sinus pauses, and often co-exists with Tachy-Brady Syndrome.
    - **AV Blocks:**
        - **1st Degree:** Prolonged PR interval (> 0.20s), no dropped beats.
        - **2nd Degree Type I (Wenckebach):** Progressive PR prolongation followed by a dropped QRS.
        - **2nd Degree Type II:** Constant PR interval with intermittently dropped QRS complexes.
        - **3rd Degree (Complete):** Complete AV dissociation (P waves and QRS complexes beat independently). P rate > QRS rate. Presents with fatigue and presyncope/syncope.
- **Tachyarrhythmias (Rate > 100 bpm):**
    - **Premature Complexes (PACs & PVCs):** Frequent PVCs can take patterns (bigeminy, trigeminy) and run into Non-Sustained VT (NSVT, < 30 seconds).
    - **Supraventricular Tachycardia (SVT):** Most commonly AV Nodal Re-entrant Tachycardia (AVNRT). Regular, narrow QRS (unless aberrant). Typically presents in patients with structurally normal/healthy hearts. P waves are often hidden or retrograde (short RP).
    - **Wolff-Parkinson-White (WPW) Syndrome:** Pre-excitation syndrome featuring a Delta wave, short PR, and wide QRS on resting ECG. WPW + SVT can conduct antidromically (wide QRS).
    - **Atrial Fibrillation (Afib):** Irregularly irregular, absent P waves. High risk of thromboembolism (evaluate with CHA2DS2-VASc score) and LAA thrombus.
    - **Atrial Flutter:** Regular or irregular, characterized by typical "sawtooth" flutter waves (especially in inferior leads).
    - **Multifocal Atrial Tachycardia (MAT):** Irregularly irregular narrow-complex tachycardia with ≥ 3 distinct P wave morphologies. Highly associated with severe pulmonary disease (e.g., COPD exacerbations).
    - **Ventricular Tachycardia (VT):** Wide QRS complexes. Sustained if > 30 seconds. Most common cause is prior MI (scar-mediated re-entry). Polymorphic VT (Torsades de Pointes) is associated with prolonged QT.
    - **Ventricular Fibrillation (VFib):** Chaotic, irregular wide QRS deflections with no identifiable structure. Represents cardiac arrest.

Investigations

- **ECG Analysis Framework for Tachycardia:**

QRS WIDTH	REGULAR RHYTHM	IRREGULAR RHYTHM
Narrow	Sinus tachycardia, SVT (AVNRT/AVRT), Atrial Flutter	Atrial fibrillation, MAT, Atrial Flutter with variable block
Wide	Ventricular Tachycardia, SVT with aberrancy, Antidromic WPW	Polymorphic VT, Afib with aberrancy or WPW

- **Risk Stratification Scores:**
  - **CHA2DS2-VASc:** Determines anticoagulation need in Afib (CHF, HTN, Age ≥ 75 [2], DM, Stroke/TIA [2], Vascular disease, Age 65-74, Female).
  - **HAS-BLED:** Estimates major bleeding risk in Afib patients on anticoagulation.

Management

- **Bradyarrhythmias & Blocks:**
  - *Asymptomatic:* Observation.
  - *Symptomatic (Sinus brady / 1st degree / 2nd degree Type I):* Atropine, beta-agonists.
  - *High-grade blocks (2nd degree Type II & 3rd degree) or SSS:* Indications for pacemaker placement. 3rd-degree block is a medical emergency requiring emergent pacing.
- **Supraventricular Tachycardia (SVT):**
  - *Acute Stable:* Vagal maneuvers followed by IV Adenosine (drug of choice for termination).
  - *Unstable:* Synchronized Direct Current Cardioversion (DCCV).
  - *Preventative:* Beta-blockers, CCBs, or Catheter Ablation.
- **WPW Syndrome:**
  - *Stable wide-complex tachycardia (WPW + Afib or Antidromic AVRT):* **IV Procainamide** is the treatment of choice.
  - *Contraindications:* **AV nodal blockers are strictly contraindicated** (Adenosine, Beta-blockers, CCBs, Digoxin) because they block normal conduction, driving all impulses down the accessory pathway and risking degeneration into VFib.
- **Multifocal Atrial Tachycardia (MAT):**
  - Treat the underlying cause (e.g., improve oxygenation and ventilation for COPD).
  - Medical control with Non-dihydropyridine CCBs (Diltiazem/Verapamil).
  - *Avoid:* Beta-blockers (if severe bronchospasm/wheezing is present) and Electrical Cardioversion (which is ineffective for MAT).
- **Atrial Fibrillation:**
  - *Stable:* Rate control (Beta-blockers, CCBs, Digoxin) + Anticoagulation (DOACs or Warfarin). Rhythm control (Amiodarone, Sotalol, Ablation, DCCV) if symptomatic despite rate control or in young/new-onset patients.

    - *Unstable:* Immediate synchronized cardioversion.
    - *Cardioversion Rule:* If Afib duration is > 48 hours (or unknown), a TEE must be done to rule out left atrial appendage (LAA) thrombus, OR the patient must be anticoagulated for 3 weeks prior to cardioversion.
- **Ventricular Arrhythmias:**
    - *Stable VT:* Treat underlying cause (ischemia, electrolytes). IV Amiodarone.
    - *Unstable VT (Pulse but hypotensive):* Synchronized Cardioversion.
    - *Pulseless VT / VFib:* Immediate Defibrillation and CPR (Code Blue).
    - *Polymorphic VT (Torsades) / Long QT with syncope:* Implantable Cardioverter Defibrillator (ICD) is indicated for structural heart disease or high-risk genetic long QT causing syncope.
- **Pacemakers & Cardiac Devices:**
    - **PPM (Permanent Pacemaker):** For persistent bradycardia/blocks.
    - **ICD:** Can pace AND shock. Contains Anti-Tachycardia Pacing (ATP) function.
    - **CRT (Cardiac Resynchronization Therapy):** Biventricular pacing for heart failure.
    - **Magnet use:** Placing a magnet over a pacemaker turns it to *asynchronous pacing*; placing it over an ICD turns the *defibrillator OFF*.

Complications / Prognosis

- **Afib Post-CABG:** A common postoperative complication. Preoperative administration of beta-blockers (e.g., Metoprolol) or Amiodarone/Sotalol effectively prevents it. Digoxin does *not* prevent post-op Afib.
- **Electrolyte-driven Arrhythmias:** Hypomagnesemia fundamentally disrupts calcium and potassium homeostasis, causing refractory hypokalemia and hypocalcemia. It must be aggressively corrected via IV Magnesium sulfate to stabilize myocardial membranes.

Past-Paper High Yield

- **SVT vs. MAT distinction:** A young patient with palpitations, HR > 150, normal BP -> SVT -> manage with IV Adenosine. A COPD patient with severe wheezing, palpitations, and irregular rhythm -> MAT -> manage with CCBs (Verapamil/Diltiazem); *never give beta-blockers to a wheezing COPD patient, and know that adenosine/cardioversion fail in MAT.*
- **WPW Tachycardia Traps:** If an Afib/WPW patient presents with wide-complex tachycardia, the absolute best next step is **Procainamide** (if stable) or Cardioversion (if unstable). Choosing Adenosine, CCBs, or Digoxin is a classic board trap that kills the patient.
- **The Unstable Patient:** "Unresponsive, BP 75/40, chaotic irregular wide QRS" means Ventricular Fibrillation. Do not give Amiodarone or synchronized cardioversion. **Defibrillation** is the only correct answer.
- **SVT characteristics:** It is heavily tested that SVT generally affects *healthy (structurally normal)* hearts, can absolutely be diagnosed via ECG, and is universally terminated by adenosine.
- **QT Modifiers:** Amiodarone, TCAs, and Macrolides *prolong* the QT interval (risk for Torsades). Digitalis therapy *shortens* the QT interval.

- **Electrolyte cascades:** If given a patient on chronic PPIs presenting with low Mg, low Ca, and low K, the best *next step* is replacing the magnesium (IV Magnesium Sulfate) to allow the correction of Ca and K.
- **AV Block recognition:** An older patient presenting with fatigue and presyncope, with an ECG showing P waves marching independently of QRS complexes (3rd-degree block) mandates a **Permanent Pacemaker**.

Memory Pearls

- **Short QT?** Think Digitalis. **Long QT?** Think Torsades (and Macrolides, TCAs, Amiodarone).
- **WPW + Afib = FBI** (Fast Broad Irregular). Avoid AV node blockers!
- **Adenosine** is the diagnostic and therapeutic reset button for regular, narrow complex tachycardias.
- **Synchronized vs. Unsynchronized:** If they have a pulse but are crashing (unstable SVT/Afib/VT), *Synchronize*. If they are pulseless (VFib/Pulseless VT), *Defibrillate* (Unsynchronized).
- **MAT = Lung issue.** Fix the lungs, and give a CCB.

Hypertension

Core Concepts

- **Essential Hypertension:** Primary elevation of blood pressure (BP) without an identifiable underlying cause; accounts for ~90% of cases.
- **Secondary Hypertension:** Elevation of BP due to an identifiable, often treatable, underlying cause (e.g., renovascular disease, primary aldosteronism).
- **White Coat Hypertension:** Consistently elevated office readings but normal out-of-office (home/ambulatory) readings.
- **Masked Hypertension:** Normal office readings but elevated out-of-office readings; carries a cardiovascular risk similar to sustained hypertension.
- **Resistant Hypertension:** BP that remains above goal despite concurrent use of 3 antihypertensive agents of different classes (one must be a diuretic) at optimal doses, OR BP controlled but requiring ≥ 4 medications.
- **Refractory Hypertension:** Resistant HTN that cannot be controlled even with maximal medical therapy (≥ 4 drugs) under a specialist.
- **Pseudo-Resistant Hypertension:** Uncontrolled BP attributable to external factors (poor adherence, inaccurate measurement/cuff size, suboptimal dosing, or white coat effect) rather than true pharmacologic resistance.

Diagnosis / Clinical Features

- **Accurate BP Measurement (The "5 Rs"):**
  - **R**est for 5 minutes before measurement.
  - **R**efrain from talking, caffeine, smoking, or exercise for 30 minutes prior.
  - **R**emove upper arm clothing.

- **R**est arm on a supported surface at heart level.
- **R**est feet flat on the floor in a seated position.
- *Note:* The bladder width should be at least 40% of arm circumference, and length 80%.

- **Diagnostic Thresholds:**
  - **Clinic:** ≥ 140/90 mm Hg (based on JNC-8/traditional) or ≥ 130/80 mm Hg (ACC/AHA 2017 guidelines for elevated risk). Requires at least 2 readings on at least 2 separate visits (unless >180/110 or target organ damage).
  - **Home BP Monitoring (HBPM):** ≥ 135/85 mm Hg.
  - **24-Hour Ambulatory BP Monitoring (ABPM):** 24-hr average ≥ 130/80 mm Hg; Daytime ≥ 135/85 mm Hg; Nighttime ≥ 120/70 mm Hg.
- **Signs of Target Organ Damage:**
  - **Cardiac:** Left ventricular hypertrophy (LVH) presenting as an **S4 gallop and a left ventricular heave**.
  - **Vascular:** Aortic dissection (tearing chest/back pain, widened mediastinum), generalized atherosclerosis.
  - **Renal:** Proteinuria, albuminuria, elevated creatinine.
  - **Retinopathy:** Cotton wool spots, silver wiring, AV nipping (Grade II), flame hemorrhages, papilledema (Grade IV/Malignant).
- **Clues for Secondary Hypertension:**
  - *Renal Artery Stenosis:* Abdominal bruits, abrupt onset, recurrent "flash" pulmonary edema, unexplained rise in Cr after starting ACEI/ARB.
  - *Primary Aldosteronism:* Unprovoked or diuretic-induced hypokalemia, muscle cramps.
  - *Pheochromocytoma:* Paroxysmal headaches, sweating, tachycardia, pallor.
  - *Coarctation of the Aorta:* Young patient, high BP in arms + low BP in legs, radial-femoral delay, systolic murmur over the back or right 2nd intercostal space.
  - *Obstructive Sleep Apnea (OSA):* Obesity, loud snoring, daytime sleepiness.

Investigations

- **Primary Workup (for all newly diagnosed patients):**
  - Fasting blood glucose / HbA1c (screen for DM).
  - Lipid profile (calculate ASCVD risk).
  - Serum creatinine with eGFR, Serum Na+, K+, Ca2+.
  - Urinalysis (dipstick for protein/blood) and optional Urinary albumin-to-creatinine ratio (UACR).
  - TSH.
  - 12-lead ECG (screen for LVH, prior MI, atrial fibrillation).
- **Secondary Workup (Indicated if abrupt onset, <30 years old, drug-resistant, or disproportionate organ damage):**
  - **Renovascular disease:** Renal Doppler ultrasound (best initial), MRA, or CTA.
  - **Primary Aldosteronism:** Plasma aldosterone/renin ratio.

- **Pheochromocytoma:** 24-hour urinary fractionated metanephrines or plasma free metanephrines.
- **Coarctation of Aorta:** Echocardiogram.
- **OSA:** Sleep study with polysomnography.

Management

- **Lifestyle Modifications:**
  - **DASH Diet:** Most effective non-pharmacological intervention (approx. 11 mm Hg reduction).
  - **Weight Loss:** Approx. 1 mm Hg reduction per 1 kg of body weight lost.
  - **Sodium Reduction:** <1,500 mg/day optimal (approx. 5-6 mm Hg reduction).
  - **Exercise:** 90–150 min/week of dynamic/aerobic resistance.
- **Pharmacological Therapy:**
  - **First-line agents:** Thiazide diuretics, Calcium Channel Blockers (CCBs), ACE inhibitors (ACEI), Angiotensin Receptor Blockers (ARBs).
  - **Beta-blockers are NOT first-line** unless there is a compelling indication (e.g., post-MI, HFrEF, stable ischemic heart disease).
  - **Thiazide specifics: Chlorthalidone** is preferred over Hydrochlorothiazide (HCTZ) due to its significantly longer half-life (40 hrs vs 6-9 hrs) and greater potency.
  - *Important Contraindication:* **Never combine an ACEI with an ARB** (increases risk of hyperkalemia and acute kidney injury).
- **Comorbidity-Specific Choices:**
  - **Diabetes / CKD with albuminuria:** ACEI or ARB (renal protective). Best combination: ACEI/ARB + CCB.
  - **Heart Failure (HFrEF):** ACEI/ARB + Beta-blocker + Spironolactone + Diuretic. Avoid non-DHP CCBs (Verapamil/Diltiazem).
  - **Pregnancy/Pre-eclampsia:** IV Labetalol, oral Methyldopa, or Nifedipine. ACEIs and ARBs are strictly contraindicated.
  - **Atrial Fibrillation:** ARBs are useful for preventing recurrence. Ensure stroke risk stratification (HTN gives +1 point on CHA2DS2-VASc; uncontrolled HTN also increases bleeding risk on HAS-BLED).
- **Managing Resistant Hypertension (Stepwise):**
  1. Confirm compliance, exclude white coat effect (using ABPM), and ensure low sodium diet.
  2. Remove interfering medications (e.g., **NSAIDs**, oral contraceptives, sympathomimetics, licorice).
  3. Substitute optimally dosed thiazide-like diuretic (use Chlorthalidone or Indapamide).
  4. Add a mineralocorticoid receptor antagonist (MRA) (e.g., **Spironolactone**).
  5. Add a Beta-blocker (if HR > 70) or central alpha-agonist.
  6. Add a direct vasodilator (Hydralazine or Minoxidil).

Complications / Prognosis

- **Hypertensive Crises:** SBP >180 and/or DBP >120 mm Hg.
  - **Urgency:** No target organ damage. Reinstitute/intensify oral therapy; do not drop BP too rapidly.
  - **Emergency:** Acute, ongoing target organ damage (e.g., encephalopathy, acute pulmonary edema, MI). Requires ICU admission and IV medications.
  - *General BP Lowering Rule:* Reduce SBP by max 25% in the first hour, then to 160/100 over 2-6 hours.
  - *Exceptions (Rapid lowering required):*
    - **Aortic Dissection:** Rapidly lower SBP to <120 mm Hg and HR to <60 bpm within the 1st hour (IV Labetalol or Esmolol).
    - **Pre-eclampsia/Eclampsia:** Rapidly lower to <140 mm Hg (IV Labetalol).
- **Acute Pulmonary Edema Secondary to HTN:** Treat with IV Nitroglycerin, IV Furosemide, and O2. *Morphine is no longer standard of care and is generally avoided.*

Past-Paper High Yield

- **Resistant HTN + Flash Pulmonary Edema or Bruit:** Suspect renal artery stenosis. **Next step:** Renal Doppler ultrasound.
- **Pregnancy / Postpartum Seizures (Eclampsia):** BP management relies heavily on **IV Labetalol**.
- **Aortic Dissection Trap:** A patient presenting with severe tearing chest/back pain and high BP needs diagnostic imaging **(CT Aorta with contrast)** before intervention if asked for the "next step in diagnosis/ED management".
- **JNC 8 First-Line Rule:** Beta-blockers are explicitly *excluded* as first-line general therapies.
- **Thiazide Side Effects:** Hydrochlorothiazide and Chlorthalidone elevate uric acid and can trigger **acute Gout** attacks.
- **Physical Exam in Chronic HTN:** Non-compliance over decades leads to severe LVH, manifesting as an **S4 gallop and left ventricular heave**.
- **Medication Contraindications:**
  - Combining ACE inhibitors (e.g., Lisinopril) and ARBs (e.g., Valsartan) is contraindicated.
  - Sildenafil (PDE5 inhibitor) is absolutely contraindicated with **Isosorbide mononitrate (nitrates)** due to profound hypotension.
- **Coarctation of the Aorta:** Suspect in young healthy patients with headaches, high BP in upper extremities, normal/low in lower extremities, and a systolic murmur. **Next step:** Echocardiogram.
- **Valvular Complications:** An elderly patient with HTN and severe aortic stenosis (valve area 1 cm^2, gradient 50 mmHg) should be referred for **aortic valve replacement**.
- **Drug Interference:** Remember that NSAIDs can antagonize the effects of almost all antihypertensive classes (except CCBs) by promoting sodium/water retention.

Memory Pearls

- **First-line anti-hypertensives:** Think **A-C-D** (ACEI/ARB, CCB, Diuretics). Leave the **B** (Beta-blockers) for the Broken hearts (HF, IHD).

- **Aortic Dissection BP Target:** "120 in 20" – SBP <120 mm Hg as fast as safely possible (within the first hour).
- **Chlorthalidone vs HCTZ:** Chlorthalidone is the "Champion" (longer half-life, stronger evidence for CV reduction).
- **Aldosterone/Renin ratio:** High Aldo + Low Renin = Primary Aldosteronism (Conn's). High Aldo + High Renin = Secondary (Renovascular stenosis).

Valvular Heart Disease

Core Concepts

- **General Principle for Valvular Intervention:** Operate for severe disease when accompanied by *any symptoms*, a drop in LVEF below specific thresholds, or marked LV dilation.
- **Volume vs. Pressure Overload:**
  - *Regurgitant lesions (MR, AR):* Cause volume overload. Long asymptomatic phase with progressive LV dilation until decompensation (low output, pulmonary congestion).
  - *Stenotic lesions (AS):* Cause pressure overload, leading to concentric hypertrophy (Laplace's law) and eventual LV dysfunction.
- **Acute vs. Chronic Regurgitation:**
  - *Acute (MR, AR):* Heart lacks time to dilate/compensate. Presents as abrupt cardiogenic shock or pulmonary edema. Murmurs are often short, soft, or completely absent.
  - *Chronic (MR, AR):* Gradual dilation accommodates volume, leading to loud, classic murmurs and a prolonged asymptomatic phase.

Diagnosis / Clinical Features

- **Aortic Stenosis (AS)**
  - *Etiology by Age:* Congenital bicuspid/unicuspid (<30 yrs), Calcified bicuspid or rheumatic (40–60 yrs), Senile degenerative calcification (>70 yrs, **most common overall, occurs on native 3-cusp valve**).
  - *Symptoms:* Angina, Syncope, Dyspnea (Heart Failure).
  - *Exam:* Late-peaking systolic ejection murmur, soft or absent A2, S4.
  - *Subtypes:* Supravalvular (loud A2, thrill in suprasternal notch/R carotid); Subvalvular (discrete ridge, frequently accompanied by AR).
- **Aortic Regurgitation (AR)**
  - *Etiology:* Intrinsic valve (degenerative, bicuspid, endocarditis, rheumatic, anorectics) vs. Aortic root (dissection, Marfan, Giant cell arteritis).
  - *Exam:* Wide pulse pressure, de Musset's (head bobbing), Quincke's (capillary pulsations), Corrigan's (water-hammer pulse), Duroziez's (pistol-shot femoral).
  - *Acute AR Exception:* May lack bounding pulses; urgent presentation.
- **Mitral Regurgitation (MR)**

- *Etiology:* Primary/Valve (Degenerative, Rheumatic); Secondary/Ventricle (Dilated CM, Ischemic/Papillary muscle tethering). Acute causes include chordal rupture, endocarditis, ischemic papillary rupture.
- *Exam:* Pansystolic murmur, loud P2, S3 (early filling).

- **Mitral Stenosis (MS)**
  - *Etiology:* Rheumatic (most common), degenerative calcification.
  - *Exam:* Loud S1, opening snap, mid-to-late diastolic rumble.
  - *Pathophysiology:* Normal LV function, but elevated LA pressure → pulmonary hypertension, atrial fibrillation, RV failure, hemoptysis, and systemic emboli.
- **Tricuspid Regurgitation (TR)**
  - *Etiology:* Primary (rheumatic, pacemaker lead, carcinoid, endocarditis) vs. Secondary (pulmonary HTN, dilated CM, AFib/annular dilation).
  - *Exam:* Elevated JVP, pulsatile enlarged liver, peripheral edema/ascites.
  - *Murmur:* Pansystolic murmur at the left lower sternal border that **increases with inspiration (Carvallo's sign)**.

Investigations

- **Transthoracic Echocardiogram (TTE):** First-line test to assess severity, etiology, and chamber anatomy.
  - *Note on Acute Lesions:* Acute MR may show a hyperdynamic LV with only "mild" MR due to equalization of pressures.
- **Transesophageal Echocardiogram (TEE):** Indicated if TTE is negative/inconclusive, especially for suspected infective endocarditis (IE), chordal rupture, or aortic dissection.
- **AS Hemodynamic Criteria:** Mean gradient ≥ 40 mmHg is severe (a mean gradient of ~20-22 mmHg is moderate, not severe).

Management

- **Aortic Stenosis**
  - *Medical:* Mild AS + AFib → standard AFib management (rate control/anticoagulation); valve does not require intervention yet.
  - *Surgical (AVR/TAVR):* Indicated for severe AS with symptoms, LV dysfunction, or exercise-induced symptoms. **Advanced age is not a contraindication** for valve replacement.
- **Aortic Regurgitation**
  - *Acute AR:* **Beta-blockers and vasopressors (afterload enhancers) are strictly contraindicated!** Use afterload reducers (vasodilators) and inotropes as a bridge to urgent surgery.
  - *Chronic AR:* AVR indicated if severe AR + (Symptoms OR LVEF < 50% OR severe LV dilation). No vasodilators if asymptomatic with normal LV.
- **Mitral Regurgitation**

- *Acute MR:* Afterload reduction (vasodilators, IABP). Immediate surgery for papillary muscle rupture or dehisced prosthesis.
- *Chronic Primary MR:* Surgery (repair/MVR) if symptomatic, LVEF < 60%, or LV dilation. No vasodilators if asymptomatic with normal LV.
- *Chronic Secondary MR:* GDMT for heart failure, treat ongoing ischemia. Consider percutaneous Mitra-Clip if severe symptoms persist.

- **Mitral Stenosis**
  - Symptom-driven. Percutaneous mitral balloon commissurotomy (PMBC) if feasible; otherwise, surgery. Mandatory anticoagulation for concomitant AFib.
- **Tricuspid Regurgitation**
  - Operate if severe/symptomatic and failing diuretics, or if left-sided surgery is already planned. If pacemaker-induced, remove lead. If AFib-induced, attempt rhythm control first.
- **Infective Endocarditis (IE) Prophylaxis**
  - **Indicated:** Prosthetic valves (e.g., prior MVR/AVR, bioprosthetic or mechanical) undergoing dental procedures.
  - **Not Indicated:** Native bicuspid aortic valves, or a history of rheumatic fever *without* valvular involvement.

Complications / Prognosis

- **Aortic Stenosis Progression:** Once symptomatic, prognosis drops precipitously. Heart failure (dyspnea) has the worst prognosis (~2 years), followed by syncope (~3 years) and angina (~5 years).
- **Acute Non-Valvular Mimics:** A young patient with acute heart failure (e.g., LVEF 30%, S3, pulmonary congestion), fever, and tachycardia but *no evidence of valvular disease* likely has viral myocarditis. Treatment is Guideline-Directed Medical Therapy (GDMT) for HFrEF (e.g., Captopril and Carvedilol)—do not empirically give antibiotics, tPA, or steroids.

Past-Paper High Yield

- **The 81yo with severe AS and angina:**
  - The most likely etiology is senile degenerative, meaning the native valve usually has **3 cusps** (not bicuspid or rheumatic).
  - **Age is never an absolute contraindication** for aortic valve replacement (TAVR is highly utilized).
  - A mean gradient of 22 mmHg is *not* severe (must be >40 mmHg).
  - Dyspnea (Heart Failure) has the worst prognosis, not angina.
- **Murmur Differentiation:** A pansystolic murmur at the left lower sternal angle that **increases with inspiration** is TR, not MR.
- **Myocarditis vs. Valvular Emergency:** A patient presenting with fever, acute dilated cardiomyopathy/HFrEF, and normal valves on echo does *not* get Vancomycin/Ceftriaxone. Standard HF therapy (Captopril + Carvedilol) is the correct answer.

- **Prophylaxis Trap:** Dental prophylaxis is required for an MVR placed 5 years ago, but *not* for an unoperated bicuspid valve or a history of rheumatic fever without valve damage.
- **Asymptomatic AFib + Mild AS:** Do not intervene on the valve. Manage the AFib medically (rate control/anticoagulants) and monitor the AS.

Memory Pearls

- **Surgery LVEF cutoffs for Asymptomatic Regurgitation:**
  - MR = EF drops below **60%**
  - AR = EF drops below **50%**
- **Acute AR Medical Rules:** Vasodilators = Good. Pressors/Beta-blockers = Fatal (worsens regurgitant time/pressure).
- **AS Symptoms (SAD): S**yncope (3 yrs), **A**ngina (5 yrs), **D**yspnea (2 yrs - worst prognosis).
- **Right-sided murmurs (TR):** IN-spiration IN-creases right-sided murmurs.

Infective Endocarditis

Core Concepts

- **Definition:** Infection of the endocardial surface of the heart, most commonly affecting the heart valves.
- **Microbiology:**
  - *Staphylococcus aureus:* Most common cause of **acute** infective endocarditis (IE), right-sided (IV drug use) IE, and cardiac device-related infections.
  - *Viridans group Streptococci:* Most common cause of subacute IE, heavily associated with dental procedures.
  - *Enterococcus species:* Associated with genitourinary or gastrointestinal pathology.
- **When to suspect:**
  - New left-sided valvular regurgitation.
  - Unexplained fever ≥ 48 hours + Risk factors (valvular heart disease, prosthetic valves, IV drug use, congenital heart disease, immunocompromised state).

Diagnosis / Clinical Features

Diagnosis is established using the **Modified Duke Criteria**.

- **Definite IE:** 2 Major OR 1 Major + 3 Minor OR 5 Minor (or pathological evidence).
- **Possible IE:** 1 Major + 1 Minor OR 3 Minor.
- **Rejected IE:** Alternative diagnosis established, resolving with <4 days of antibiotics, or no pathological evidence with <4 days of antibiotics.

Major Criteria

1. **Positive Blood Cultures:** Multiple positive sets of typical microorganisms, or a *single* positive culture for *Coxiella burnetii*.
2. **Endocardial Involvement:** Vegetation, abscess, prosthetic valve dehiscence, or *new* valvular regurgitation.

Minor Criteria

1. **Predisposition:** High-risk heart condition or IV drug use.
2. **Fever:** ≥ 38.0°C (100.4°F).
3. **Vascular Phenomena (Septic/Embolic):**
    - **Janeway lesions:** *Painless* septic emboli on palms/soles.
    - Splinter hemorrhages (embolic).
    - Mycotic aneurysms, cerebral hemorrhage, conjunctival hemorrhages, embolic infarcts (e.g., renal, splenic).
4. **Immunologic Phenomena (Immune-complex mediated):**
    - **Osler's nodes:** *Painful* necrotizing vasculitis on pads of fingers/toes.
    - **Roth spots:** Exudative retinal lesions with pale centers.
    - Glomerulonephritis, positive Rheumatoid Factor (RF).
5. **Microbiologic Evidence:** Positive blood cultures not meeting Major criteria.

Investigations

- **Blood Cultures:** Must be drawn **BEFORE** initiating antibiotics.
    - *Acute:* 2-3 sets drawn >1 hour apart.
    - *Subacute:* 3 sets drawn >6 hours apart.
- **Echocardiography:**
    - **TTE (Transthoracic):** First-line test for all suspected IE.
    - **TEE (Transesophageal):** Indicated if TTE is non-diagnostic, complications are suspected (e.g., abscess), intra-cardiac leads are present, prosthetic valve + persistent fever, or *S. aureus* bacteremia.
- **Cardiac CT:** Useful if perivalvular extension/abscess is suspected.

Management

Medical Therapy

- Requires **prolonged** (typically weeks), **parenteral** (IV), and **bactericidal** antibiotics.
- Target most likely organisms (*Viridans Strep, Staphylococcus, Enterococcus*).
- *Right-Sided IE (Classic in IVDU with S. aureus):*
    - Uncomplicated MSSA: Beta-lactam x 2–6 weeks.
    - MRSA: Vancomycin x 6 weeks.

Anticoagulation in IE

- **Absolute Rule:** Discontinue ALL forms of anticoagulation for ≥ 2 weeks if a patient with mechanical valve IE develops a CNS embolic event (ischemia or hemorrhagic stroke).
- Do **NOT** start aspirin or antiplatelet agents as adjunctive therapy in IE.

Surgical Management

- **Indications for early surgery:** Valvular destruction causing heart failure, perivalvular extension (e.g., abscess causing heart block), extensive stroke/hemorrhage (though surgery is delayed 4 weeks if extensive CNS hemorrhage occurs), relapsing prosthetic valve IE, or large vegetation ≥ 20 mm with recurrent pulmonary emboli.
- **Device Infections (Pacemakers/ICDs):**
  - *S. aureus* bacteremia + vegetation requires **complete removal** of both the device generator and all leads, even if the pocket appears clean.
  - Re-implantation: Wait for negative blood cultures (72 hours post-removal for simple bacteremia, 14 days if valves were involved). Place in the contralateral site.

Complications / Prognosis

- **Local:** Valvular destruction → Heart Failure (most common cause of death).
- **Perivalvular extension:** Abscess formation into the conduction system → **Heart Block** (look for new PR prolongation or complete block).
- **Systemic:** Embolization to CNS (stroke/mycotic aneurysm), kidneys (flank pain/hematuria), or spleen.

Past-Paper High Yield

- **Most Common Pathogen:** *Staphylococcus aureus* is the most common cause of **acute** infective endocarditis.
- **Prophylaxis Indications Trap:** You must have *both* a high-risk patient AND a high-risk procedure.
  - *High-Risk Patients:* Prosthetic valves/material, prior IE history, unrepaired cyanotic congenital heart disease, or heart transplant with valvulopathy. *(Note: Bicuspid aortic valve, MVP, and acquired valve disease do NOT require prophylaxis)*.
  - *High-Risk Procedures:* Dental procedures involving gingival manipulation/mucosal perforation, or respiratory tract incision/biopsy (e.g., bronchoscopy *with* biopsy).
  - *NO Prophylaxis Needed:* Routine GI/GU procedures (e.g., **colonoscopy**) require NO prophylaxis, *even in a patient with a mechanical valve*.
- **Prophylaxis Regimen:** Amoxicillin 2g PO (single dose 30-60 minutes before the procedure) targeting *Viridans group Streptococci*.
- **Anticoagulation Trap:** If a patient on warfarin for a mechanical valve gets IE and suffers a stroke/TIA, the correct answer is to **STOP warfarin completely** (do not bridge, do not switch to DOAC/Aspirin).

Memory Pearls

- **O**sler's nodes = **O**uch (painful, immune complex).

- **J**aneway lesions = **J**ust septic emboli (painless).
- **New conduction abnormality (Heart Block) + Endocarditis = Aortic root abscess** (perivalvular extension).
- **Right-sided IE (Tricuspid) = IVDU =* S. aureus. ***Embolizes to the*** *L**ungs (septic pulmonary emboli).

Heart Failure

Core Concepts

- **Definition:** A clinical syndrome caused by structural or functional cardiac abnormalities that impair ventricular filling (diastole) or ejection (systole).
- **Pathophysiology:** Initial compensatory mechanisms (Frank-Starling law, neurohumoral activation via RAAS and sympathetic nervous system) maintain cardiac output but eventually cause deleterious left ventricular (LV) remodeling, myocyte apoptosis, and systemic fluid overload.
- **Phenotypes based on LVEF:**
  - **HFrEF (Reduced):** LVEF ≤ 40% (systolic dysfunction).
  - **HFpEF (Preserved):** LVEF ≥ 50% (diastolic dysfunction).
  - **Borderline/Mid-range:** LVEF 41–49%.
- **Clinical Classification:**
  - **ACC/AHA Stages (A–D):** Based on structural disease progression (A = high risk, no structural disease; D = refractory end-stage).
  - **NYHA Class (I–IV):** Based on functional capacity and symptom severity (I = no limitations; IV = symptoms at rest).
  - **Hemodynamic Profiles:** Assessed by perfusion ("Warm" vs. "Cold") and congestion ("Dry" vs. "Wet").

Diagnosis / Clinical Features

- **Left-Sided Failure (Low Output & Pulmonary Congestion):**
  - Fatigue, orthopnea, paroxysmal nocturnal dyspnea (PND).
  - Physical exam: Bibasilar rales, S3 gallop (in acute volume overload), laterally displaced point of maximal impulse (PMI), pulsus alternans (end-stage indicator).
- **Right-Sided Failure (Systemic Congestion):**
  - Elevated JVP, hepatosplenomegaly, peripheral edema, weight gain.
  - **Cardiac Ascites:** Presents with a high Serum-Ascites Albumin Gradient (SAAG > 1.1) *and* high ascitic fluid protein (> 2.5 g/dL or 25 g/L), distinguishing it from cirrhotic ascites (which has low protein).

Investigations

- **Echocardiography:** The single most important initial test to evaluate chamber sizes, wall thickness, valvular function, and calculate LVEF.

- **Biomarkers (BNP & NT-proBNP):**
  - The most accurate biomarker for diagnosing HF and differentiating cardiac from non-cardiac causes of dyspnea.
  - A normal level in an untreated patient virtually excludes heart failure.
  - **Prohormone Physiology:** Cleaved into biologically active BNP and inactive NT-proBNP.
  - **Caveats:** Levels *increase* naturally with age and renal dysfunction; levels are falsely *decreased* in obese patients.
- **Electrocardiogram (ECG):** Look for arrhythmias (AFib), evidence of prior MI (Q waves), or conduction abnormalities like LBBB (which impacts device therapy decisions).
- **Chest X-Ray:** Cardiomegaly, pulmonary venous redistribution, interstitial edema (Kerley B lines), and pleural effusions.
- **Invasive Hemodynamics (Swan-Ganz):** A pulmonary capillary wedge pressure (PCWP) > 18 mmHg confirms cardiogenic pulmonary edema, whereas a PCWP < 18–19 mmHg indicates ARDS.

Management

Core Prognostic Therapy for HFrEF (The "Pillars" that reduce mortality):

1. **ARNI / ACEI / ARB:** Sacubitril/valsartan (ARNI) is now the preferred first-line agent over ACEI/ARB to reduce hospitalizations and death.
2. **Beta-Blockers:** Specifically bisoprolol, carvedilol, or sustained-release metoprolol.
3. **Mineralocorticoid Receptor Antagonists (MRAs):** Spironolactone or eplerenone. (Watch for hyperkalemia and gynecomastia).
4. **SGLT2 Inhibitors:** Dapagliflozin or empagliflozin are heavily recommended for HFrEF, *regardless* of whether the patient has diabetes.

Symptomatic Therapy:

- **Loop Diuretics (Furosemide):** Relieve congestion but have *no proven mortality benefit*.

Adjunctive Therapies (Condition-Specific):

- **Hydralazine + Isosorbide Dinitrate:** Indicated for symptomatic African American patients despite optimal therapy, or for patients unable to tolerate RAAS inhibitors due to hyperkalemia or renal failure.
- **Ivabradine:** Selectively inhibits the I_f current in the SA node. Indicated for patients in normal sinus rhythm with a resting HR ≥ 70 bpm and EF ≤ 35% who are already on maximally tolerated beta-blockers.
- **Digoxin:** Acts via positive inotropy and negative dromotropy. Reduces HF hospitalizations and improves symptoms but **does not reduce all-cause mortality**.

Device Therapy:

- **ICD (Implantable Cardioverter-Defibrillator):** Primary prevention of sudden cardiac death for patients with an LVEF ≤ 35%.

- **CRT (Cardiac Resynchronization Therapy):** Biventricular pacing to reverse LV remodeling. Indicated for symptomatic patients (NYHA II–IV) with an LVEF ≤ 35% and a wide QRS complex (LBBB with QRS ≥ 120 ms).

Complications / Prognosis

- Heart failure is progressive and carries severe mortality (~20% at 1 year, ~40% at 5 years).
- Complications include pulmonary edema, deep vein thrombosis (DVT), arrhythmias, and in severe right heart failure, protein-losing enteropathy.
- Note: While diabetes is a common comorbidity and risk factor, developing Type 2 Diabetes is *not* a direct complication of heart failure.

Past-Paper High Yield

- **Differentiating ARDS vs. Cardiogenic Edema:** Always look at the PCWP. A wedge pressure < 19 mmHg confirms ARDS, ruling out a primary cardiogenic cause.
- **Digoxin Toxicity:** Commonly presents with anorexia, nausea, and vomiting. Remember the metabolic precipitants: hypokalemia, hypomagnesemia, hypoxia, and renal failure. **Trap:** *Hypocalcemia* does NOT predispose to digoxin toxicity; rather, *hypercalcemia* is the sensitizing factor.
- **BNP Traps:** You must know that circulating levels of natriuretic peptides *increase* with age (do not be tricked by an option stating they decrease).
- **Ascites Analysis:** If a patient presents with increased abdominal girth, a high SAAG (> 1.1) coupled with high fluid protein (> 2.5 g/dL) is classic for congestive heart failure, NOT cirrhosis or nephrotic syndrome.
- **Aortic Stenosis & HF:** Heart failure is the most ominous presentation of severe AS. **Trap:** Using vasodilators in these patients is contraindicated and does *not* improve the presentation, as it can cause catastrophic hypotension.

Memory Pearls

- **Survival Drugs in HFrEF: B**eta-blockers, **A**RNI/ACEI/ARB, **A**ldosterone antagonists (MRAs), **S**GLT2 inhibitors. (BAAS improves survival; Diuretics/Digoxin do not).
- **CRT Indication Rule of 3s:** EF < **35%**, NYHA class ≥ **II**, LBBB QRS > **120** ms.
- **Digoxin Toxicity Precipitants:** Low K+, Low Mg2+, High Ca2+.

Cardiomyopathies

Core Concepts

- **Definition:** A heterogeneous group of myocardial diseases associated with mechanical/electrical dysfunction, usually exhibiting inappropriate hypertrophy or dilation. They can be confined to the heart or part of a systemic disorder.
- **WHO Classification:**
  - **Dilated:** Enlarged ventricles with *systolic* dysfunction.

- **Hypertrophic:** Thickened walls with *diastolic* dysfunction.
- **Restrictive:** Stiff/rigid ventricles with *diastolic* dysfunction.
- **Arrhythmogenic RV Dysplasia (ARVD):** Fibrofatty replacement of the RV.
- **Unclassified:** Includes LV noncompaction and fibroelastosis.

- **MOGES Classification System:** Categorizes by **M**orphology (phenotype), **O**rgan involvement, **G**enetics, **E**tiology, and **S**tage.

Diagnosis / Clinical Features

Hypertrophic Cardiomyopathy (HCM)

- **Genetics:** Autosomal dominant in ~50-55% of cases. Caused by mutations in genes encoding sarcomere proteins (most commonly β-Myosin Heavy Chain [β-MHC], Myosin binding protein C, Cardiac troponin T, and α-tropomyosin).
- **Pathophysiology:** Vigorous systolic function but severely impaired *diastolic* function (impaired relaxation leading to elevated diastolic pressures). Left ventricular hypertrophy occurs *without* pressure overload.
- **Clinical Presentation:** Exertional dyspnea is the most common symptom.
- **Physical Exam:**
  - Bisferiens pulse ("spike and dome") / jerky carotid pulse.
  - S4 gallop.
  - Crescendo-decrescendo systolic ejection murmur.
  - May also have a holosystolic apical blowing murmur (due to Mitral Regurgitation from Systolic Anterior Motion [SAM] of the mitral valve).
- **Murmur Dynamics (HCM vs. Aortic Stenosis):**

MANEUVER	PHYSIOLOGIC EFFECT	HCM MURMUR INTENSITY	AS MURMUR INTENSITY
Valsalva / Standing	↓ Preload, ↓ Afterload	**Increases**	Decreases
Squatting	↑ Preload, ↑ Afterload	**Decreases**	Increases

Dilated Cardiomyopathy (DCM)

- Characterized by myocyte damage leading to reduced systolic function ± heart failure.
- Frequently idiopathic; 3x more prevalent in males and African-Americans.
- May present primarily with arrhythmias before overt heart failure.

Restrictive Cardiomyopathy (RCM)

- Characterized by severely impaired ventricular filling (intraventricular pressure rises precipitously with small volume increases) with normal systolic function.
- **Amyloidosis:** Restrictive physiology due to interstitial deposits of misfolded protein fibrils (AL or ATTR) replacing contractile elements.

- **Sarcoidosis:** Non-caseating granulomas causing restriction, conduction system blocks, and ventricular arrhythmias (risk of Sudden Cardiac Death [SCD]).
- **Endomyocardial Fibrosis:** Endemic in equatorial Africa (15-25% of cardiac deaths). Associated with hypereosinophilic syndrome (Löffler's endocarditis). Causes apical obliteration, MR, and basal inferior wall thickening.

Arrhythmogenic RV Dysplasia (ARVD)

- **Genetics:** Autosomal dominant mutations in desmosome genes (e.g., *PKP2* [plakophilin-2] and *DSP* [desmoplakin]).
- **Pathophysiology:** Cell death and fibrofatty replacement of the RV free wall.
- **Clinical:** Causes regional RV wall motion abnormalities, ventricular arrhythmias, and SCD, classically in young athletes.

LV Noncompaction

- Hereditary condition featuring prominent trabeculations and deep recesses in the LV apex.

Investigations

- **HCM:**
  - **ECG:** Normal sinus rhythm, LVH, prominent septal Q waves.
  - **Echocardiogram (Diagnostic):** Shows asymmetric septal hypertrophy (septum >1.4x free wall), Systolic Anterior Motion (SAM) of the mitral valve, and an LVOT gradient.
  - **Cardiac Catheterization:** Brockenbrough-Braunwald Sign (failure of aortic pulse pressure to rise post-PVC).
- **ARVD:**
  - **ECG: Epsilon wave** (delayed repolarization notch following the QRS complex).
  - **Echocardiogram:** Enlarged RV with strictly normal LV size and function.
  - **Imaging:** Contrast-enhanced Cardiac MRI (CMR) is highly sensitive for assessing RV dysplasia and fibrofatty replacement.
- **DCM / LV Noncompaction:** Genetic testing is generally indicated for non-ischemic cardiomyopathies to determine etiology, prognosis, and ICD indications. Screen offspring.

Management

- **HCM:**
  - **Medical:** β-blockers (1st line to ↓ myocardial O2 demand, ↓ exercise gradient, and ↓ arrhythmias). Calcium channel blockers are also used.
  - **Surgical:** Surgical myectomy or alcohol septal ablation for severe symptoms with high outflow gradients.
  - **Endocarditis:** Antibiotic prophylaxis is recommended.
- **ARVD:**
  - Strict cessation of heavy physical exertion and competitive athletics.

    - Epicardial catheter ablation for recurrent VT.
    - Cardiac transplantation for intractable HF.
- **Sarcoidosis:** Glucocorticoids, supplemented by immunosuppressants if needed.
- **ICD Indications:**
    - *HCM:* Prior SCD, non-sustained VT, family history of SCD in young relatives, septal thickness ≥30 mm, unexplained syncope.
    - *ARVD:* Indicated for survivors of VF or refractory VT.

Complications / Prognosis

- **HCM Sudden Cardiac Death:** The incidence of SCD directly correlates with maximum left ventricular wall thickness (especially ≥30 mm). Mortality is ~1% per year.
- **Endomyocardial Fibrosis:** Extremely poor prognosis; 80-90% die within 1-2 years.
- **LV Noncompaction:** High risk of CHF, Ventricular Tachycardia/SCD, and intraventricular thrombosis.

Past-Paper High Yield

- **HCM Physiology Trap:** HCM is a **diastolic dysfunction**, *not* a systolic dysfunction. The echo is diagnostic, inheritance is ~50% autosomal dominant, exertional dyspnea is the most common symptom, and a jerky carotid pulse is classic.
- **Pulsus Paradoxus Trap:** A significant drop in blood pressure during inspiration (>10 mmHg) is a classic sign of Cardiac Tamponade, Severe COPD, Asthma, or massive PE. **HCM does NOT cause pulsus paradoxus** (highly tested distractor).
- **ARVD Classic Presentation:** A young female or athlete presenting with syncope after exercise, a family history of SCD, an **ECG with Epsilon waves**, and an **Echo showing an isolated enlarged RV (normal LV)** has ARVD.

Memory Pearls

- **HCM Murmur Dynamics:** "Stand up to HOCM" (Standing up / Valsalva decreases venous return, shrinks the LV cavity, worsens the obstruction, and makes the murmur **louder**).
- **Cardiomyopathy Genes:**
    - HCM = **Sarcomere** mutations (β-MHC, binding proteins).
    - ARVD = **Desmosome** mutations (cell-to-cell adhesion fails under mechanical stress of exercise).
- **Brockenbrough-Braunwald Sign:** Unique to dynamic LVOT obstruction (HCM). After a PVC, the compensatory pause leads to a stronger contraction, which actually worsens the outflow tract obstruction and drops the post-PVC aortic pulse pressure.

Pericardial Diseases

Core Concepts

- **The Pericardium:** A fibroelastic sac with visceral and parietal layers separated by the pericardial cavity (normally contains 15–50 mL of plasma ultrafiltrate). Provides mechanical protection, anchoring, and lubrication.
- **Acute Pericarditis:** Inflammation of the pericardial sac. Often viral/idiopathic but can be the first sign of systemic disease. Termed *myopericarditis* if myocardial inflammation is also present (positive biomarkers).
- **Pericardial Tamponade:** Accumulation of fluid under high pressure that compresses the heart, severely restricting venous return and cardiac output.
- **Constrictive Pericarditis:** Thick, dense fibrous obliteration and calcification of the pericardial sac. Encases the heart, limiting diastolic expansion and restricting cardiac output.

Diagnosis / Clinical Features

Acute Pericarditis

- **Chest Pain (>95% of cases):** Sudden onset, anterior, sharp, and pleuritic (worse with inspiration/coughing).
- **Positional Relief:** Characteristically improves by sitting up and leaning forward (reduces pressure on the parietal pericardium and allows diaphragmatic splinting).
- **Pericardial Friction Rub:** Highly specific. A superficial, scratchy/squeaking sound best heard with the stethoscope diaphragm over the left sternal border.
- **Associated Symptoms:** May be preceded by flu-like, respiratory, or GI symptoms.

Pericardial Tamponade

- **Causes:** Neoplasm (e.g., lymphoma), trauma, uremia, anticoagulation, infection.
- **Beck's Triad:** Hypotension, Jugular Venous Distension (JVD), and Muffled/distant heart sounds.
- **Pulsus Paradoxus:** An abnormally large drop in systolic blood pressure (>10 mmHg) during inspiration.
- **Other features:** Dyspnea, significant tachycardia.

Constrictive Pericarditis

- **Causes:** Prior cardiac surgery, viral infection/acute pericarditis, mediastinal radiation, rheumatoid arthritis, or connective tissue disease (CTD).
- **Right Heart Failure Signs:** Fatigue, JVD, hepatomegaly, ascites, and peripheral edema.
- **Kussmaul's Sign:** Paradoxical lack of fall, or actual elevation, of the JVP during inspiration.
- **Pericardial Knock:** An early diastolic sound.
- **Arrhythmia:** Atrial fibrillation occurs in 20% of cases.

Investigations

Electrocardiogram (ECG)

- **Acute Pericarditis:**
  - *Stage 1 (Hours–Days):* Diffuse, concave-upward ST elevation with PR segment depression. Reciprocal ST depression and PR elevation in leads aVR and V1 (reflects atrial current of injury).
  - *Stage 2 (First Week):* Normalization of ST and PR segments.
  - *Stage 3:* Diffuse T wave inversions (develops after ST segments become isoelectric).
  - *Stage 4:* Normalization, or indefinite persistence of T wave inversions ("chronic" pericarditis).
- **Tamponade:** Electrical alternans (beat-to-beat alteration in QRS amplitude) and low voltage QRS complexes.
- **Chronic Post-MI (Differentials):** Persistent ST-elevation years after an MI suggests a **left ventricular aneurysm**, *not* acute pericarditis.

Echocardiography (TTE)

- **Acute Pericarditis:** Often normal unless an associated effusion is present.
- **Tamponade:** Pericardial effusion, **Right Ventricular (RV) diastolic collapse** (highly specific), increased respiratory variation of peak inflow velocities across tricuspid and mitral valves, and a dilated IVC without respiro-phasic variation.

Imaging & Labs

- **Chest X-Ray (CXR):**
  - *Pericarditis:* Typically normal. Large effusions may show an enlarged cardiac silhouette with clear lung fields.
  - *Constrictive Pericarditis:* Pericardial calcification (Note: Absence of calcification does *not* rule out constrictive pericarditis).
- **Labs:** Leukocytosis, elevated ESR, elevated CRP. Elevated Troponin or CK-MB indicates *myopericarditis*.

Management

Acute Pericarditis

- **First-line (Idiopathic/Viral):** NSAIDs + Colchicine (combination therapy preferred).
- **Post-Myocardial Infarction:** Aspirin + Colchicine.
  - *Crucial rule:* **AVOID** other NSAIDs and glucocorticoids post-MI, as they interfere with myocardial healing and scar formation (risk of rupture).
- **Glucocorticoids (Steroids):** NOT first-line. Reserved for CTD, autoreactive pericarditis, uremic pericarditis non-responsive to dialysis, contraindications to NSAIDs, or refractory cases.
- **Recurrent Pericarditis (up to 30% of cases):** NSAID with a 2- to 4-week taper + at least 6 months of weight-adjusted Colchicine. Refractory cases use steroids, IL-1 inhibitors (anakinra, rilonacept), or immunosuppressants (Azathioprine, MTX, IVIG).

- **High-Risk Features (Require admission/aggressive tx):** High fever (>38°C), subacute onset, large effusion/tamponade, lack of response to NSAIDs after 1 week, myocardial involvement, immunosuppression, trauma, or oral anticoagulation.

Pericardial Tamponade

- **Hemodynamically Unstable: Pericardiocentesis** is the immediate next step (or surgical drainage). Provide aggressive IV fluids. Use Intra-Aortic Balloon Pump (IABP) for refractory hypotension. Minimize PEEP.
- **Hemodynamically Stable:** IV fluids, close monitoring, serial TTE, and treat the underlying cause.

Constrictive Pericarditis

- **Initial:** Diurese and rate-control with caution. Provide a 2-3 month trial of conservative measures.
- **Definitive:** Pericardiectomy.
  - *Indicated in:* NYHA Class II or III with persistent symptoms.
  - *Negligible benefit in:* NYHA Class IV, cachexia, cirrhosis, or markedly reduced cardiac output.

Past-Paper High Yield

- **Tamponade vs. Next Step:** A patient with a history of neoplasm (e.g., lymphoma) presenting with shock (hypotension, tachycardia), pulsus paradoxus, and Beck's triad has cardiac tamponade. The *immediate next step* is **Pericardiocentesis**.
- **Constrictive Pericarditis Diagnosis:** A patient with recurrent URTIs (viral etiology) presenting with dyspnea, Kussmaul's sign (↑ JVP on inspiration), and a CXR showing pericardial calcification has **Constrictive Pericarditis**.
- **Colchicine's Role:** In the treatment of acute pericarditis, Colchicine is specifically utilized because it **decreases the recurrence rate**. (Steroids are *not* first-line).
- **ECG Distractors:** A patient presenting years after an anterior MI with mild exertional dyspnea and stable, persistent ST-segment elevations (e.g., V2-V4) is exhibiting a **Left Ventricular Aneurysm**, not acute pericarditis, Dressler's syndrome (which occurs weeks post-MI), or coronary spasm.

Memory Pearls

- **Kussmaul's Sign vs. Pulsus Paradoxus:**
  - *Kussmaul's sign* (JVP ↑ with inspiration) = **Constrictive Pericarditis** (and restrictive cardiomyopathies/RV failure).
  - *Pulsus Paradoxus* (Systolic BP ↓ >10 mmHg with inspiration) = **Cardiac Tamponade** (also seen in severe asthma/COPD).
- **Post-MI Pain:** If the patient leans forward and the pain improves, it's acute pericarditis. Use **Aspirin**, not Ibuprofen or Corticosteroids.
- **Electrical Alternans:** The heart is literally swinging back and forth in a massive pool of fluid (Tamponade), changing the electrical axis beat by beat.

Hypertensive Emergencies

Core Concepts

- **Definition:** Severe hypertension characterized by a systolic BP > 180 mmHg and/or diastolic BP > 120 mmHg.
  - **Hypertensive Emergency (Crisis):** Elevated BP accompanied by **acute impairment of an organ** (end-organ damage).
  - **Hypertensive Urgency:** Elevated BP with potential risk but **no** acute end-organ damage.
- **Pathophysiology:**
  - The **rate** at which Mean Arterial Pressure (MAP) rises is more important than the absolute rise.
  - Acute rise → Autoregulation failure (failure of vasoconstriction) → Endothelial damage (shear stress).
  - Results in **Fibrinoid Necrosis** of arterioles → Activation of coagulation/inflammation and protein deposition in the vessel wall.
  - RAAS activation perpetuates the BP rise via vasoconstriction and fluid retention.
- **Epidemiology:** Highest risk in males, African Americans, and middle-aged patients (peak age 40–50 years).

Diagnosis / Clinical Features

Assess primarily for signs of acute end-organ damage across three main systems:

- **Central Nervous System (CNS):**
  - Hypertensive encephalopathy (headache, blurred vision, confusion, altered mental status, nausea/vomiting, seizures, stupor, coma).
  - Ischemic or hemorrhagic stroke (focal neuro deficits).
  - Fundoscopy: Papilledema, hemorrhages, and exudates.
- **Cardiovascular System (CVS):**
  - Heart failure / Pulmonary edema (shortness of breath, crackles, JVD, S3/S4 extra heart sounds, peripheral edema).
  - Acute myocardial infarction (angina).
  - Aortic dissection (tearing chest pain, unequal BP/pulses bilaterally).
- **Renal System:**
  - Acute renal failure (oliguria).
  - Hematuria.

Investigations

- **Laboratory:**
  - Urinalysis (look for hematuria, proteinuria, RBCs, and **RBC casts**).
  - CBC, Chemistry panel (BUN/Cr for AKI), cardiac enzymes.

- Toxicology screen (rule out cocaine), pregnancy test (rule out eclampsia), endocrine work-up (pheochromocytoma, hyperaldosteronism) if secondary HTN suspected.

- **Imaging & Diagnostics:**
  - ECG (ischemia, LVH).
  - Chest X-ray (pulmonary edema, widened mediastinum).
  - Head CT (rule out stroke/hemorrhage), Chest CT (aortic dissection).

Management

General Principles:

- **Hypertensive Urgency:** Discharge with follow-up. **Avoid** giving rapid-acting oral meds (e.g., immediate-release nifedipine) in the ER; this is a common misconception and is dangerous, as chronic elevation implies adjusted autoregulation, and rapid drops cause severe organ hypoperfusion.
- **Hypertensive Emergency:** Admit to ICU. Lower BP rapidly but safely using **IV medications**, tailored to the damaged end-organ.

Condition-Specific Treatment Goals:

CLINICAL CONDITION	BP TARGET / GOAL	PREFERRED AGENTS
Hypertensive Encephalopathy	Reduce MAP by **max 25% over 8 hours**.	Labetalol, Fenoldopam
Acute Aortic Dissection	**Immediate** reduction of BP and shear stress (prevent extension).	Labetalol OR Nitroprusside + β-blocker (e.g., propranolol)
Acute Ischemic Stroke	Reduce ONLY if SBP > 220 mmHg. If giving **thrombolytics**, BP must be < 185/110 mmHg.	Labetalol, Nicardipine
Intracerebral Hemorrhage	Balance CPP (CPP = MAP - ICP). Don't lower too aggressively (limits perfusion).	Labetalol, Esmolol
Subarachnoid Hemorrhage	Maintain SBP < 160 mmHg.	Labetalol, Esmolol (Nimodipine for vasospasm)
Acute Pulmonary Edema / LVF	Titrate to alleviate HF signs.	IV NTG, Nitroprusside, Furosemide
Acute MI / Ischemia	Alleviate ischemia.	IV NTG, β-blockers, ACE inhibitors
Sympathetic Crises (Cocaine, Pheochromocytoma, MAOI tyramine crisis)	Reverse adrenergic excess.	Phentolamine + Benzodiazepines
Renal Insufficiency	Maintain adequate blood flow.	Nitroprusside

High-Yield Intravenous Agents & Adverse Effects:

- **Nitroprusside:** Instant onset. Risk of **Cyanide / Thiocyanate toxicity**.
- **Nitroglycerin (NTG):** 1-5 min onset. Causes flushing, headache, **Methemoglobinemia**.
- **Nicardipine:** CCB. Avoid in heart failure.

- **Hydralazine:** Causes reflex tachycardia. **Avoid in Aortic Dissection and MI**.
- **Labetalol (α + β blocker) / Esmolol (β1 selective):** Risk of heart block, orthostatic hypotension. **Avoid in heart failure and asthma**.
- **Fenoldopam:** Causes flushing, headache, tachycardia.
- **Enalaprilat (IV ACEi):** Risk of hypotension, renal failure, hyperkalemia.
- **Phentolamine (α-blocker):** Causes tachycardia, flushing, headache.

Complications / Prognosis

- Morbidity and mortality depend on the extent of initial end-organ damage and the quality of subsequent BP control.
- Untreated hypertensive emergencies carry a **> 90% 1-year mortality rate**.

Past-Paper High Yield

- **The Nifedipine Trap:** Never use oral/sublingual immediate-release nifedipine to rapidly lower BP in asymptomatic severe hypertension (urgency)—it predictably causes dangerous cerebral or myocardial hypoperfusion.
- **Stroke Permissive Hypertension:** Do not lower BP in acute ischemic stroke unless it exceeds 220/120 mmHg, *unless* the patient is a candidate for tPA (thrombolysis), where the strict threshold is **< 185/110 mmHg**.
- **Aortic Dissection Paradigm:** Unlike most hypertensive emergencies where gradual reduction is key, aortic dissection requires *immediate and aggressive* reduction of both shear stress (HR) and BP. Always give a beta-blocker *before* vasodilators like nitroprusside to prevent reflex tachycardia from worsening the dissection.
- **Sympathetic Crisis Management:** Cocaine toxicity, MAOI interactions, or pheochromocytoma require alpha-blockade (**phentolamine**) + benzodiazepines. Giving beta-blockers alone can lead to unopposed alpha-stimulation and paradoxical severe worsening of hypertension.

Memory Pearls

- **Hydralazine rule:** Reflex tachycardia limits its use; **never** use it in acute MI or Aortic Dissection.
- **Nitroprusside toxicity:** Prolonged use = Cyanide toxicity (altered mental status, lactic acidosis).
- **Pathology buzzword:** "Fibrinoid necrosis" of arterioles is the hallmark structural lesion of a hypertensive emergency.

Cardiogenic Shock

Core Concepts

- **Definition:** Severe impairment of myocardial performance resulting in diminished cardiac output (CO), hypoxia, and hypotension refractory to volume resuscitation. It causes end-organ hypoperfusion and requires pharmacological or mechanical intervention.
- **Epidemiology & Etiology:**

- **Acute MI** is the leading cause (accounts for 81% of cases). Complicates 5–10% of acute MIs and is the leading cause of death post-MI.
- **STEMI vs. NSTEMI:** STEMI has a 2-fold higher risk for developing cardiogenic shock (CS). However, NSTEMI-associated CS patients often face delayed cardiac catheterization/revascularization, leading to an increased mortality risk compared to those with STEMI-associated CS.
- **Demographics:** Higher incidence observed in females, age >75 years, and Asian/Pacific Islanders.

Diagnosis / Clinical Features

- **Clinical Criteria for Shock:** Requires both hypotension and features of hypoperfusion.
  - **Hypotension:** SBP < 90 mmHg for > 30 minutes, OR MAP < 60 mmHg for > 30 minutes, OR requires vasopressors to maintain these targets.
  - **Hypoperfusion:** Decreased mentation, cold/mottled extremities (livedo reticularis), oliguria (UOP < 30 mL/h), and lactate > 2.0 mmol/L.
- **SCAI (Society for Cardiovascular Angiography and Interventions) Stages of Shock:**
  - **Stage A (At Risk):** Normal BP and normal perfusion, but high-risk pathology (e.g., large anterior MI, HF).
  - **Stage B (Beginning / "Pre-shock"):** Hypotension (SBP < 90, MAP < 60) and tachycardia (HR > 100), but **normal perfusion** (clear mentation, warm extremities, normal lactate).
  - **Stage C (Classic):** Hypotension **plus** hypoperfusion. Cold, ashen, altered mentation, low UOP, elevated lactate/LFTs, acidosis.
  - **Stage D (Deteriorating):** Worsening hemodynamics/perfusion despite escalating use of pressors or mechanical circulatory support (MCS).
  - **Stage E (Extremis):** Refractory shock, cardiac arrest with ongoing CPR, pulseless electrical activity (PEA), or recurrent VT/VF.

Investigations

- **Hemodynamic Criteria (Right Heart Catheterization / PA Line):**
  - **Cardiac Index (CI):** < 2.2 L/min/m²
  - **Pulmonary Capillary Wedge Pressure (PCWP):** > 15 mmHg
  - **Cardiac Power Output (CPO):** < 0.6 W *(Formula: [CO × MAP]/451)*
  - **Shock Index:** > 1.0 *(Formula: HR / SBP)*
- **Isolated Right Ventricular (RV) Shock Indicators:**
  - CVP > 15 mmHg
  - CVP / PCWP ratio > 0.6
  - Pulmonary Artery Pulsatility Index (PAPi) < 1.0 *(Formula: [PASP - PADP] / CVP)*

Management

- **General Approach:** Early revascularization is the most critical intervention to improve survival. Protocol-driven approaches by multidisciplinary shock teams are strongly recommended (Class IIa).
- **Pharmacological Support (Class I):** Use intravenous inotropes to maintain systemic perfusion.
  - *Caution:* Escalating numbers and doses of catecholamines correlates with higher mortality due to pro-arrhythmic effects and increased myocardial oxygen demand.
  - **Dobutamine:** Inotrope (increases CO, HR). Variable BP effects.
  - **Dopamine:** 5–10 mcg/kg/min (inotropic), >10 mcg/kg/min (vasopressor). Can cause significant tachyarrhythmias and tissue necrosis.
  - **Norepinephrine:** Potent vasopressor (strongly increases SVR). Can cause reflex bradycardia and tissue necrosis.
  - **Epinephrine:** Potent inotrope and vasopressor. Highly arrhythmogenic.
  - **Milrinone (PDE-3 Inhibitor):** "Inodilator" (increases CO, decreases SVR/PVR).
    - *Special Consideration:* Excreted renally; accumulates in acute kidney injury. Closely monitor kidney function and adjust dose.
- **Mechanical Circulatory Support (MCS) (Class IIa):**
  - *Indication:* Reasonable when end-organ function cannot be maintained by pharmacology.
  - *Advantage:* Provides robust cardiovascular support without the increased myocardial oxygen consumption seen with catecholamines.
  - **Device Options:**
    - **IABP (Intra-Aortic Balloon Pump):** Counter-pulsation decreases afterload and improves coronary perfusion.
    - **Impella (Axial Flow Pump):** Pulls blood from the LV and ejects it into the aortic root. Unloads the LV (decreases LVEDP/LVEDV and wall tension) while increasing forward flow (MAP and end-organ perfusion), definitively lowering myocardial O2 demand.
    - **TandemHeart:** Left atrial-to-femoral artery ventricular assist device.
    - **VA-ECMO:** Veno-arterial extracorporeal membrane oxygenation for full cardiopulmonary support.

Complications / Prognosis

- Despite overall improvements in diagnosis and access to in-hospital care, the 6- to 12-month mortality for cardiogenic shock remains exceptionally high at **~50%** (unchanged over the past 2 decades).
- High risk for irreversible multi-organ failure (shock liver, AKI) and lethal arrhythmias if the ischemia-hypoperfusion cycle is not rapidly broken.

Past-Paper High Yield

- **Hemodynamic Cut-Offs:** Memorize the classic triad for confirming cardiogenic shock invasively: **SBP < 90 mmHg, CI < 2.2 L/min/m², and PCWP > 15 mmHg.**

- **NSTEMI vs. STEMI Trap:** Understand that while STEMI is more likely to cause shock, an NSTEMI patient presenting in shock has historically higher mortality directly driven by *delays in cardiac catheterization and revascularization*.
- **SCAI Staging Distinction:** The differentiator between Stage B (Pre-shock) and Stage C (Classic) is end-organ perfusion. A patient with SBP 85 but warm extremities and normal mentation/lactate is Stage B.
- **MCS vs. Inotropes:** Be prepared to identify that Mechanical Circulatory Support (like Impella) is superior physiologically because it unloads the heart and reduces myocardial O2 demand, whereas escalating inotropes increase O2 demand and provoke ischemia/arrhythmias.
- **Milrinone toxicity:** Always check renal function before initiating milrinone to avoid drug accumulation and refractory hypotension.

Memory Pearls

- **Shock Index = HR / SBP.** A normal index is < 0.8. An index > 1.0 means the heart rate has overtaken the systolic pressure, indicating profound shock.
- **SCAI ABCDEs of Shock: A**t risk, **B**eginning (hypotension without hypoperfusion), **C**lassic (hypotension + hypoperfusion), **D**eteriorating (refractory to initial meds), **E**xtremis (cardiac arrest/PEA).
- **Inotropes vs. MCS analogy:** Catecholamines whip a tired, ischemic horse to run faster (increasing O2 demand). MCS (like Impella) takes the load off the horse's cart so it can recover (decreasing LVEDP/LVEDV).

Endocrine

Exam Map

Past-Paper Question Distribution

TOPIC	QUESTION COUNT	PRIORITY LEVEL
Diabetes Mellitus (All modules)	35	⭐⭐⭐⭐⭐
Thyroid Disorders	24	⭐⭐⭐⭐⭐
Adrenal Disorders	17	⭐⭐⭐⭐
Calcium Disorders (Hypercalcemia)	8	⭐⭐⭐
Pituitary & Reproductive Syndromes	6	⭐⭐

Recurring Exam Patterns & Revision Priorities

- **DKA & HHS Triage Traps:** The most heavily tested concept in diabetic crises is the mandatory sequence of management. Always choose **IV Fluids** first, check **Potassium** second, and only initiate **Insulin** third. Never select insulin before confirming potassium levels.
- **Hypoglycemia Workup:** You will frequently be asked to differentiate the cause of a hypoglycemic event using the 72-hour fast labs. Memorize the triad: High Insulin + High C-peptide + Negative OHA screen = **Insulinoma**. High Insulin + Low C-peptide = **Exogenous injection**.
- **Confirming the DM Diagnosis:** A classic trick involves an asymptomatic patient with one slightly elevated FBG or random glucose. The correct answer is always to **repeat the test**, not to initiate metformin or insulin. Conversely, classic symptoms + one abnormal test = definitive DM.
- **Metformin-Induced B12 Deficiency:** Be highly suspicious of a well-controlled diabetic on Metformin presenting with new-onset peripheral neuropathy or macrocytic anemia. The exam frequently uses this to trap students into selecting "diabetic neuropathy."
- **Stepwise Cushing's Evaluation:** Examiners rigorously test the diagnostic order. You must first screen (24h urine free cortisol or low-dose dexamethasone test) to confirm hypercortisolism *before* checking ACTH, and check ACTH *before* ordering any imaging (MRI/CT).
- **Adrenal Crisis vs. Stable Workup:** For hypotensive shock post-steroid withdrawal, the immediate next step is **IV Hydrocortisone** (do not wait for labs). For stable, vague symptoms of adrenal insufficiency, the next step is the **ACTH stimulation test**.
- **Pheochromocytoma Pharmacotherapy:** A recurring safety principle—never give beta-blockers before establishing alpha-blockade (phenoxybenzamine) to avoid unopposed alpha-adrenergic hypertensive crisis.
- **Thyroid Nodule Algorithm:** The initial step for a nodule is always TSH. If TSH is normal/high, the next step for a suspicious/solid nodule is **Ultrasound-guided FNA**. Only choose a radionuclide scan if the TSH is *low*.

- **Hyperthyroidism in Pregnancy:** Highly tested pharmacology crossover. Use **PTU** for the 1st trimester (or planning pregnancy) and switch to **Methimazole/Carbimazole** for the 2nd/3rd trimesters.
- **Calcium Diagnostic Pathways:** When evaluating hypercalcemia, the critical branch point is Intact PTH. If PTH is high/normal, the exam will test your ability to differentiate Primary Hyperparathyroidism from FHH using **Urine Calcium**. If PTH is suppressed, look for malignancy (PTHrP) or sarcoidosis (1,25-OH-Vit D).
- **Hypogonadism Syndromes:** Memorize the clinical buzzwords for definitive next steps: Anosmia + low LH/FSH = **Kallmann syndrome**. Small firm testes + tall stature + high LH/FSH = **Klinefelter syndrome** (next step: Karyotype).

Diabetes Mellitus 1

Core Concepts

- **Pathogenesis of T1DM**: Autoimmune destruction of beta cells (97%) or idiopathic (3%).
  - Bimodal age of onset: Peaks at 4–6 years and early puberty (10–14 years).
  - Risk factors: Viral infections, immunizations, early introduction of cow's milk, Vitamin D deficiency.
  - *Counter-intuitive risk factor*: **Low birth weight decreases the risk** of developing T1DM.
  - Genetics: Monozygotic twin lifetime risk is 50%. Affected father (5-8%) confers a higher risk than an affected mother (2-4%).
- **Pathogenesis of T2DM**: Progressive beta-cell dysfunction + Insulin resistance.
  - Insulin processing is impaired: **Proinsulin makes up 40%** of secreted insulin (normally 10-15%).
  - Risk factors: Obesity, aging, genetics, lipotoxicity, glucotoxicity.
  - Genetics: Very strong heritability. Monozygotic twins have 90% concordance. A first-degree relative has 5–10x higher lifetime risk.
- **T1DM vs. T2DM Autoimmunity**:
  - T1DM features antibodies to: **GAD**, **Tyrosine phosphatase (IA2)**, **Insulin**, and **Zinc transporter**.

Diagnosis / Clinical Features

- **Diagnostic Criteria for DM**:
  1. Fasting Plasma Glucose (FPG) ≥ 126 mg/dL (no caloric intake for ≥ 8 hrs).
  2. 2-hour Plasma Glucose ≥ 200 mg/dL during a 75g OGTT.
  3. HbA1c ≥ 6.5%.
  4. Random Plasma Glucose ≥ 200 mg/dL **with classic symptoms** (polyuria, polydipsia, weight loss).
  - *Note*: In the absence of symptomatic hyperglycemia, criteria 1–3 **must be confirmed by repeat testing**.

- **Interpreting Borderline/Repeated Labs**:
  - FPG of 106 mg/dL then 124 mg/dL: Patient has **Prediabetes** (Impaired Fasting Glucose).
  - Asymptomatic patient with FPG 136 mg/dL: Next step is to **repeat FPG** to confirm.
  - Patient with polydipsia, polyuria, weight loss, and FPG of 135 mg/dL: **Diagnosis of DM is confirmed** (symptoms + 1 abnormal test).
- **Clinical Presentation**:
  - Symptoms: Polyuria, nocturia, thirst, weight loss, blurred vision, fatigue, numbness, impotence.
  - Signs: Muscle weakness, loss of tendon reflexes, decreased sensation, interdigital fungal infections, retinal changes.

Investigations

- **Hypoglycemia Workup (72-Hour Fast)**:
  - Triggered in seemingly well subjects presenting with Whipple's Triad (Symptoms + Glucose ≤ 45/55 mg/dL + Relief with glucose).
  - *Parameters measured*: Plasma glucose, Insulin, C-peptide, Proinsulin, Beta-hydroxybutyrate (BOHB), and oral hypoglycemic agents (OHA) screen.
  - **Insulinoma / Nesidioblastosis**: ↑ Insulin (≥ 3), ↑ C-peptide (≥ 0.6), ↓ BOHB (≤ 2.7), Negative OHA screen.
  - **Exogenous Insulin Abuse**: ↑ Insulin (>> 3), **↓ C-peptide** (< 0.6) (suppressed endogenous production), ↓ BOHB.
  - **Sulfonylurea Abuse**: ↑ Insulin (≥ 3), ↑ C-peptide (≥ 0.6), ↓ BOHB, **Positive OHA screen**.
- **Insulinoma Localization**:
  - Initial: CT, MRI, transabdominal US.
  - If negative: Endoscopic ultrasound (EUS) or **Selective arterial calcium stimulation** (sampling hepatic venous effluent; positive if insulin doubles or triples).

Management

- **Diabetes Prevention**:
  - *Intensive lifestyle changes* (7% weight loss, 150 min/week exercise) reduce risk by **58%**.
  - *Metformin* reduces risk by **31%**.
  - **16% reduction in DM risk for every 1 kg reduction in weight**.
- **Diabetic Ketoacidosis (DKA) Crisis Management**:
  - In a T1DM patient presenting with N/V, polyuria, oliguria, tachycardia, hypotension, and Kussmaul respirations: **Check K+ before giving Insulin** (Insulin drives potassium intracellularly; giving it blindly can cause fatal hypokalemia).
- **Pharmacotherapy Pearls**:
  - **Metformin**: Decreases hepatic glucose output. Weight neutral. Contraindicated in renal impairment (SCr > 1.5 in males, > 1.4 in females), liver failure, advanced HF, and sepsis.

- **GLP-1 Agonists (Exenatide, Liraglutide)**: Glucose-dependent insulin release, slows gastric emptying. Causes **weight loss**. Side effects: pancreatitis, GI upset, possible medullary thyroid cancer risk.
- **SGLT2 Inhibitors**: Provides **CVS protection**. Side effects: UTI, hypotension, dehydration.
- **TZDs (Pioglitazone)**: Insulin sensitizers. Side effects: Fluid retention/HF, hepatotoxicity, bone fractures, macular edema.
- **DPP4 Inhibitors**: Weight neutral.
- **Pramlintide (Amylin analogue)**: Approved for T1DM and insulin-treated T2DM. Reduces food intake.

- **Insulinoma Management**:
  - Primary: Surgical resection.
  - Medical (if surgery not possible): **Diazoxide** (first-line), Octreotide.

Past-Paper High Yield

- **Confirming T1DM/T2DM Diagnosis**: Do not initiate therapy on a single asymptomatic elevated FBG. The strictly correct next step is to **repeat the FBG** (or another diagnostic test). Conversely, classic symptoms + one random glucose > 200 or FBG > 126 definitively confirms the diagnosis.
- **DKA Triage**: Always check electrolytes (**potassium**) before initiating an insulin drip in hyperglycemic crises.
- **Perioperative Steroid Management**: An SLE patient on chronic prednisone (e.g., 10 mg) undergoing a major stressor like CABG surgery requires stress-dose steroids. Next step: **Start 100 mg hydrocortisone**.
- **Erectile Dysfunction in Youth**: The most common cause of erectile dysfunction in a young (e.g., 29-year-old) healthy male is **psychologic**, rather than diabetes-related microvascular/neuropathic disease.
- **Endocrine Miscellany (Tested alongside DM)**:
  - **Turner Syndrome (45, XO)**: Characterized by primary ovarian failure. Due to lack of estrogen feedback, FSH and LH are highly elevated. **Unlikely to find: FSH 3** (normal/low). Expect poor breast development.
  - **Klinefelter Syndrome (47, XXY)**: Diagnosis confirmed by **Karyotype**. Characterized by small, *firm* testicles, azoospermia, and altered upper/lower body segment ratios. **Unlikely to find: Soft normal testicles**.
  - **Pheochromocytoma**: Presents with episodic HTN, headaches, palpitations, and sweating. When treating the HTN, **Propranolol (beta-blockers) should NEVER be given before alpha-blockers** to avoid unopposed alpha-adrenergic hypertensive crisis.
  - **Hypercalcemia**: A psychotic patient presenting with elevated calcium is likely taking **Lithium**.
  - **Multiple Myeloma & Calcium**: In a patient with multiple myeloma, constipation, and mildly elevated Ca (10.2), the next step is to check **serum albumin** to calculate the corrected calcium level.

Memory Pearls

- **Whipple's Triad**: 1) Hypoglycemic symptoms, 2) Low blood glucose, 3) Relief with glucose administration. Required to initiate a 72-hour fast workup.
- **High Insulin + High C-peptide**: Endogenous source (Insulinoma or SU). Check SU screen.
- **High Insulin + LOW C-peptide**: Exogenous injection (Factitious).
- **1 kg = 16%**: Every 1 kg of weight loss reduces DM risk by 16%.
- **Low birth weight paradox**: Increases risk for insulin resistance/T2DM later in life, but *decreases* the risk of T1DM.

Diabetes Mellitus 2: Complications and Hypoglycemic Disorders

Core Concepts

- **Acute Complications**: Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), and Hypoglycemia.
- **DKA vs. HHS Pathogenesis**:
  - Both involve insulin deficiency/resistance and glucagon excess.
  - Glucagon increases carnitine palmitoyl transferase I (CPT-I) activity, driving ketogenesis.
  - In HHS, there is enough endogenous insulin (only 10% needed) to suppress lipolysis and ketogenesis, but not enough to promote peripheral glucose utilization, preventing ketosis but allowing profound hyperglycemia.
- **Whipple's Triad**: The hallmark of true hypoglycemia: (1) Low plasma glucose, (2) Symptoms of hypoglycemia, (3) Resolution of symptoms upon glucose administration.

Diagnosis / Clinical Features

Diabetic Ketoacidosis (DKA)

- **Demographics**: More common in younger patients (<65 years), primarily Type 1 DM (or T2DM under severe stress/infection).
- **Timeline**: Evolves rapidly (typically within 24 hours).
- **Classic Signs**: Compensatory hyperventilation (Kussmaul respirations), fruity breath odor.
- **Abdominal Pain**: Present in 46% of cases. Due to delayed gastric emptying and ileus from metabolic acidosis/electrolyte imbalance. *Does not* correlate with the severity of hyperglycemia.

Hyperglycemic Hyperosmolar State (HHS)

- **Demographics**: Older patients (>65 years), primarily Type 2 DM.
- **Timeline**: Evolves insidiously over several days.
- **Classic Signs**: Severe volume depletion. Neurologic symptoms are the hallmark (lethargy, obtundation, coma, focal signs like hemiparesis/hemianopsia, and seizures). Neurologic deterioration typically occurs when effective plasma osmolality > 320–330 mOsm/kg.
- **Abdominal pain**: Very unusual in HHS.

Hypoglycemia & Insulinoma

- **Symptoms**:
  - *Sympathoadrenal*: Palpitations, diaphoresis (sweating), tremors.
  - *Neuroglycopenic*: Confusion, visual changes, behavioral changes.
- **Insulinoma Profile**: Fasting hypoglycemia is most common. Associated with weight gain (18% of patients). Median duration of symptoms before diagnosis is 1.5 years; often misdiagnosed as a psychiatric or seizure disorder.
- **MEN1 Association**: 6% of insulinoma patients have MEN1 (in MEN1, 86% have *multiple* tumors, whereas sporadic insulinomas are typically solitary and benign).

Chronic Complications of DM

- **Neuropathy**: Distal symmetric polyneuropathy ("stocking-glove" pattern).
  - *Large-fiber loss*: Loss of vibration sense and proprioception. Decreased/absent ankle reflexes occur early.
  - *Small-fiber loss*: Impairment of pain, light touch, and temperature.
- **Nephropathy**: Progresses from normal (<30 mg/day) → Microalbuminuria (30-300 mg/day) → Macroalbuminuria (>300 mg/day).
- **Retinopathy**:
  - *Nonproliferative (NPDR)*: Microaneurysms, hemorrhages, soft/hard exudates, venous beading.
  - *Proliferative (PDR)*: Neovascularization of the disk/vitreous, preretinal hemorrhage.

Investigations

DKA vs. HHS Diagnostic Criteria

- **Glucose**: DKA >250 mg/dL | HHS >600 mg/dL (often >1000 mg/dL).
- **Arterial pH**: DKA <7.30 | HHS >7.30.
- **Serum Bicarbonate**: DKA <18 mEq/L | HHS >18 mEq/L.
- **Anion Gap**: DKA >10 | HHS Variable.
- **Ketones (Serum/Urine)**: DKA Positive | HHS Small/Trace.
- **Effective Serum Osmolality**: Calculated as `2[Na] + [Glucose/18]`. DKA is variable; HHS is definitively >320 mOsm/kg.

Hypoglycemia Evaluation (72-Hour Fasting Test)

- **Endpoints to stop the test**: Plasma glucose ≤45 mg/dL, signs/symptoms of hypoglycemia, 72 hours elapsed, or glucose <55 mg/dL if Whipple's triad was previously documented.
- **Labs to draw**: Glucose, Insulin, C-peptide, Pro-insulin, Oral Hypoglycemic Agent (OHA) screen, and Insulin antibodies.

DIAGNOSIS	GLUCOSE	INSULIN	C-PEPTIDE	OHA SCREEN
Normal	< 55	< 3	< 0.6	Negative

DIAGNOSIS	GLUCOSE	INSULIN	C-PEPTIDE	OHA SCREEN
Exogenous Insulin	< 55	**>> 3** (High)	**< 0.6** (Low)	Negative
Insulinoma	< 55	**≥ 3** (High)	**≥ 0.6** (High)	Negative
Sulfonylurea (OHA)	< 55	**≥ 3** (High)	**≥ 0.6** (High)	**Positive**

Insulinoma Localization

- **Imaging**: CT, MRI, and transabdominal ultrasound are first-line.
- **Invasive**: If imaging is negative, use endoscopic ultrasound or Arterial Calcium Stimulation (injection of calcium gluconate with hepatic venous sampling for insulin).
  - *Positive in ONE artery* = Insulinoma.
  - *Positive in MULTIPLE arteries* = Islet cell hypertrophy / Nesidioblastosis.

Chronic Complications Screening

- **Nephropathy**: Screen yearly with Urine Albumin/Creatinine Ratio (ACR). Elevated ACR must be confirmed with 2-3 samples over several months.
- **Neuropathy**: Michigan neuropathy screening score (checks vibration sense, Achilles reflex, and foot inspection for ulcers/dry skin).

Management

DKA & HHS Protocol

1. **IV Fluids**: Initiate with 1–2 L Normal Saline (NS) bolus. Switch to ½ NS based on hemodynamics. *Crucial transition*: Switch to D5 ½ NS when blood glucose drops below 200 mg/dL (DKA) or 250-300 mg/dL (HHS) to prevent hypoglycemia while continuing to clear ketones.
2. **Potassium**: *Check K+ before giving insulin!*
   - If K < 3.3 mmol/L: HOLD IV insulin and add KCl.
   - If K 3.3 – 5.3 mmol/L: Add KCl to IV fluids once urine output >50 mL/hr.
   - If K > 5.3 mmol/L: Delay K supplementation and monitor.
3. **Insulin**: 0.1 U/kg IV bolus followed by 0.1 U/kg/hr IV infusion. Continue until resolution. Start SC insulin once the patient is eating.
4. **Bicarbonate**: *Rarely indicated.* Only give if arterial pH <6.90, severe hyperkalemia, or decreased cardiac contractility.
5. **Phosphate**: Add if PO4 <1.0 mg/dL, or in the presence of cardiac dysfunction, hemolytic anemia, or respiratory depression.

Hypoglycemia Management

- **Mild-Moderate (Conscious)**: Oral glucose (15-20g), e.g., fruit juice.
- **Severe (Unconscious/Hospitalized)**: Draw blood for diagnostic labs (C-peptide/insulin) if etiology is unknown, then immediately administer **50 mL of 50% Dextrose IV**, or IM glucagon if no IV access.

- **Insulinoma**: Surgical resection is primary. Medical management (if poor surgical candidate): Diazoxide (1st line; adverse effects include edema and hirsutism) or Octreotide.

Chronic Complications Management

- **Nephropathy**: Optimal initial therapy in T2DM is an ACE inhibitor or ARB (do not combine them due to increased mortality). Indicated if persistent microalbuminuria or BP >140/80. SGLT2 inhibitors are also utilized.
- **Neuropathy Pain Control**:
  - *First-tier*: Tricyclic antidepressants (TCAs), duloxetine, pregabalin, controlled-release oxycodone.
  - *Second-tier*: Carbamazepine, gabapentin, tramadol.
- **Macrovascular Risk Reduction**: Near-normal glycemic control *does not* significantly reduce cardiovascular events in longstanding diabetes. Focus on BP control, treating dyslipidemia, smoking cessation, and daily aspirin.

Complications / Prognosis

- **Cerebral Edema (DKA)**: Almost exclusively affects children/teens (<20 years). Symptoms begin 12-24 hours after initiating treatment (headache, lethargy, pupillary changes, bradycardia, respiratory arrest). *Treatment*: Prompt administration of Mannitol or 3% Hypertonic Saline. High mortality (20-40%).
- **Mortality**: HHS has a significantly higher mortality rate (5-20%) compared to DKA.
- **Cardiovascular Death**: Up to 80% of people with diabetes will die from cardiovascular disease.

Past-Paper High Yield

- **Diagnostic priority in fasting hypoglycemia**: If a patient presents with episodic sweating, weight gain, and fasting hypoglycemia (e.g., FBG 40 mg/dL), the immediate next diagnostic step is to order **Fasting insulin and C-peptide** to differentiate endogenous hyperinsulinism (insulinoma) from exogenous sources.
- **Severe hypoglycemia emergency management**: A hospitalized or unconscious patient with acute hypoglycemia should have blood drawn for C-peptide/insulin workup first (if etiology is unknown), and immediately be given **50 mL of Dextrose 50%**. Do not rely on oral juice in severe/unresponsive cases.
- **Differentiating Diabetic vs. Drug-induced Neuropathy**: If a patient with *well-controlled* DM presents with new-onset peripheral neuropathy and is on a polypharmacy regimen including Metformin, highly suspect **Metformin-induced Vitamin B12 Deficiency** rather than typical diabetic neuropathy. This is a classic diagnostic trap.
- **Evaluating hospital-onset hypoglycemia**: If a patient develops hypoglycemia after an 8-hour hospital fast, measuring **C-peptide** is the definitive test to rule out exogenous insulin administration.

Memory Pearls

- **High C-peptide = Endogenous; Low C-peptide = Exogenous**: Exogenous insulin suppresses natural insulin and C-peptide production. If both insulin and C-peptide are high, think Insulinoma or Sulfonylurea abuse (check OHA screen to differentiate).
- **DKA fluids rule**: "Clear the sugar, then clear the ketones." Once glucose is <200 mg/dL, add dextrose (D5) to the fluids. This allows you to keep running the insulin infusion to fix the acidosis/ketosis without causing iatrogenic hypoglycemia.
- **Insulinoma triad**: Fasting hypoglycemia + Weight gain + High C-peptide.

Pituitary Disorders and Hypogonadism

Core Concepts

- **Hypothalamic-Pituitary Axis Dynamics:**
  - **Dopamine (DA):** Tonically *inhibits* Prolactin (strongest effect) and TSH.
  - **TRH:** *Stimulates* both TSH and Prolactin. (e.g., Hypothyroidism [↓T3/T4 → ↑TRH] can cause hyperprolactinemia).
  - **Prolactin:** *Inhibits* GnRH (Hyperprolactinemia → ↓GnRH → ↓LH/FSH → hypogonadism).
  - **Somatostatin:** *Inhibits* Growth Hormone (GH) and TSH.
- **Gonadotropins:**
  - **LH:** Stimulates Testosterone production in males.
  - **FSH:** Stimulates Spermatogenesis in males; Follicle stimulation and Estrogen production in females.
- **Primary vs. Central Hypogonadism:**
  - **Primary (Gonadal failure):** ↓ Sex hormones, **↑ LH/FSH** (lack of negative feedback).
  - **Central (Hypothalamic/Pituitary failure):** ↓ Sex hormones, **↓ or inappropriately normal LH/FSH**.

Diagnosis / Clinical Features

1. Hyperprolactinemia

- **Pathophysiology:** Symptoms result directly from ↑ Prolactin (galactorrhea) OR indirectly from ↓ Sex hormones (due to GnRH inhibition).
- **Causes:**
  - *Physiologic:* Pregnancy, breastfeeding, stress.
  - *Pharmacologic:* Dopamine antagonists (antipsychotics, metoclopramide), methyldopa, cimetidine, OCPs.
  - *Pathologic:* Hypothyroidism, Prolactinoma (micro <1cm; macro ≥1cm with mass effects like bitemporal hemianopsia).
- **Clinical Presentation:**
  - *Females:* Galactorrhea, oligomenorrhea/amenorrhea, infertility, hirsutism, osteoporosis.

- *Males:* Erectile dysfunction, decreased libido, infertility, gynecomastia, rare galactorrhea.

2. Growth Hormone Disorders

- **Acromegaly (Adults) / Gigantism (Children):** GH over-secretion. GH is diabetogenic (anti-insulin effect).
- **Dwarfism:** Under-secretion of GH in children.

3. Hypogonadism Syndromes

- **Kallmann Syndrome (Central):** Hypogonadotropic hypogonadism (↓ GnRH) accompanied by **anosmia** (absent sense of smell) and delayed puberty.
- **Klinefelter Syndrome (Primary - 47, XXY):** Male karyotype with small firm testes, delayed puberty, tall stature with disproportionately long limbs, gynecomastia (relative ↑ Estrogen compared to ↓ Testosterone), and infertility.
- **Turner Syndrome (Primary - 45, XO):** Female karyotype with short stature, streak (absent/underdeveloped) ovaries causing primary amenorrhea, webbed neck, widely spaced nipples, aortic coarctation, and sensorineural hearing loss.
- **Other Primary Male Causes:** Viral orchitis, radiation, chemotherapy, hemochromatosis (infiltrative).

4. Associated Reproductive Endocrinology Conditions

- **Congenital Adrenal Hyperplasia (21-hydroxylase deficiency):**
  - ↓ *Aldosterone:* Hypovolemia, hyperkalemia, ↑ Renin.
  - ↓ *Cortisol:* Hypoglycemia, nausea/vomiting, ↑ ACTH (causing skin hyperpigmentation).
  - ↑ *Androgens:* Ambiguous genitalia (females), precocious puberty (males).
- **Polycystic Ovarian Syndrome (PCOS):** Driven by hyperinsulinemia/insulin resistance → alters hypothalamic feedback → **↑ LH:FSH ratio** → ↑ Androgens from theca interna cells → unruptured follicles/anovulation.

Investigations

Hyperprolactinemia

- **Prolactinoma vs. "Stalk Effect":**
  - *Prolactinoma:* Tumor size directly correlates with prolactin levels (e.g., 3mm tumor = ~100 ng/mL; 2cm tumor = ~1000 ng/mL).
  - *Stalk Effect:* A large non-prolactinoma pituitary tumor (e.g., 2cm) compresses the infundibular stalk, preventing Dopamine from reaching the anterior pituitary. This disinhibits lactotrophs, causing a **mild** elevation in prolactin (e.g., 80 ng/mL) despite a huge tumor size.

Growth Hormone Disorders

- *GH is secreted in a pulsatile manner and affected by sleep/circadian rhythm, making random GH levels unreliable.*
- **Acromegaly:**

- **Screening:** Serum **IGF-1** levels (produced by the liver in response to GH; stable half-life).
- **Definitive: Oral Glucose Tolerance Test (OGTT) / Glucose Suppression Test**. (Normal response is GH suppression; in acromegaly, GH fails to suppress).

- **Dwarfism:**
  - **Screening:** Serum **IGFBP-3** (decreased because lower IGF-1 means less binding protein is needed/produced).
  - **Definitive: Insulin-induced hypoglycemia** (GH stimulation test). (Normal response is GH elevation; in dwarfism, GH fails to rise).

Hypogonadism

- **Male Evaluation:** Check free testosterone (morning, fasting, optimally 3 samples taken 1 hour apart).
- **Differentiating Next Steps:**
  - If ↓ Testosterone and normal/↓ LH/FSH (Central) → **Pituitary MRI**.
  - If ↓ Testosterone and extremely ↑ LH/FSH (Primary) → **Chromosomal analysis** (suspect Klinefelter).

Management

- **Prolactinoma:**
  - First-line: **Dopamine agonists** (Cabergoline 2x/week, Bromocriptine daily). They shrink tumor size effectively.
  - *Note:* Even with macroprolactinomas compressing the optic chiasm, DA agonists remain the primary treatment. Surgery is reserved *only* for refractory cases.
- **Acromegaly:**
  - Best definitive treatment: **Trans-sphenoidal surgery**.
- **PCOS:**
  - Weight reduction (↓ peripheral estrone formation).
  - OCPs (regulate cycle and prevent endometrial hyperplasia).
  - Clomiphene (for ovulation induction/fertility).
  - Anti-androgens like Spironolactone, Finasteride, or Flutamide (for hirsutism).

Complications / Prognosis

- **PCOS:** Increased risk of **endometrial cancer** due to unopposed estrogen from chronic anovulatory cycles.
- **Untreated Hypogonadism:** Osteoporosis, decreased muscle mass, persistent infertility, psychological distress.

Past-Paper High Yield

- **Kallmann syndrome presentation:** A young male with delayed puberty, underdeveloped secondary sexual characteristics, small testes, **anosmia (absent sense of smell)**, and labs

showing **↓ FSH, ↓ LH, and ↓ Testosterone**. (Recognize as central hypogonadism).

- **Acromegaly diagnostic test:** The most accurate/best diagnostic test is the **Oral Glucose Tolerance Test (OGTT)** / **Glucose Suppression Test**.
- **Acromegaly treatment:** The best management is **trans-sphenoidal surgery**.

Memory Pearls

- **"Stalk Effect" Rule of Thumb:** Big tumor + mildly elevated Prolactin (<100 ng/mL) = Stalk effect (not a macroprolactinoma). Big tumor + massively elevated Prolactin (>1000 ng/mL) = Macroprolactinoma.
- **Primary vs Central Labs:** The defect is where the hormone is LOW. If Testosterone is low, gonads are failing (Primary) unless LH is *also* low (Central/Pituitary).
- **TRH acts twice:** Remember that uncontrolled Primary Hypothyroidism can masquerade as a prolactinoma because ↑ TRH stimulates prolactin release. Check TSH!

Adrenal Disorders

Core Concepts

- **Anatomy**: The adult adrenal gland is a 4g pyramidal structure lying immediately above the kidney.
- **Hormone Secretion**: Cortisol and ACTH have a circadian, pulsatile secretion rhythm. Levels peak in the early morning and hit a nadir at midnight. *Note: Circadian rhythm is lost in Cushing's disease.*
- **Pharmacologic Steroid Potencies**:

STEROID	GLUCOCORTICOID POTENCY (ANTI-INFLAMMATORY)	MINERALOCORTICOID POTENCY (SALT RETENTION)
Cortisol (Hydrocortisone)	1	1
Prednisolone	4	0.75
Dexamethasone	17-26	0
Fludrocortisone	12	125

Diagnosis / Clinical Features

Cushing’s Syndrome (Glucocorticoid Excess)

- **Clinical signs**: Centripetal obesity, moon facies, hirsutism, plethora, livid abdominal striae, easy bruising (thin skin), and dorsal kyphosis (buffalo hump).
- **True Cushing vs. Pseudo-Cushing**: **Proximal myopathy** (e.g., difficulty rising from a sitting position) is a key clinical differentiator that strongly points toward true Cushing's syndrome rather than pseudo-Cushing's (e.g., severe obesity, depression, PCOS, alcoholism).
- **Causes**:
  - *ACTH-dependent:* Cushing's disease (pituitary adenoma), ectopic ACTH/CRH.
  - *ACTH-independent:* Adrenal adenoma/carcinoma, iatrogenic (pharmacologic steroids).

Glucocorticoid Deficiency

- **Primary (Addison's Disease)**: Autoimmune is the most common cause. Other causes include TB, HIV, bilateral adrenalectomy, and Waterhouse-Friderichsen syndrome.
  - *Classic sign:* **Hyperpigmentation** (palmar creases, buccal mucosa) due to excess POMC/ACTH cleavage.
  - *Features:* Both glucocorticoid and mineralocorticoid deficiency (salt-wasting).
- **Secondary**: **Exogenous steroid withdrawal** is the most common cause. Other causes include hypopituitarism and pituitary tumors.
  - *Features:* Only glucocorticoid deficiency; aldosterone is preserved (RAAS dependent). No hyperpigmentation.
- **Adrenal Crisis**: Severe hypotension, hyperkalemia, fever, and decreased level of consciousness. Frequently triggered by sudden cessation of chronic steroids or acute stress.

Congenital Adrenal Hyperplasia (CAH)

- **21-hydroxylase deficiency** accounts for 90% of cases. Defective conversion of 17-OH progesterone to 11-deoxycortisol → low cortisol → high ACTH → androgen excess.
- **Variants**:
  - *Salt-wasting (75%)*: Concomitant aldosterone deficiency. High neonatal mortality (hypotension, crisis in first week of life).
  - *Simple virilizing*: Ambiguous genitalia in females, precocious pseudopuberty in males.
  - *Nonclassic (Late-onset)*: Presents in young adulthood with hirsutism, anovulatory infertility, and acne (often mimics PCOS).

Investigations

Stepwise Workup for Cushing's Syndrome (Highly Tested)

1. **Does the patient have Cushing's?** (Screening)
   - *Initial test for symptomatic patients (obesity, striae, myopathy):* **24-hour urine free cortisol**, low-dose dexamethasone suppression test (LDDST), or late-night salivary cortisol.
2. **What is the cause?** (Once biochemically confirmed)
   - *Next step:* **Check serum ACTH level**.
   - **Low ACTH** + High Cortisol: ACTH-independent → Adrenal source. Confirms an **adrenal tumor**. *Next step: Adrenal CT.*
   - **High/Normal ACTH** + High Cortisol: ACTH-dependent. *Next step:* ***Pituitary MRI***.

Workup for Adrenal Insufficiency

- **Diagnostic Test of Choice**: **ACTH (Cosyntropin) stimulation test** with baseline cortisol and ACTH.
- *Imaging*: Primary hypoadrenalism requires Adrenal CT; Secondary requires Pituitary MRI.

Workup for Adrenal Incidentalomas All incidentally discovered adrenal masses (found on imaging for unrelated reasons) must be screened for functionality and malignancy.

- **Rule out hypersecretion**: 24-hour urinary fractionated metanephrines (pheochromocytoma), LDDST (preclinical Cushing's).
- **If hypertensive**: Measure the **Plasma Aldosterone Concentration to Plasma Renin Activity ratio (PAC/PRA ratio)**.

Management

Adrenal Insufficiency & Crisis

- **Acute Adrenal Crisis** (e.g., sudden cessation of chronic steroids):
  - Do NOT wait for laboratory results.
  - **Immediate management**: **IV hydrocortisone** (100 mg STAT, then q6h) + aggressive IV fluid resuscitation (2-3 L of 0.9% NaCl or D5W in 0.9% NaCl).
- **Long-Term Primary AI (Addison's)**:
  - Requires dual replacement: **Glucocorticoid** (Hydrocortisone BID) + **Mineralocorticoid** (Fludrocortisone orally).
  - Liberal salt intake, medical alert bracelet, and education on stress-dosing.
  - *Note:* The presence of essential hypertension is **not** an indication to increase the daily steroid replacement dose.

Adrenal Incidentalomas

- **Non-functioning, Benign, < 4 cm**: **Do nothing** acutely (conservative management, follow-up imaging in 6-12 months).
- **> 6 cm or Suspicious features**: Surgical removal (open adrenalectomy, not laparoscopic).

Pheochromocytoma

- **Medical Management**: Must establish alpha-blockade before beta-blockade to prevent unopposed alpha-receptor stimulation and severe hypertensive crisis.
- *Next best step for a patient on ACEi/CCB with uncontrolled BP:* Add **phenoxybenzamine** (alpha-blocker).

Primary Hyperaldosteronism (Conn's Syndrome)

- Classic presentation: Treatment-resistant hypertension and hypokalemia.
- *Next step for incidentaloma + HTN:* Aldosterone to renin ratio.

Complications / Prognosis

- **Nelson's Syndrome**: Occurs post-bilateral adrenalectomy for Cushing's disease. Lack of negative feedback causes rapid growth of a corticotropinoma (pituitary adenoma), leading to intense hyperpigmentation and local mass effect (e.g., CN III palsy).

- **Adrenocortical Carcinoma**: Aggressive tumor (often >6cm). 80% are functional (secreting glucocorticoids/androgens). Very poor prognosis (5-year survival <20%). Mitotane is used for medical control of hypersecretion and tumor growth.

Past-Paper High Yield

- **Cushing's Diagnosis Sequence**: You must follow the exact stepwise approach:
  - *Suspected signs (obesity, myopathy)* → Next step: **24-hour urine cortisol**.
  - *Confirmed hypercortisolism (high 24h urine/positive LDDST)* → Next step: **Serum ACTH**.
  - *High UFC + Low ACTH* → Confirms **Adrenal tumor**.
  - *High UFC + High ACTH* → Next step: **Pituitary MRI**.
- **Adrenal Crisis vs Stable Workup**:
  - If a patient presents with hypotensive crisis (especially after stopping long-term steroids), the next step is **IV Hydrocortisone**.
  - If a patient presents with vague symptoms (fatigue, mild hypotension) and you need to confirm the diagnosis, the next step is the **ACTH stimulation test**.
- **Incidentaloma Traps**:
  - Incidentaloma + Normal BP + Negative Cushing/Pheo workup + Small (<4cm/e.g., 3cm) → **Do nothing**.
  - Incidentaloma + **Hypertension** (even if metanephrines/cortisol are normal) → Next step: **Aldosterone to renin ratio (PAC/PRA)**.
- **Addison's Therapy**: A patient with autoimmune Addison's (indicated by hyperpigmentation) requires both mineralocorticoid and glucocorticoid replacement (e.g., Fludrocortisone + Hydrocortisone/Prednisone).
- **True vs. Pseudo-Cushing**: **Difficulty raising from a sitting position (proximal myopathy)** is a hallmark of true Cushing syndrome and is generally absent in pseudo-Cushing states.
- **Pheochromocytoma BP Control**: If BP is high on standard antihypertensives, the next best step is adding **phenoxybenzamine**. Never schedule immediate surgery without adequate alpha-blockade.

Memory Pearls

- **Cushing's Algorithm**: **S**creen with **S**ecretions (Urine/Saliva), **A**ssess **A**CTH, **I**nvestigate **I**maging.
- **Steroid Replacement Rule**: Primary AI needs *Primary* + *Secondary* hormones (Glucocorticoids + Mineralocorticoids). Secondary AI needs *Secondary* hormone replacement only (Glucocorticoids).
- **Pheo Blockade**: **A** before **B** (**A**lpha blockade with phenoxybenzamine before **B**eta blockade).

Thyroid Disorders

Core Concepts

- **Anatomy:** Normal weight is 15–20 g. Composed of two lobes and an isthmus.
- **Blood Supply:** Superior thyroid artery (from external carotid) and inferior thyroid artery (from subclavian). High blood flow (4–6 mL/min/g); in Graves' disease, flow can exceed 1 L/min,

producing an audible bruit or palpable thrill.

- **Histology:**
  - **Follicles:** Spherical units filled with proteinaceous colloid (major constituent of thyroid mass).
  - **Parafollicular (C) cells:** Source of calcitonin. Hyperplasia occurs early in MEN2, giving rise to medullary thyroid carcinoma.
- **Pathophysiology of Hypothyroidism-induced Hyperprolactinemia:** Primary hypothyroidism elevates TRH, which directly stimulates lactotrophs, leading to hyperprolactinemia. This resolves with levothyroxine replacement.
- **Polyglandular Autoimmune Syndromes:** A patient with hypothyroidism, vitiligo, fatigue, weight loss, and hypotension suggests concurrent adrenal insufficiency (Schmidt syndrome/PAS type 2). Next step is an **ACTH stimulation test**.

Diagnosis / Clinical Features

- **Hyperthyroidism (Graves' Disease):**
  - **Specific signs (highly tested):** Thyroid bruit, exophthalmos, pretibial myxedema, and thyroid acropachy (clubbing/nail changes).
  - Labs: High free T4/T3, low TSH.
- **Subacute Viral Thyroiditis:**
  - Presents with palpitations, tachycardia, and a tender thyroid (or post-viral symptoms).
  - Labs/Imaging: Suppressed TSH, elevated T4, **decreased** iodine uptake.
- **Thyroid Storm:**
  - Acute, life-threatening hypermetabolic state.
  - Presentation: Fever, severe tachycardia, hypertension, neurological (agitation/delirium), and GI abnormalities. Diagnosis is primarily clinical.
- **Myxedema Coma:**
  - Life-threatening, decompensated hypothyroidism precipitated by cold, infection, or drugs.
  - Presentation: Altered mental status (lethargy, stupor, coma), severe bradycardia, and hypothermia.
- **Thyroid Malignancies:**
  - **Papillary Carcinoma (70–80%):** Most common. Females (30–50 yrs). Indolent, lymphatic spread. Associated with childhood radiation exposure. Histology: finger-like projections.
  - **Follicular Carcinoma (10–15%):** Females (40–60 yrs). Histology: spherical cells. **Hematogenous spread** (invades blood vessels -> bone/lung).
  - **Medullary Carcinoma (5–10%):** Arises from C-cells (calcitonin). Associated with MEN2A, MEN2B, or sporadic.
  - **Anaplastic Carcinoma (<5%):** Elderly (>65 yrs). Loss of normal structure, highly aggressive, invasive, and least responsive to treatment.

Investigations

- **Thyroid Function Tests (TFTs):** Initial step for almost all thyroid complaints.
  - *Central Hypothyroidism:* Post-pituitary surgery (e.g., transsphenoidal adenoma removal), TSH is an unreliable marker. **Measure Free T4** to assess thyroid function.
- **Radioactive Iodine Uptake (RAIU) Scan:**
  - **Increased Uptake:** Graves' disease, toxic MNG, toxic adenoma, TSH-oma, hCG-induced (pregnancy, trophoblastic tumors).
  - **Decreased Uptake:** Subacute thyroiditis, iatrogenic/factitious thyrotoxicosis, struma ovarii, metastatic thyroid carcinoma.
  - *Contraindication:* Absolutely **do not do** during pregnancy.
- **Thyroid Nodule Workup:**
  - **Step 1:** Check TSH.
  - **Step 2 (Normal or High TSH):** Indicates a euthyroid or hypothyroid state. Next step for a suspicious, complex, or solid nodule (e.g., >1 cm, microcalcifications) is **Ultrasound-guided Fine Needle Aspiration (FNA)**.
  - **Step 2 (Low TSH):** Next step is a **Radionuclide Uptake Scan** to differentiate "hot" (rarely malignant) vs. "cold" (higher malignancy risk) nodules.
  - *Gold Standard for diagnosis:* FNA or surgical pathology.

Management

- **Hyperthyroidism:**
  - *General:* Anti-thyroid drugs (carbimazole/methimazole, PTU), radioactive iodine (I-131), or surgery. Temporary beta-blockers for symptom control.
  - *Pregnancy:* **PTU** is used if planning pregnancy or in the **1st trimester** (Methimazole is teratogenic in the 1st trimester). Switch to **Carbimazole/Methimazole** in the **2nd/3rd trimesters**.
- **Subacute Thyroiditis:**
  - Self-limiting. Management is **observation + Propranolol** (for palpitations/tachycardia), NSAIDs, or steroids. Anti-thyroid meds are not indicated.
- **Thyroid Storm:**
  - Supportive care, Propylthiouracil (PTU), and Beta-blockers.
- **Hypothyroidism:**
  - *Standard:* Levothyroxine (no need for T3).
  - *Elderly/Cardiac Patients:* Start with a **low dose** and titrate slowly to avoid precipitating angina/ischemia.
  - *Myxedema Coma:* Supportive measures + **IV levothyroxine**. Must give **stress-dose steroids** after drawing cortisol, due to the risk of concurrent adrenal insufficiency.
- **Thyroid Nodules / Goiter:**

    - ATA does *not* recommend levothyroxine suppression therapy for benign solitary nodules or sporadic non-toxic MNGs in iodine-sufficient populations.
    - *Surgical Indications:* Malignancy, indeterminate/repeatedly non-diagnostic FNA, cosmetic concerns, obstructive symptoms.
- **Thyroid Cancer:** Total/hemi-thyroidectomy (needs experienced surgeon) -> I-131 ablation -> External beam radiation/chemo if advanced.

Past-Paper High Yield

- **Nodule Workup:** Euthyroid patient with a solid, hypoechoic, or complex thyroid nodule (e.g., 1.5 cm with microcalcifications) + normal TSH -> **Next step: FNA.** (Do not pick observe, levothyroxine, or scan).
- **Low-Uptake Thyrotoxicosis:** Commonly tested causes include subacute viral thyroiditis and **factitious thyrotoxicosis** (exogenous hormone abuse).
- **Hyperemesis Gravidarum vs. Thyrotoxicosis:** A pregnant woman (e.g., 11 weeks) with severe N/V, low TSH, and upper-limit-normal T3/T4 has **hCG-induced hyperthyroidism**. This is transient and cross-reactivity-driven. If severe sweating/palpitations occur at 8 weeks with a profoundly high T4, do an **abdominal US to rule out molar pregnancy**.
- **Pregnancy Management:**
    - Planning pregnancy / 1st trimester -> **PTU**.
    - 2nd/3rd trimester thyrotoxicosis -> **Carbimazole/Methimazole**.
    - Never use RAI uptake/scans or radioactive ablation in pregnancy.
- **Levothyroxine Dosing:** Elderly patients with a history of heart disease *must* start on a low dose of levothyroxine, unlike young healthy adults.
- **Hypothyroidism + Hyperprolactinemia:** Reassure the patient that correcting the hypothyroidism with levothyroxine will resolve the hyperprolactinemia.
- **Central Hypothyroidism:** Post-transsphenoidal surgery, monitor thyroid function by measuring **T4**, not TSH.
- **Hyperparathyroidism Differential:** A 70F with back pain, abdominal pain, constipation, High Ca, High PTH, Low PO4 -> **Primary Hyperparathyroidism**. An asymptomatic patient with mildly elevated Ca (e.g., 10.6), high PTH, and high urine Ca is typically managed with **Observation** if not meeting surgical criteria.

Memory Pearls

- **Papillary vs. Follicular: P**apillary has **P**rojections (finger-like) and stays local (lymphatic). **F**ollicular flows **F**ar (hematogenous/blood vessel invasion).
- **Graves' specific signs: A**cropachy, **B**ruit, **E**xophthalmos, **P**retibial myxedema. (Other hyperthyroid states only have adrenergic signs).
- **PTU vs. Methimazole: P**TU for **P**lanning **P**regnancy.

Calcium Disorders: Hypercalcemia

Core Concepts

Hypercalcemia occurs when calcium entry into the circulation (via accelerated bone resorption or excessive GI absorption) exceeds calcium excretion (urine) or deposition (bone). Primary hyperparathyroidism and malignancy account for >90% of cases.

Classification by PTH status:

- **PTH-Mediated (High or Inappropriately Normal PTH):**
  - Primary hyperparathyroidism (adenoma, hyperplasia, rare carcinoma)
  - Familial Hypocalciuric Hypercalcemia (FHH)
  - MEN Type I and IIa
  - Tertiary hyperparathyroidism (seen in advanced CKD)
  - Lithium-induced hyperparathyroidism
- **PTH-Independent (Low/Suppressed PTH < 20 pg/mL):**
  - **Malignancy:** PTHrP production (squamous cell, solid tumors), osteolysis (bone mets, multiple myeloma), ectopic PTH (rare).
  - **Granulomatous diseases:** Sarcoidosis, TB (macrophages have extrarenal 1-α-hydroxylase → ↑ 1,25-OH Vitamin D).
  - **Medications:** Thiazide diuretics, Vitamin D/A toxicity, Theophylline toxicity, Milk-alkali syndrome.
  - **Endocrine/Other:** Hyperthyroidism, Adrenal insufficiency, Pheochromocytoma, Immobilization, Paget disease (especially with bed rest).

Diagnosis / Clinical Features

- **Presentation (Symptoms correlate with acuity and degree of elevation):**
  - **Bones:** Bone pain.
  - **Stones:** Nephrolithiasis, polyuria, nocturia, dehydration, renal failure.
  - **Groans (GI):** Constipation, nausea, anorexia, pancreatitis, peptic ulcer disease.
  - **Psychic Moans (CNS):** Lethargy, weakness, confusion, coma.
  - **Cardiac:** Syncope, arrhythmias.
- **Primary Hyperparathyroidism:** Usually chronic, asymptomatic, mild hypercalcemia (< 12 mg/dL).
- **Malignancy-associated:** Usually acute, symptomatic, severe hypercalcemia (> 12–14 mg/dL). Often signifies advanced disease and a poor prognosis.

Investigations

1. **Confirm Hypercalcemia:** Repeat the test!
   - Rule out pseudohypercalcemia by correcting for albumin: `Corrected Ca = Total Ca + [0.8 x (4.0 – Albumin)]`.
   - *Alternatively, measure ionized calcium.*

2. **Measure Intact PTH:** This is the critical branch point.
    - **High or Upper-Normal PTH:** Indicates a PTH-mediated cause (Primary HPT or FHH).
    - **Low PTH (< 20 pg/mL):** Indicates a PTH-independent cause (Malignancy, Granulomatous disease, Vitamin D toxicity).
3. **Evaluate Urine Calcium (if PTH is normal/high):**
    - **High/Normal:** Points to Primary hyperparathyroidism.
    - **Low (< 100 mg/day or Fractional Excretion < 1%):** Suspect FHH, Thiazides, or Milk-alkali syndrome.
4. **Evaluate PTH-Independent Causes (if PTH < 20 pg/mL):**
    - Measure **PTHrP**, **25-OH-Vit D** (calcidiol), and **1,25-OH-Vit D** (calcitriol).
    - If still unclear, consider TSH, SPEP/UPEP (for myeloma), and Vitamin A levels.

Management

Severity-Based Approach:

- **Mild / Asymptomatic (< 12 mg/dL):** Hydration (6–8 glasses of water/day). Avoid aggravating factors (thiazides, lithium, volume depletion, bed rest, high calcium diet >1000 mg/day).
- **Severe (> 14 mg/dL) or Highly Symptomatic:**
    1. **Isotonic Saline (0.9% NaCl):** First-line. Expands volume and promotes renal calcium excretion. Rate: 200–300 mL/h, monitoring urine output and for fluid overload.
    2. **Calcitonin (IM/SC):** Rapid onset (lowers Ca within 4–6 hrs) but subject to tachyphylaxis within 48 hours. Used as bridge therapy.
    3. **Bisphosphonates (IV Zoledronic acid or Pamidronate):** Highly effective for osteoclast-mediated resorption. Slow onset (days) but sustained effect. Preferred agents for malignancy.
    - *Note on Loop Diuretics (Furosemide):* Now reserved *only* for managing volume overload from IV saline. No longer routinely recommended for primary calcium reduction due to risks of electrolyte derangement and volume depletion.

Specific/Targeted Therapies:

- **Glucocorticoids (Prednisone):** Specifically for granulomatous diseases (e.g., sarcoidosis) or lymphomas. Decreases extrarenal calcitriol production (onset 2–5 days).
- **Calcimimetics (Cinacalcet):** Lowers PTH; used for parathyroid carcinoma or severe secondary HPT in dialysis patients.
- **Gallium Nitrate:** Inhibits osteoclastic resorption and PTH secretion; nephrotoxic, requires continuous infusion.
- **Hemodialysis:** Last resort for severe hypercalcemia with advanced CKD or heart failure where IV fluids cannot be safely given.
- **Parathyroidectomy:** Definitive treatment for Primary HPT. Indications in asymptomatic patients:
    - Age < 50 years.
    - Serum Ca > 1.0 mg/dL above the upper limit of normal.
    - Low Bone Mineral Density (BMD / osteoporosis).

- CKD / Impaired renal function (due to hypercalcemia).

Complications / Prognosis

- Hypercalcemia of malignancy heavily portends a very poor prognosis.
- Milk-alkali syndrome can result in irreversible structural renal injury if prolonged.

Past-Paper High Yield

- **FHH vs. Primary HPT:** An asymptomatic patient with high calcium, high/normal PTH, and a *family history* of hypercalcemia requires a **urine calcium-to-creatinine ratio** to diagnose FHH. (FHH will show extremely low urine calcium).
- **Diagnosing Primary HPT:** An asymptomatic patient with high calcium, *normal* (or elevated) PTH, and normal creatinine most likely has Primary HPT. (Normal PTH is inappropriately unsuppressed in the face of high calcium).
- **Sarcoidosis Mechanism:** Hypercalcemia is driven by extrarenal 1-α-hydroxylase activity increasing 1,25-OH-Vit D. You will **NOT** find high PTH (PTH will be strongly suppressed).
- **Malignancy Traps:**
  - A male with **prostate cancer** presenting with hypercalcemia → best next step is to **measure PTHrP**.
  - A heavy smoker with a cavitary right upper lobe lesion (Squamous Cell Carcinoma) presenting with hypercalcemia (e.g., 11.9 mg/dL) → Hypercalcemia is due to PTHrP from the squamous cell lung cancer.
- **Vitamin D Deficiency Traps:**
  - Vitamin D deficiency causes *low* calcium and *low* phosphate, leading to secondary hyperparathyroidism (HIGH PTH).
  - A finding of "normal PTH" or "high phosphate and low calcium" is **incorrect** for Vitamin D deficiency.

Memory Pearls

- **Causes of Hypocalciuric Hypercalcemia (Low urine Ca):** Think **F**HH, **T**hiazides, **M**ilk-alkali (**F**ewer **T**hings **M**ake urine Ca low).
- **Albumin Correction Rule:** For every 1.0 g/dL drop in albumin below 4.0, total calcium drops by 0.8 mg/dL.
- **Calcitonin vs. Bisphosphonates:** Calcitonin is fast but transient (tachyphylaxis); Bisphosphonates are slow but lasting. Use them together in severe hypercalcemic crises.

Reproductive Disorders

Core Concepts

- **Hypogonadism Definition:** Decreased function of the gonads.
  - **Male:** Decreased testosterone production and/or impaired spermatogenesis.

    - **Female:** Decreased estrogen production.
- **Primary vs. Central Hypogonadism:** Differentiated by **LH levels**.
    - **Primary:** Pathology in the gonads (Testes/Ovaries). LH is **high** (loss of negative feedback).
    - **Central:** Pathology in the pituitary or hypothalamus. LH is **low or inappropriately normal**.
- *Note: Gynecomastia and Hirsutism are strictly self-reading topics for this module but frequently tested alongside these core concepts.*

Diagnosis / Clinical Features

Symptoms of Testosterone Deficiency (Males)

- **Mild-Moderate:** Non-specific fatigue, weakness, depression, daytime sleepiness, reduced confidence, decreased libido, mild erectile dysfunction.
- **Advanced:** Loss of facial hair, loss of muscle mass, gynecomastia.
- **Severe:** Infertility.

Specific Syndromes causing Hypogonadism

- **Klinefelter Syndrome (Primary):** Chromosomal disorder (47, XXY). Characterized by tall stature, small firm testicles, gynecomastia, decreased libido, and infertility.
- **Kallmann Syndrome (Central):** Disordered migration of GnRH-producing neurons into the hypothalamus.
    - Features: Hypogonadism combined with **anosmia**.
    - Associated midline defects: Cleft lip/palate, sensorineural deafness, cerebellar ataxia, and renal agenesis.
    - Genetics: Low T, LH, and FSH. Can be X-linked, AD, or AR.
- **Turner Syndrome (Primary):** Chromosomal disorder affecting females (45, XO). Complete or partial absence of one X chromosome.

Congenital Adrenal Hyperplasia (CAH) Defect in adrenal hormone synthesis enzymes. **21-hydroxylase deficiency** is the most common. Clinical presentation depends on the severity of the enzyme deficiency:

- **Classical CAH (Severe deficiency):** Presents at birth. Females have ambiguous genitalia.
    - *Salt-losing form:* Accompanied by severe clinical adrenal insufficiency (AI).
    - *Non-salt-losing form:* Ambiguous genitalia without clinical AI.
- **Non-Classical CAH (Mild deficiency):** Presents later (puberty/adolescence) with primary amenorrhea OR irregular periods and hirsutism.

Investigations

1. Confirming Testosterone Deficiency

- **Initial Test:** Suspected hypogonadism requires measuring testosterone.

- **Ideal Test:** Free testosterone by equilibrium dialysis or bioavailable testosterone (often unavailable locally).
- **Practical Step:** Measure **Total Testosterone and SHBG**, then use a calculator to determine free and bioavailable testosterone.

2. Localizing the Defect (Next Step)

- **Measure LH:**
  - **High LH (Primary Hypogonadism):** Investigate testicular causes (karyotype for Klinefelter, history of chemo/radiation, surgical removal, or infiltrative diseases like hemochromatosis).
  - **Low/Normal LH (Central Hypogonadism):** Next best step is a **Pituitary MRI** to rule out structural hypothalamic/pituitary pathology.

3. Congenital Adrenal Hyperplasia Workup

- **Diagnostic marker:** Measure **17-hydroxyprogesterone** (elevated in 21-hydroxylase deficiency).
- *Key differentiator:* Patients with 21-hydroxylase deficiency are typically **normotensive**, in contrast to other forms of CAH (like 11β-hydroxylase deficiency, which presents with hypertension).

Past-Paper High Yield

- **Infertility Workup Next Step:** In a male patient presenting with decreased libido, fatigue, **small firm testicles**, family history of infertility, and **tall stature** (e.g., 1.92 meters), the diagnosis is Klinefelter Syndrome.
  - **Exam Trap/Next Step:** Do not immediately biopsy the testicle or order an MRI; the correct **next step is Karyotyping** (to confirm 47, XXY).

Memory Pearls

- **Anosmia + Hypogonadism + Midline defects:** Kallmann Syndrome (Failure of GnRH migration).
- **Tall stature + Small firm testes + Infertility:** Klinefelter Syndrome (47, XXY).
- **High LH:** The problem is in the gonads (Primary).
- **Low/Normal LH:** The problem is in the brain (Central) → get a Pituitary MRI.
- **Elevated 17-OH Progesterone + Normotensive:** 21-Hydroxylase Deficiency.

Diabetes Mellitus

Core Concepts

- **Definition:** A state of hyperglycemia resulting from a progressive loss of insulin secretion from beta cells, often superimposed on a background of insulin resistance.
- **Classification by Etiology:**
  - **Type 1 Diabetes (Absolute insulin deficiency):**
    - **Type 1A:** Autoimmune destruction. Associated with autoantibodies (GAD, insulin, IA-2, ZnT8).

        - **Type 1B:** Idiopathic/non-autoimmune beta-cell loss.
    - **Type 2 Diabetes (Relative deficiency):** Driven by peripheral insulin resistance and beta-cell dysfunction. Accounts for 90-95% of cases. Strongly linked to obesity (specifically visceral/intra-abdominal fat), sedentary lifestyle, and family history.
    - **Monogenic Diabetes (formerly MODY):** Autosomal dominant transmission, onset typically < 25 years, lack of autoantibodies. Associated with genetic mutations (e.g., HNF1A, GCK, HNF4A).
    - **Latent Autoimmune Diabetes in Adults (LADA):** Adult-onset, positive for ≥1 islet autoantibody, slow progression to insulin dependence. Clinically resembles T2DM initially but has a sub-therapeutic response to oral agents (like metformin or sulfonylureas).
    - **Secondary Diabetes:**
        - Conditions causing **insulin resistance:** Gestational DM, Cortisol-associated DM.
        - Conditions causing **insulin deficiency (NOT resistance):** Pancreatitis-associated DM, Cystic fibrosis-associated DM.

Diagnosis / Clinical Features

- **Clinical Presentation:**
    - The majority of T2DM patients are asymptomatic at presentation.
    - Classic symptoms (catabolic state): Polyuria, polydipsia, nocturia, blurred vision, and weight loss.
- **Diagnostic Criteria:**
    - **Symptomatic patients:** Random plasma glucose ≥ 200 mg/dL + classic symptoms.
    - **Asymptomatic patients:** Requires two abnormal test results (either concordant from the same sample or repeated on a separate day):
        - Fasting Plasma Glucose (FPG) ≥ 126 mg/dL.
        - 2-hour Plasma Glucose ≥ 200 mg/dL (during a 75g OGTT).
        - HbA1c ≥ 6.5%.

Investigations

- **Islet Autoantibody Testing:** Indicated when the diagnosis is uncertain, in young adults (<35), lean patients, or those with a sub-therapeutic response to oral medications.
- **C-Peptide Level:** Differentiates endogenous vs. exogenous hyperinsulinemia. Low C-peptide with high insulin in a hypoglycemic patient indicates **exogenous insulin** administration.
- **Pre-Insulin Labs:** Always check **potassium (K) levels** before initiating insulin, as insulin drives potassium into cells and can trigger severe hypokalemia.
- **Insulin Tolerance Test:** The gold standard test for confirming low Growth Hormone (GH) in a child presenting with short stature.

Management

- **Treatment Goals:** Achieve near-normoglycemia (typically HbA1c ≤ 7.0% for most), minimize cardiovascular risk factors, and avoid hypoglycemia.

- **Lifestyle Modifications:** Medical nutrition therapy, weight reduction, and exercise. A 3–6 month trial of strictly lifestyle changes is only appropriate for highly motivated patients with an HbA1c near target (< 7.5%).
- **Metformin:** First-line pharmacologic therapy for asymptomatic, non-catabolic T2DM.
  - *Indications:* Start immediately alongside lifestyle modifications if HbA1c > 7.5% or FBG is elevated but below the severe threshold (e.g., FBG 180–240 mg/dL).
  - *Advantages:* Highly efficacious, weight-neutral, low hypoglycemia risk.
  - *Adverse Effects:* Gastrointestinal upset (take with food to minimize), lactic acidosis (rare but high mortality), and **Vitamin B12 deficiency** (can present as macrocytic anemia or peripheral neuropathy).
- **Insulin Therapy Initiation:**
  - Indicated as initial therapy in T2DM if the patient is **symptomatic/catabolic** (weight loss, ketonuria) or has severe hyperglycemia (FBG > 250 mg/dL, Random BG > 300 mg/dL, or HbA1c > 10%).
- **Drug Selection Based on Patient Profile:**
  - *Weight loss priority:* GLP-1 receptor agonists or SGLT2 inhibitors.
  - *Cardiovascular/Renal Comorbidities:* GLP-1 receptor agonists or SGLT2 inhibitors.
  - *Cost concerns:* Sulfonylureas (e.g., glipizide) or pioglitazone.
- **Hospitalized Patient Hyperglycemia:**
  - Always use scheduled **basal and pre-prandial insulin**. Do not rely on a standalone insulin sliding scale.
- **Diabetic Ketoacidosis (DKA) Management:**
  - Mainstays are IV fluids, potassium replacement, and **regular insulin**.
  - Bicarbonate is generally **not indicated** (especially at pH levels like 7.25); it is strictly reserved for profoundly severe acidemia (pH < 6.9).
  - Address underlying precipitants (e.g., start antibiotics if the patient has signs of infection like fever and dysuria).

Complications / Prognosis

- Monitor HbA1c at least twice yearly in patients meeting glycemic goals, and quarterly in patients who are not at goal or whose therapy has changed.
- Reversing obesity can dramatically improve glycemic management and may even induce diabetes remission.

Past-Paper High Yield

- **Diagnostic confirmation:** If an asymptomatic patient has an HbA1c of 6.6% and an FBG of 127 mg/dL on the same day, they are definitively diagnosed with DM; no further testing is required.
- **Insulin Resistance vs. Deficiency trap:** Pancreatitis-associated DM and Cystic fibrosis-associated DM are due to structural destruction of the pancreas (deficiency), making them the *least likely* forms of diabetes to be associated with insulin resistance.

- **Starting Insulin:** A newly diagnosed patient with classic catabolic symptoms (e.g., random glucose 260 mg/dL, polyuria, weight loss) must be started on **insulin** as the next step, not oral agents.
- **Starting Metformin:** A patient with isolated polyuria, FBG 240 mg/dL, and HbA1c 7.5% (no weight loss or extreme elevations) should be started on **lifestyle modifications and metformin**.
- **Metformin-induced Anemia:** If a well-controlled diabetic on metformin, a sulfonylurea, and a statin develops new-onset anemia or neuropathy, it is most likely due to **B12 deficiency from metformin**.
- **DKA Insulin Choice:** For a patient in ketoacidosis, the specific type of insulin required is **regular insulin**.
- **Weight loss add-on:** For an obese patient (BMI 35) already on metformin who actively wants to lose weight, the best drug to add is a **GLP-1 agonist**.

Memory Pearls

- **LADA:** Think "Type 1.5" — autoimmune destruction presenting in adulthood. Suspect it when a non-obese adult fails metformin.
- **MODY: M**onogenic, **O**nset young (<25), **D**ominant inheritance, **Y**ields negative autoantibodies.
- **Metformin Side Effects (The 3 M's): M**acrocytic anemia (B12 deficiency), **M**etallic taste (GI upset), **M**uscle pain (Lactic acidosis).
- **Insulin pre-requisite:** Check the **K** before you give the **Key** (insulin) to the cell.
- **Hospital Glucose Management:** Basal-bolus is best; sliding scale is a mess.

Diabetes Cases

Core Concepts

- **Diagnosis Principles:** A single abnormal glucose reading (fasting ≥ 126 mg/dL or random ≥ 200 mg/dL) is only diagnostic if accompanied by unequivocal classic symptoms (polyuria, polydipsia, unexplained weight loss). Otherwise, a second confirmatory test is required.
- **DKA Sequence of Care:** Intravenous fluids and electrolyte assessment always precede insulin administration to prevent fatal shifts in potassium.
- **Glycemic Targets:** Elderly patients with significant comorbidities (e.g., CKD, CAD) require relaxed HbA1c targets to avoid life-threatening hypoglycemia.

Diagnosis / Clinical Features

- **Interpreting Random Glucose:** A random glucose ≥ 200 mg/dL after a large meal in an asymptomatic patient is *not* sufficient for diagnosis. More testing (fasting glucose, HbA1c, or OGTT) is required.
- **Clarifying Symptoms:** If a patient presents with a single elevated fasting glucose (e.g., 136 mg/dL) and an isolated symptom like weight loss, you must clarify for other classic symptoms (polyuria, polydipsia) before making a definitive diagnosis without a second test.
- **Adult-Onset Autoimmune Diabetes (LADA / T1DM):** Suspect Type 1 DM or LADA in lean adults (e.g., BMI ~22) presenting with rapid-onset unintentional weight loss, polyuria, and severe

hyperglycemia. Do not assume Type 2 DM based on age alone.

- **Cystic Fibrosis-Related Diabetes (CFRD):** A distinct clinical entity in patients with cystic fibrosis. It is neither classic Type 1 nor Type 2.

Investigations

- **Differentiating T1 vs. T2 DM:** In lean adults with severe symptomatic hyperglycemia, check **serum C-peptide** (inappropriately low in T1DM/LADA) and **autoantibodies** (e.g., GAD antibodies).
- **Initial DKA Workup:** Before starting targeted therapy, draw labs for Kidney Function Tests (KFTs - specifically potassium), serum ketones, ABG, Urinalysis (UA), and a CXR (to identify infectious triggers).

Management

- **DKA Initial Step:** The best *first* step in severe hyperglycemia/DKA (e.g., glucometer reads "Hi", accompanied by nausea/vomiting) is to **start IV Normal Saline (0.9%) and draw baseline labs**.
  - *Exam Trap:* Never start an insulin drip before knowing the serum potassium level, as insulin drives potassium intracellularly and can cause fatal arrhythmias if the patient is hypokalemic.
- **CFRD Treatment:** Patients diagnosed with Cystic Fibrosis-Related Diabetes require **insulin** therapy.
- **Basal Insulin Adjustment (Somogyi Effect / Overbasalization):**
  - *Scenario:* Elderly patient on basal-bolus insulin with a low/strict HbA1c (e.g., 6.1%), seemingly normal daytime sugars, but highly elevated morning fasting blood glucose (e.g., 180–250 mg/dL).
  - *Action:* **Decrease the basal insulin dose** (e.g., glargine/Lantus).
  - *Rationale:* A low HbA1c discordant with high morning fasting sugars strongly suggests undetected nocturnal hypoglycemia causing rebound morning hyperglycemia.
- **Diabetic Neuropathy / Erectile Dysfunction (ED):** ED is a common microvascular/autonomic complication. First-line therapy includes PDE-5 inhibitors (e.g., sildenafil).

Past-Paper High Yield

- **Sildenafil Contraindications:** In a diabetic patient prescribed sildenafil (Viagra) for ED, **nitrates (e.g., isosorbide dinitrate)** are absolutely contraindicated. Co-administration causes excessive cGMP accumulation, leading to profound, refractory vasodilation and life-threatening hypotension.

Memory Pearls

- **DKA Priority:** *Fluids first, K+ second, Insulin third.*
- **Discordant A1c vs. Fasting:** *Low A1c + High Fasting = Hidden Lows.* (Decrease the basal insulin).
- **Lean + Hyperglycemia:** *Age does not rule out Type 1.* Check C-peptide and GAD in lean adults with severe classic symptoms.
- **The "NO" Rule: N**itrates + Sildenafil = **NO** (Nitric Oxide overload → severe hypotension).

GI

Exam Map

TOPIC CATEGORY	PAST QUESTIONS	REVISION PRIORITY
Esophageal Disorders	23	**Tier 1 (Crucial)**
Inflammatory Bowel Disease	14	**Tier 1 (Crucial)**
Liver Cirrhosis & Complications	4	Tier 2 (High)
Upper GI Bleeding	4	Tier 2 (High)
Autoimmune, ASH/NASH, Hereditary Liver	7	Tier 2 (High)
Malabsorption & Viral Hepatitis	3	Tier 3 (Medium)
Pancreatitis	Lecture add-on	Targeted High Yield

High-Yield Exam Themes & Revision Priorities:

- **Esophageal Dysphagia Timelines:** You must reflexively distinguish between mechanical obstruction (solids first, progressing to liquids) and motility disorders like Achalasia (simultaneous difficulty with solids *and* liquids).
- **The Eosinophilic Esophagitis (EoE) Patient:** Frequently tested as a young adult with a history of asthma/eczema presenting with a food bolus impaction. Look for "rings and furrows" on EGD and treat with topical/swallowed steroids.
- **IBD Pathology & Extraintestinal Rules:** Differentiating UC (continuous, crypt abscesses, rectal involvement) from CD (skip lesions, granulomas, transmural) is heavily tested. **Exam Trap:** UC patients who develop Primary Sclerosing Cholangitis (PSC) require *annual* colonoscopies immediately upon PSC diagnosis due to massive cancer risk.
- **Acute GI Bleed Management:** Hemodynamic stabilization is always the correct first step. Once stable, upper GI bleeds require EGD within 24 hours. Do *not* choose NGT lavage to rule out an upper GI bleed (high false-negative rate).
- **Differentiating Lower GI Bleeds:** Painless, brisk right-sided bleeding points to Diverticulosis. Painful, left-sided (LLQ) bleeding with "thumbprinting" on X-ray points to Ischemic Colitis.
- **Autoimmune Liver Triads:** Memorize the antibody associations: PBC = AMA positive (treat with UDCA); PSC = p-ANCA positive (strongly associated with Ulcerative Colitis, diagnose with MRCP); AIH = ANA/SMA or LKM-1 positive (treat with steroids).
- **Cirrhosis Fluid Management:** Calculate the SAAG (≥ 1.1 = portal hypertension). If performing a large-volume paracentesis, you must replace albumin (8 grams per liter removed) to prevent circulatory collapse.
- **Wilson's Disease Lab Trap:** Untreated Wilson's presents with *low* total serum copper and low ceruloplasmin, but highly elevated 24-hour urine copper. Do not pick "low urine copper" or "high

serum copper" as correct statements.

- **Liver Enzyme Ratios:** Early NASH presents with AST/ALT < 1, whereas Alcoholic Hepatitis (ASH) presents with AST/ALT > 2.
- **Malabsorption Localization:** Use deficiency patterns to locate the disease: Iron = Duodenum (Celiac), Folate = Jejunum, B12/Bile Salts = Terminal Ileum (Crohn's). Use a high stool osmotic gap to identify carbohydrate malabsorption (e.g., lactose intolerance).
- **Pancreatitis Decision Traps:** Review drug-induced causes, amylase-vs-lipase interpretation, gallstone predictors, antibiotic pancreatic penetration, Ranson severity criteria, and pseudocyst intervention thresholds.

Esophageal Disorders

Core Concepts

- **GERD Pathophysiology**: Reflects an imbalance between injurious and defensive factors.
  - Primarily driven by **Transient Lower Esophageal Sphincter Relaxations (TLESRs)** or a hypotensive LES.
  - Aggravated by fat, chocolate, caffeine, smoking, alcohol, and drugs (e.g., anticholinergics, CCBs, nitrates, TCAs).
  - Anatomic disruption of the gastroesophageal junction (GEJ), such as a sliding hiatal hernia, contributes to incompetence.
- **Achalasia**: Results from the progressive degeneration of inhibitory ganglion cells (neurons) in the myenteric plexus -> failure of LES relaxation and aperistalsis in the esophageal body.
  - *Pseudoachalasia (Secondary)*: Must be ruled out. Causes include gastric carcinoma, Chagas disease, amyloidosis, sarcoidosis, Eosinophilic Esophagitis (EoE), and neurofibromatosis.
- **Eosinophilic Esophagitis (EoE)**: A chronic, immune/antigen-mediated disease heavily associated with atopic/allergic conditions (asthma, eczema).
- **Esophageal Motility Disorders**:
  - *Diffuse Esophageal Spasm*: Impaired inhibitory innervation leading to premature, simultaneous, and rapidly propagated contractions.
  - *Nutcracker Esophagus*: Smooth muscle hypertrophy or excessive excitation causing extremely high-pressure, yet sequential, contractions.
- **Hiatal Hernias**:
  - *Sliding*: Both the GEJ and part of the fundus herniate into the thorax (frequently contributes to GERD).
  - *Para-esophageal*: The fundus herniates beside a normally located GEJ (risk of incarceration, ulceration, or dysphagia).

Diagnosis / Clinical Features

- **General Symptoms**: Dysphagia (difficulty swallowing), odynophagia (painful swallowing), regurgitation, heartburn, non-cardiac chest pain.

- **GERD**: Classic heartburn and regurgitation.
  - *Extra-esophageal manifestations*: Hoarseness, chronic laryngitis, chronic cough, and exacerbation of asthma.
- **Achalasia**: Progressive dysphagia to **both solids and liquids**, chest pain, regurgitation, and difficulty belching.
- **Eosinophilic Esophagitis (EoE)**: Dysphagia, food bolus impaction, refractory heartburn, and feeding difficulties.
- **Zenker's Diverticulum**: A false diverticulum in the posterior hypopharyngeal wall. Classically presents with dysphagia, **halitosis** (bad breath), and regurgitation of undigested food (often causing a nighttime cough).
- **Esophageal Constrictions**:
  - *Schatzki Ring*: Thin constriction at the squamocolumnar junction; a common cause of dysphagia and food bolus obstruction.
  - *Esophageal Web*: Congenital or inflammatory hypopharyngeal constrictions. Associated with iron deficiency anemia in **Plummer-Vinson syndrome**.
- **Mallory-Weiss Tear**: Upper GI bleeding preceded by severe vomiting and retching (mucosal tear at the GEJ).

Investigations

- **Endoscopy (EGD)**:
  - *Barrett's Esophagus*: Visualizes metaplastic columnar epithelium replacing normal stratified squamous epithelium. Requires biopsy for diagnosis.
  - *EoE*: Classically reveals mucosal **rings and furrows**. Biopsy confirms **>15 eosinophils/HPF**.
  - *Achalasia*: Essential to perform to exclude secondary mechanical causes (pseudoachalasia).
- **Esophageal Manometry** (Gold Standard for Motility Disorders):
  - *Achalasia*: Failure of LES relaxation, elevated or normal resting LES pressure, aperistalsis, and simultaneous contractions (>40 mmHg).
  - *Esophageal Spasm*: >20% of swallows show premature, simultaneous contractions.
  - *Nutcracker Esophagus*: Sequential contractions but with abnormally high pressures.
- **Barium Swallow**:
  - *Achalasia*: Dilated esophagus, absent peristalsis, and a **"bird-beak"** narrowing at the lower end.
  - *Esophageal Spasm*: **"Corkscrew"** or "rosary bead" appearance.
- **24-Hour pH Monitoring / Impedance**: Used to definitively diagnose GERD or quantify reflux.
- **Chest X-Ray (Achalasia)**: May show an absent gastric bubble, an air-fluid level, and a widened mediastinum.

Management

- **GERD**: Lifestyle modifications -> H2 receptor blockers -> Proton Pump Inhibitors (PPIs). Surgical fundoplication is an option for refractory cases.

- **Barrett's Esophagus**: Aggressive GERD treatment (PPIs) and regular surveillance for dysplasia. Dysplasia is managed with endoscopic therapy (ablation/resection) or surgery (esophagectomy).
- **Achalasia**: Aimed at decreasing LES pressure.
  - *Mechanical*: Endoscopic balloon dilation, Peroral Endoscopic Myotomy (POEM), Heller myotomy.
  - *Pharmacological*: Botulinum toxin injection, oral nitrates, or Calcium Channel Blockers (CCBs).
- **Eosinophilic Esophagitis**: PPIs, **topical (swallowed) glucocorticoids**, dietary elimination, and endoscopic dilation for strictures.
- **Zenker's Diverticulum**: Cricopharyngeal myotomy + diverticulectomy.
- **Esophageal Spasm & Nutcracker Esophagus**: PPIs, peppermint oil, Calcium Channel Blockers (CCBs).
- **Rings and Webs**: Endoscopic dilation.

Complications / Prognosis

- **GERD Complications**: Esophageal stricture, Barrett's esophagus, esophageal adenocarcinoma, and exacerbated asthma.
- **Barrett's Esophagus**: Carries a >30-fold increased risk of esophageal adenocarcinoma (0.1–3% annual incidence).
- **Caustic Ingestion**: Severe ulceration can rapidly progress to profound fibrosis and intractable stricture formation.
- **Mallory-Weiss Tear**: Most cases resolve spontaneously without specific intervention.

Past-Paper High Yield

- **Achalasia presentation**: Highly tested as a patient (often middle-aged, normal physical exam) complaining of progressive dysphagia to **both solids and liquids** simultaneously. Manometry is required to confirm.
- **Zenker's Diverticulum clues**: Look for the classic triad of dysphagia, **halitosis**, and **night-time coughing/regurgitation** in an elderly patient.
- **Eosinophilic Esophagitis indicators**: Frequently tested as a young patient with a history of **asthma or eczema** presenting with a food bolus obstruction. Endoscopy showing **"rings and furrows"** is the diagnostic giveaway. The cornerstone of medical management is **topical (swallowed) steroids**.
- **Nutcracker Esophagus vs. Spasm**: Examiners differentiate Nutcracker esophagus by defining it as **extremely forceful peristaltic activity** causing chest pain/dysphagia, but crucially maintaining *normal sequential peristalsis* (unlike the simultaneous contractions of diffuse esophageal spasm).

Memory Pearls

- **Dysphagia Timeline Rule**:
  - *Solids only* (progressing to liquids) = Mechanical obstruction (Stricture, Schatzki ring, Web, Carcinoma).
  - *Solids AND liquids* (simultaneously) = Motility disorder (Achalasia, Spasm).
- **Barium Buzzwords**:

- Achalasia = **"Bird-beak"**
- Diffuse Esophageal Spasm = **"Corkscrew"**

- **Plummer-Vinson Triad**: Dysphagia + Esophageal Webs + Iron Deficiency Anemia.
- **EoE Biopsy Cutoff**: **>15 Eosinophils/HPF** with rings and furrows on EGD.
- **Zenker's Location**: A "false" diverticulum located in the *posterior hypopharyngeal wall*.

Upper Gastrointestinal Bleeding

Core Concepts

- **Definition:** Bleeding originating proximal to the Ampulla of Vater (Ligament of Treitz).
- **Epidemiology:** Accounts for 50% of all gastrointestinal bleeding.
- **Major Etiologies:**
  - **Peptic Ulcer Disease (PUD):** Most common. Risk factors include *H. pylori*, NSAIDs/COX-2 inhibitors, antithrombotics, smoking.
  - **Varices/Portal Hypertensive Gastropathy:** Suspect in chronic liver disease or heavy alcohol use.
  - **Angiodysplasia (AVMs):** Associated with renal disease, aortic stenosis (Heyde syndrome), or Hereditary Hemorrhagic Telangiectasia (HHT).
  - **Aorto-enteric Fistula:** Highly lethal; suspect in patients with a history of an abdominal aortic aneurysm (AAA) or aortic graft.
  - **Marginal Ulcers:** Occur at anastomotic sites (e.g., prior gastroenteric anastomosis).
  - **Malignancy:** Clues include dysphagia, early satiety, weight loss, and cachexia.

Diagnosis / Clinical Features

- **Classic Presentation:** Hematemesis, melena, upper abdominal pain, pallor, dizziness.
- **Signs of Severe Bleeding:** Orthostatic dizziness, confusion, angina, severe palpitations, cold/clammy extremities.
- **Hemodynamic Correlation with Blood Loss:**
  - **<15% loss:** Resting tachycardia.
  - **~20-40% loss: Orthostasis** (The most accurate non-invasive indicator of blood loss severity). Defined as: ↓ Systolic BP > 20 mmHg, ↓ Diastolic BP > 10 mmHg, or ↑ HR > 15 bpm within 3 minutes of standing.
  - **>40% loss:** Supine hypotension/shock.
- **Medication Mimickers:** Bismuth, charcoal, licorice, and iron supplements can alter stool color (turning it black), resulting in false melena.

Investigations

- **Risk Stratification Scores:**
  - **Blatchford Score:** Pre-endoscopic risk assessment.

    - **Rockall Score:** Post-endoscopic risk assessment.
- **Nasogastric Tube (NGT) Lavage:** Has **no proven benefit** and carries a 15% false-negative rate. Do not rely on it to rule out UGIB.
- **Endoscopy (EGD):** The definitive diagnostic and therapeutic test.
- **Small Bowel Capsule Endoscopy:** Indicated for obscure GI bleeding (e.g., persistent melena/anemia with normal upper *and* lower endoscopies).

Management

1. Initial Resuscitation & Stabilization (Always Step 1)

- Obtain adequate IV access and initiate volume resuscitation.
- Keep the patient NPO.
- **Airway protection:** Intubate if there is ongoing hematemesis, altered mental status, or loss of the gag reflex to prevent aspiration.

2. Blood Transfusion Thresholds

- **General target:** Transfuse PRBCs if **Hb ≤ 7 g/dL** (Hematocrit <21%).
- **High-risk target:** Transfuse PRBCs if **Hb ≤ 9–10 g/dL** (Hematocrit <30%) in patients with CAD or shock.
- **Platelets:** Transfuse if < 50,000 in active/life-threatening bleeding. For stable EGD, a threshold of > 20,000 is acceptable.

3. Pharmacotherapy (Pre-Endoscopy)

- **Prokinetics:** Erythromycin 250mg IV (3 mg/kg) given 30–60 minutes before EGD to clear the stomach of blood/clots and improve visualization.
- **Suspected Non-Variceal (PUD):** Start IV PPI infusion (80 mg bolus → 8 mg/hr).
    - *Note:* PPIs decrease high-risk stigmata and the need for endoscopic intervention, but they do **not** decrease mortality, re-bleeding rates, or the need for surgery.
- **Suspected Variceal Bleeding:**
    - **Vasoactive agents:** Octreotide (50 mcg bolus → 50 mcg/hr infusion for 2–5 days) or Terlipressin to cause splanchnic vasoconstriction.
    - **Antibiotic Prophylaxis:** Mandatory in cirrhotic patients presenting with UGIB (preferably given before endoscopy).

4. Endoscopy (EGD) Timing

- *Never perform EGD before hemodynamic stabilization.*
- **Routine:** Within **24 hours** of admission for stable patients (reduces transfusion needs, emergent surgery, re-bleeding, and hospital stay length).
- **Urgent:** Within **12 hours** for high-risk features (tachycardia, hypotension, bloody emesis/NG aspirate, cirrhosis, Hb <8 g/dL).

5. Post-Hemostasis Management

- **Antiplatelets (Secondary Prevention):** Resume Aspirin/Clopidogrel in 1–3 days (no later than 7 days). *If the patient had a stent placed within the last year or recent ACS, consult cardiology prior to stopping these drugs.*
- **Anticoagulation:** Resume Warfarin the same afternoon. Resume LMWH after 12 hours in high-risk patients (e.g., mechanical valves, recent VTE <3mo, AFib + MS/Prosthesis).
- **SSRIs:** Consider switching to a non-SSRI antidepressant, ensuring a PPI is co-prescribed, and discontinuing NSAIDs.
- **Repeat Endoscopy:** Routine "second-look" EGD is **not** recommended unless there is clinical evidence of recurrent bleeding.
- **Refractory Bleeding:** If bleeding recurs after a second therapeutic EGD session, proceed to surgery or interventional radiology (transcatheter arterial embolization).

Past-Paper High Yield

- **The initial step for Melena:** In a stabilized patient presenting with melena and a drop in hemoglobin, the immediate next best step is **Esophagogastroduodenoscopy (EGD)**.
- **Timing of EGD in PUD:** If a patient is stabilized in the ED with fluids and PPIs for a bleeding peptic ulcer, the next best step is to perform **Endoscopy within 24 hours**. Do not delay to observe, and do not place an NGT.
- **Obscure GI Bleed Evaluation:** For a patient with longstanding melena, anemia, and *multiple normal upper and lower endoscopies*, the next best step is a **Small intestine capsule endoscopy**.
- **Cirrhosis Traps (New Ascites vs. Varices):** In a patient with chronic hepatitis C presenting with *new-onset ascites*, the next best step is a **diagnostic paracentesis** to assess the fluid. Do not jump straight to initiating beta-blockers for variceal prophylaxis before working up the acute decompensation/fluid etiology.

Memory Pearls

- **Orthostasis = Volume Loss:** It is the single most accurate non-invasive indicator of significant (>20%) blood loss.
- **PPI pre-EGD:** Helps the endoscopist (less active bleeding/stigmata to treat) but does *not* save lives (no mortality benefit).
- **NG Tubes:** Useless for reliably ruling out an upper GI bleed (15% false-negative rate). Do not pick NGT lavage as a necessary diagnostic step.
- **Forrest Classification:** Used endoscopically to stage peptic ulcers based on their risk of re-bleeding (active spurting vs. clean base).

Lower Gastrointestinal Bleeding

Core Concepts

- **Definition:** Bleeding originating distal to the **Ligament of Treitz** (a fibromuscular band originating from the right diaphragmatic crus that fixes the duodenojejunal flexure).
- **Lower GI Bleeding Sources:**

- **Diverticula (30–40%)** – Most common cause of acute massive colonic blood loss.
- **Colitis (15–20%)** – Ischemic, infectious, or Inflammatory Bowel Disease (IBD).
- **Neoplasia (13%)** – Carcinoma, polyps.
- **Upper GI Bleeding (10–13%)** – Rapid transit UGIB can present as lower GI bleeding.
- **Anorectal Disease (10%)** – Hemorrhoids, fissures.
- **Angiodysplasia (10%)**

- **Mid GI Bleeding Sources (Small Bowel):**
  - Angiodysplasia (20–60%)
  - Ulcerations (10–40%) – IBD, NSAIDs.
  - Neoplasia (1–10%)
- **Melena vs. Hematochezia:**
  - Fresh blood usually implies a lower GI cause, *unless* there is massive/rapid bleeding from an upper GI source (indicated by hemodynamic instability + **elevated blood urea**).
  - Blood in the bowel for >14 hours converts to melena. Up to 35% of patients with melena have a bleeding source distal to the Ligament of Treitz.

Diagnosis / Clinical Features

History & Clues to Etiology:

- **Blood Mixed vs. Separate:** Bright red blood separate from stool strongly suggests a benign anorectal cause.
- **Iatrogenic:** Post-polypectomy bleeding can be delayed for **up to 10 days**.
- **Medications:** Always check for NSAIDs, Warfarin, and antiplatelet usage.
- **Hidden Bleeding:** Hypotension/shock without overt bleeding dictates an obligatory **digital rectal examination (DRE)**.

Key Clinical Presentations by Etiology:

- **Diverticular Bleeding: Painless**, brisk, large-volume arterial bleeding (due to local trauma to the vasa recti). Often right-sided (despite most diverticula being left-sided).
- **Ischemic Colitis:** Sudden-onset cramping **Left Lower Quadrant (LLQ)** pain followed by bloody stools and mild-to-moderate tenderness. Due to low-flow states (most common) > embolization/thrombosis affecting watershed areas.
- **Meckel's Diverticulum:** Due to a persistent vitelline duct (fails to absorb by the 7th week of pregnancy). Ectopic gastric cells secrete acid, causing adjacent mucosal ulceration and bleeding.

Investigations

General Algorithm for Lower GI Bleeding:

- **If bleeding stops spontaneously:** Elective colonoscopy ± EGD.
- **If continued bleeding:** Urgent colonoscopy ± EGD.

Condition-Specific Diagnostics:

- **Ischemic Colitis:**
  - Plain X-Ray: Classic **"thumbprinting"** (representing submucosal hemorrhage and edema).
  - Further imaging: Contrast-enhanced CT scan and careful endoscopy.
- **Meckel's Diverticulum:**
  - **Meckel's Scan:** IV Technetium-99m is taken up by ectopic gastric mucosa and detected via a gamma camera.

Management

Medical Management:

- **Ischemic Colitis:**
  - *Uncomplicated:* Bowel rest, IV hydration, correct the underlying low-flow state ± IV antibiotics (>50% resolve conservatively).
  - *Complicated (Infarction/Perforation):* Urgent surgery is required if there is increasing tenderness, fever, or ileus.
- **IBD Flare:** IV hydration, IV steroids, and IV antibiotics.
- **Infectious Colitis:** IV hydration and IV antibiotics.

Endoscopic Intervention:

- **Arterial Lesions (e.g., diverticula, post-polypectomy):** Electrocoagulation (Heat Probe), Hemostatic clipping, Adrenaline injection, Snare polypectomy/Endoloop.
- **Angiodysplasia & Radiation Colitis: Argon Plasma Coagulation (APC)**.

Radiologic & Surgical Intervention:

- **Interventional Radiology:** Angiography with selective embolization.
- **Surgery:** Accurate pre-operative localization is essential (associated with 5–10% mortality).

Diverticular Bleeding Algorithm:

1. **Resuscitate** → Diagnose and locate source.
2. **Colonoscopy** (first-line therapeutic and diagnostic tool).
3. **If colonoscopy is unsuccessful AND bleeding is massive:**
   - *Hemodynamically Stable:* **Angiography** (with embolization).
   - *Hemodynamically Unstable:* **Surgery**.

Past-Paper High Yield

- **UGIB masquerading as LGIB:** A patient presenting with fresh hematochezia, hemodynamic instability, and significantly elevated BUN has a massive Upper GI bleed, not a Lower GI bleed.
- **Diverticular bleeding paradox:** The majority of diverticula are left-sided, but diverticular bleeding more frequently originates from the **right colon**.
- **Post-polypectomy timeline:** Do not rule out iatrogenic bleeding just because the procedure wasn't yesterday; it can present up to 10 days post-procedure.

- **Ischemic Colitis X-ray:** "Thumbprinting" is the classic radiologic buzzword indicating submucosal edema/hemorrhage.
- **Meckel's Pathophysiology:** Bleeding is caused by acid secretion from *ectopic gastric mucosa* ulcerating the adjacent normal bowel wall.

Memory Pearls

- **Treitz Landmark:** Above Treitz = UGIB; Below Treitz = LGIB.
- **Melena Rule:** Melena does *not* absolutely rule out a lower GI bleed (35% are mid-to-lower, provided transit time is >14 hours).
- **Pain vs. Painless:** Ischemic Colitis = *Painful* (crampy LLQ). Diverticular Bleed = *Painless* (brisk, large volume).

Inflammatory Bowel Disease

Core Concepts

- **Definition:** Chronic, remitting, and relapsing inflammatory diseases of the gut, encompassing Ulcerative Colitis (UC) and Crohn’s Disease (CD).
- **Epidemiology:** Bimodal age distribution (peaks at 15–40 years and 50–80 years). Affects males and females equally; more common in white populations.
- **Pathogenesis:** Involves the IL-23–IL-17 axis and TNF-α. Associated with reduced gut microbiota diversity. CD is specifically linked to increased intestinal permeability.

Diagnosis / Clinical Features

FEATURE	ULCERATIVE COLITIS (UC)	CROHN'S DISEASE (CD)
Location	Colon only. *Invariably* involves rectum, continuous proximal spread.	Entire GI tract (mouth to anus). Rectum is typically *spared*.
Lesion Pattern	Continuous.	Skip lesions.
Depth	Mucosa and submucosa.	Transmural (leads to fistulas, fissures, strictures).
Endoscopy	Erythema, loss of vascular pattern, friability, continuous ulceration.	Cobblestone appearance, deep ulcers, strictures.
Histology	Crypt distortion, **crypt abscesses**, basal plasma cells.	Epithelioid **non-caseating granulomas**, transmural infiltrates.
Classic Presentation	Bloody diarrhea (>6 wks), urgency, tenesmus.	Dull RIF pain, non-bloody diarrhea, weight loss, RLQ mass, perianal skin tags.
Serology	p-ANCA positive (often).	ASCA positive (often).

Extra-Intestinal Manifestations (EIMs):

- **Hepatobiliary:** Primary Sclerosing Cholangitis (PSC) – *highly associated with UC*, gallstones (CD).
- **Ocular:** Uveitis, episcleritis, conjunctivitis. *(Exam trap: Uveitis in CD can occur entirely independently of intestinal disease activity).*
- **Musculoskeletal:** Peripheral arthritis, ankylosing spondylitis, sacroiliitis, metabolic bone disease.
- **Dermatologic:** Erythema nodosum, pyoderma gangrenosum.
- **Hematologic/Vascular:** Autoimmune hemolytic anemia, Venous Thromboembolism (VTE).
- **Renal:** Ureteric obstruction, fistulas, renal calculi (CD).

Investigations

- **Endoscopy with Biopsy:** Confirmatory test (differentiates UC from CD).
- **Stool Studies:** Fecal calprotectin (marks intestinal inflammation), culture, and *Clostridium difficile* toxins (must rule out infectious mimics in acute flares).
- **Imaging:** Capsule endoscopy (useful for small bowel CD), MRCP (if PSC is suspected).
- **Labs:** CBC (anemia), LFTs (cholestasis in PSC), CRP/ESR, B12 levels (often deficient in CD due to terminal ileum involvement).

Management

Ulcerative Colitis:

- **Mild-to-Moderate (Induction & Maintenance):** 5-ASA (Mesalamine) is the mainstay (oral and/or rectal).
- **Severe/Fulminant Flare:**
  - Admit, daily abdominal X-rays, NPO, monitor inflammatory markers.
  - Initiate **IV Steroids (3–5 days)** and **VTE prophylaxis (LMWH)**.
  - *Contraindication:* Do NOT initiate Azathioprine during an acute flare (takes weeks to work).
  - If no response: Cyclosporine or Infliximab.
  - *Surgical Consult:* Must be done on Day 1 of admission. Colectomy if refractory or toxic megacolon develops.
- **Maintenance:** Azathioprine/6-MP, Biologics (Infliximab, Vedolizumab, etc.). *Note: Methotrexate is generally NOT used for UC maintenance.*
- **Steroids:** Used ONLY for induction. **No role in maintenance.**

Crohn's Disease:

- **Induction:** Corticosteroids (e.g., Prednisone, Budesonide for ileocecal disease).
- **Maintenance:** Azathioprine/6-MP, **Methotrexate (MTX)**, Biologics.
- **5-ASA:** Least effective in CD (high NNT of 17); mainly used for post-op colonic disease.
- **Antibiotics:** Metronidazole for perianal disease, abscesses, or fistulae.
- **Surgery:** Indicated for complications (obstruction, perforation, abscess) or medical failure. *Surgery is not a cure for CD; the disease will recur.*

Complications / Prognosis

- **Colorectal Cancer (CRC) Risk:** Increased in both UC and CD (if colonic involvement).
  - *Pancolitis:* Risk increases 8–10 years after onset.
  - *Left-sided colitis:* Risk increases 15–20 years after onset.
  - *Proctitis:* No significant increased risk.
- **PSC and CRC Risk:** A diagnosis of PSC in a UC patient drastically increases CRC risk. **Surveillance colonoscopy must be performed annually** starting from the time of PSC diagnosis.
- **Crohn's Specific:** Fistulae, bowel obstruction, acute perforation, B12 deficiency (terminal ileum destruction/resection).

Past-Paper High Yield

- **Differentiating Mimics:**
  - *Pseudomembranous Colitis:* Suspect in an older patient with recent antibiotics (e.g., treated for osteomyelitis) presenting with watery diarrhea and yellowish-white colonic plaques.
  - *Ischemic Colitis:* Suspect in elderly patients with vascular risk factors (HTN, DM) presenting with lower abdominal pain, bleeding, and focal ulceration strictly at the **splenic flexure** (watershed area).
- **Upper GI CD:** Crohn's can affect the entire GI tract. A patient with watery diarrhea and multiple *duodenal ulcers* that fail PPI therapy and test negative for *H. pylori* is a classic presentation for upper GI Crohn's.
- **Physical Exam Clues:** Anemia + per rectal bleeding + right lower quadrant (RLQ) mass + **anal skin tags** = Crohn’s disease.
- **Diagnosing PSC:** In an IBD patient presenting with painless jaundice, pruritus, elevated direct bilirubin, and markedly elevated ALP/GGT, the next best step is **MRCP** to diagnose Primary Sclerosing Cholangitis.
- **Appropriate Maintenance Therapy:** Steroids are strictly for *induction*. Do not choose steroids for maintaining remission. Methotrexate is highly effective for CD but is *not* standard maintenance for UC.
- **Managing the Acute UC Flare:** When a patient is admitted for a severe UC flare, initiate IV steroids, LMWH (pro-thrombotic state), and mesalamine enemas. Do NOT start Azathioprine acutely.

Memory Pearls

- **UC = U**lcerative **C**olitis = **U**pward **C**ontinuous (starts in rectum, moves up).
- **C**rohn's = **C**obblestone, **C**onfirmed by non-caseating granulomas, **C**omplete GI tract.
- **Uveitis in CD:** Follows its own rules (independent of gut inflammation).
- **PSC + UC = 1 Year:** If a UC patient gets PSC, scope them every 1 year for colon cancer.
- **Biopsy distinctions:** Crypt abscess = UC; Granuloma = CD.

Malabsorption and Celiac Disease

Core Concepts

Malabsorption broadly encompasses defects in the digestion and absorption of food nutrients along the 6-meter small intestine (amplified by villi and microvilli). It is divided into maldigestion and true malabsorption, mapped to the three phases of nutrient assimilation:

- **Maldigestion (Luminal Phase Defect):** Impaired breakdown of nutrients into absorbable units.
  - **Pancreatic Exocrine Insufficiency:** *The most common cause.* (e.g., chronic pancreatitis, cystic fibrosis). Leads to decreased lipase/protease and fat/protein malabsorption.
  - **Inactivation of Pancreatic Enzymes:** Hypersecretion of gastric acid (Zollinger-Ellison Syndrome) lowers pH, inactivating enzymes.
  - **Inadequate Mixing:** Post-gastrectomy.
  - **Impaired Micelle Formation (Bile Salt Defect):** Decreased synthesis (liver disease), impaired recycling (terminal ileum resection/Crohn's), or bile salt deconjugation (Small Intestinal Bacterial Overgrowth [SIBO] due to strictures, blind loops, or dysmotility).
  - **Specific Enzyme Deficiencies:** e.g., Lactase deficiency (Lactose intolerance).
- **Malabsorption (Mucosal Phase Defect):** Defective mucosal uptake/transport due to inadequate absorptive surface or mucosal damage (villous atrophy).
  - *Causes:* Celiac disease, extensive Crohn’s disease, Giardiasis, Whipple’s disease, intestinal lymphoma, Common Variable Immunodeficiency (CVID), and drug-induced (cholestyramine, neomycin, alcohol).
- **Deranged Lymphatics (Post-Absorptive Phase Defect):** Obstruction of the lymphatic system impairs the absorption of chylomicrons and lipoproteins.
  - *Congenital:* **Intestinal Lymphangiectasia**.
  - *Acquired:* Lymphoma, Whipple’s disease, tuberculosis, CHF, constrictive pericarditis, radiation, retroperitoneal fibrosis.

Diagnosis / Clinical Features

Diarrhea is the most common symptom (defined as stool mass >200 g/day). Clinical manifestations directly map to specific unabsorbed nutrients:

General Malabsorption Signs:

- **Steatorrhea:** Fat malabsorption resulting in pale, bulky, malodorous stools that float (oil droplets in the toilet) and are difficult to flush.
- **Osmotic Diarrhea & Flatulence:** Carbohydrate malabsorption leading to bacterial fermentation (hydrogen/methane gas), abdominal distention, and an increased stool osmotic gap.
- **Edema / Ascites:** Hypoalbuminemia from protein malabsorption or lymphatic loss (e.g., intestinal lymphangiectasia).
- **Anemia:**
  - *Microcytic:* Iron deficiency (often proximal bowel defect, classic for Celiac).

- *Macrocytic:* Vitamin B12 deficiency (often terminal ileal defect, classic for Crohn's or resection).

- **Metabolic Bone Disease:** Vitamin D/Calcium malabsorption leading to osteopenia, osteomalacia, bone pain, and secondary hyperparathyroidism.
- **Other Deficiencies:** Bleeding (Vitamin K), Night blindness (Vitamin A), Peripheral neuropathy (Vitamin B12, thiamine), Tetany (Calcium, Magnesium), Glossitis/Cheilosis (Iron, B12, folate, Vit A).

Celiac Disease (Gluten-Sensitive Enteropathy): An immune disorder triggered by gliadin (a component of gluten) in genetically predisposed individuals (T-cell mediated mucosal damage).

- **Classic Intestinal:** Chronic diarrhea, weight loss, flatulence, aphthous stomatitis, angular cheilosis.
- **Extra-Intestinal:** Dermatitis herpetiformis, abnormal LFTs, hyposplenism, large-joint non-erosive symmetrical arthropathy, cerebellar ataxia, epilepsy (with bilateral parieto-occipital calcifications), peripheral neuropathy, and infertility.
- **High-Risk Associations:** Type 1 DM, autoimmune thyroid/liver diseases, Rheumatoid arthritis, Down syndrome, Turner syndrome, and IgA deficiency.

Investigations

Celiac Disease Diagnostic Pathway:

- **Serology:**
  - IgA anti-tissue transglutaminase (tTG) and IgA endomysial antibodies.
  - *Critical Step:* Must check total serum IgA levels (IgA deficiency is common; if low, check IgG tTG or IgG deamidated gliadin peptides).
- **Small Intestinal Biopsy (Definitive):**
  - Endoscopic biopsy of the **proximal duodenum** (maximally affected).
  - *Histopathology:* Subtotal or total villous atrophy with intraepithelial lymphocytic infiltration.
- **Genetic Testing:**
  - HLA-DQ2 (found in 98% of Northern European patients) and HLA-DQ8. Note: highly sensitive but non-specific (~25% of the normal population has HLA-DQ2). Excellent for *excluding* Celiac if negative.
- **Testing Algorithm:**
  - *Low Probability (<2-5%):* Start with serology + total IgA. If positive, proceed to biopsy.
  - *High Probability (>2-5%):* Proceed to simultaneous serology and biopsy (e.g., family history, Type 1 DM, unexplained iron-deficiency anemia).

General Malabsorption Tests:

- **Stool Osmotic Gap:** A significantly elevated stool osmotic gap (e.g., >100-150 mOsm/kg) in the setting of non-bloody diarrhea strongly indicates unabsorbed, osmotically active substances (e.g., carbohydrates in **lactose intolerance**).

Management

- **Celiac Disease:** Strict, lifelong adherence to a gluten-free diet (avoiding wheat, rye, and barley).

- **Gluten Rechallenge (Diagnostic tool, rarely used):** Involves consuming 10g of gluten/day for 4-6 weeks to document histologic/symptomatic return. *Hazard:* Risk of "gliadin shock" (fulminant diarrhea, dehydration, and acidosis).
- **Pancreatic Insufficiency:** Pancreatic enzyme replacement therapy (PERT).
- **SIBO:** Antibiotics and addressing the underlying anatomical/motility defect.

Complications / Prognosis

- Patients with untreated, long-term classical Celiac disease have a significantly increased risk of malignancies:
  - **Enteropathy-associated T-cell lymphoma (EATL) / Non-Hodgkin's lymphoma.**
  - **Small-bowel adenocarcinoma.**
  - Esophageal and oropharyngeal squamous cell carcinoma.

Past-Paper High Yield

- **Lactose Intolerance Diagnosis:** A patient presenting with non-bloody diarrhea and a highly elevated stool osmotic gap (e.g., 150) points directly to an unabsorbed carbohydrate driving osmotic fluid shifts. Lactose intolerance is the most likely diagnosis.
- **Intestinal Lymphangiectasia:** Recognize this as a classic, direct cause of malabsorption via the post-absorptive (lymphatic) phase. It causes impaired chylomicron transport and protein-losing enteropathy. (Do not confuse it with intestinal telangiectasia or diverticulosis, which are not primary causes of classic malabsorption syndrome, though blind loops in diverticula can occasionally cause SIBO).
- **Key Malabsorption Causes to differentiate:** Celiac disease (mucosal), Crohn's disease (mucosal/bile salt recycling), Intestinal lymphangiectasia (post-absorptive).

Memory Pearls

- **Anatomy of Absorption Deficits:**
  - **Iron** is absorbed in the **Duodenum** (Classic deficiency in Celiac).
  - **Folate** is absorbed in the **Jejunum**.
  - **B12 and Bile Salts** are absorbed in the **Terminal Ileum** (Classic deficiency in Crohn's).
- **Celiac Genetics:** HLA-**DQ2** and **DQ8** ("I ate (**8**) **too** (**2**) much gluten").
- **Maldigestion vs Malabsorption:** If enzymes are missing (pancreas, lactase) or bile is poor (SIBO, liver), it is *maldigestion*. If the gut wall is damaged (Celiac, Crohn's) or lymph is blocked (Lymphangiectasia), it is *malabsorption*.

Functional Gastrointestinal Disorders (FGID)

Core Concepts

- **Definition**: A medical condition impairing the normal function of a bodily process (movement, nerve sensitivity, brain-gut axis) with **completely normal anatomy** on macroscopic (endoscopy, X-ray)

and microscopic (biopsy, blood tests) evaluation.

- **Prevalence**: The **most common** GI disorders in the general population.
  - Affect ~25% of the US population (though 75% of these individuals are asymptomatic).
  - Account for ~40% of all GI problems seen by physicians.
- **Classification**: Exclusively defined by symptom-based diagnostic criteria categorized by the **Rome Criteria**.

Diagnosis / Clinical Features

1. Esophageal Disorders

- **Functional Chest Pain**: Esophageal-origin chest pain. **Must rule out cardiac causes (angina) first.**
- **Globus**: Sensation of a lump, tightness, or something "stuck" in the throat.
- **Functional Heartburn**: Persistent burning *without* evidence of GERD, motility disorders, or structural abnormalities.
- **Functional Dysphagia**: Subjective difficulty swallowing without organic obstruction/motility issue.
- **Reflux Hypersensitivity**.

2. Gastro-Duodenal Disorders

- **Functional Dyspepsia (Non-Ulcer Dyspepsia - NUD)**
  - Most common cause of dyspepsia overall (60% of all dyspepsia). Overlaps with IBS in 30% of cases.
  - **Rome III Criteria**: Onset ≥ 6 months + Duration ≥ 3 months. Must include **≥ 1 of**: postprandial fullness, early satiety, epigastric pain, or epigastric burning.
  - *Crucial Exclusions*: Normal EGD (no structural cause) and symptoms are *not* exclusively relieved by defecation/stool changes (which would point to IBS).
  - **Sub-Types**:

SUB-TYPE	CLINICAL FEATURES	MEDICAL THERAPY
Postprandial Distress Syndrome (PDS)	Meal-related symptoms (Fullness, Early satiety)	**Prokinetics**
Epigastric Pain Syndrome (EPS)	Meal-unrelated symptoms (Epigastric pain, Burning)	**PPIs**

- **Cyclic Vomiting Syndrome (CVS)**
  - Stereotypical episodes of N/V lasting < 1 week.
  - ≥ 3 episodes/year with *completely asymptomatic* periods in between.
  - Often associated with a personal/family history of migraines.
- **Rumination Syndrome**
  - Effortless, controlled vomiting *without* nausea.
  - Non-acidic; typically involves reswallowing or spitting.

3. Bowel Disorders: Irritable Bowel Syndrome (IBS)

- **Rome III Criteria**: Recurrent abdominal pain/discomfort ≥ 3 days/month for the last 3 months, with symptom onset ≥ 6 months prior to diagnosis. Must be associated with **≥ 2 of the following**:
  1. Improvement with defecation.
  2. Onset associated with a change in stool frequency.
  3. Onset associated with a change in stool form/appearance.
- **Etiologies / Pathophysiology**:
  - **Food intolerance**: ↑ Mast cells + Food Antigens.
  - **Post-infectious IBS (10% of cases)**: Risk factors include ↑ duration/severity of initial infection (strongest factor), cramping during infection, female gender, psychiatric disorders, and younger age.
  - **Diarrhea-predominant (D-IBS)**: Often driven by rapid transit (45%), cholerheic diarrhea due to ↓ FGF-19 leading to ↑ colonic bile acids (25%), SIBO (10%), or ↑ serotonin enteroendocrine cells.
  - **Constipation-predominant (C-IBS)**: Driven by slow colonic transit (only 25%; majority actually have normal transit).

Investigations

General Rule: FGIDs are diagnoses of exclusion. You must evaluate for and definitively rule out **Alarm Symptoms** ("Red Flags").

- **Upper GI Alarm Symptoms (Esophageal / Dyspepsia)**: Age ≥ 50-55, typical symptoms lasting ≥ 5 years, dysphagia/odynophagia, persistent vomiting, GI bleed / hematemesis / melena / FOB+, iron deficiency anemia, unexplained weight loss, palpable mass or LNs (e.g., epigastric mass), jaundice, FHx of UGI cancer, poor response to medical Tx.
- **Lower GI Alarm Symptoms (IBS)**: Age > 50, unexplained weight loss, rectal bleeding, recent change in bowel habits lasting ≥ 6 weeks (caliber/frequency/consistency), **nocturnal symptoms**, FHx of GI cancer or IBD, abnormal abdominal/rectal exam, unexplained anemia or biochemical abnormalities.

Specific Workup Pathways:

- **Esophageal Chest Pain**: **R/O Angina first.**
  - *If Alarm Symptoms present*: EGD ± Biopsy.
  - *If NO Alarm Symptoms*: Empiric PPI trial for 4–8 weeks → If failed, consider 24-hr pH monitoring and Manometry.
- **IBS Workup**: Mandates a completely normal baseline lab profile:
  - Normal CBC.
  - Normal inflammatory markers: CRP (<10), ESR (Males < 20, Females < 30).
  - Negative Celiac serology: Anti-tTG IgA & IgG.
  - Optional depending on clinical picture: TSH, routine stool analysis.

Management

Dyspepsia & Vomiting Disorders

- **PDS Dyspepsia**: Prokinetics.
- **EPS Dyspepsia**: PPIs.
- **Refractory Dyspepsia**: Antidepressants.
- **Cyclic Vomiting Syndrome (CVS)**: Tricyclic Antidepressants (TCAs).
- **Rumination Syndrome**: Behavioral therapy (specifically **diaphragmatic breathing**).

Irritable Bowel Syndrome (IBS)

- **Step 1: Lifestyle and Dietary Modification**
  - **FODMAP Restriction**: Eliminate Fermentable Oligo-, Di-, Mono-saccharides And Polyols.
  - **Gluten restriction**: Can alleviate IBS symptoms even in the absence of Celiac disease.
  - Behavioral therapy and addressing psychosocial stressors.
- **Step 2: Symptom-Directed Pharmacotherapy**
  - **Abdominal Pain**: Spasmolytics (Anticholinergics, Peppermint Oil) → Low-dose TCAs → SSRIs (Note: Sertraline may worsen diarrhea).
  - **Bloating**: Probiotics (*Bifidobacteria*) ± Simethicone/Dimethicone.
  - **Constipation (C-IBS)**: ↑ dietary fibers → Osmotic laxatives → Stimulant laxatives.
  - **Diarrhea (D-IBS)**: Bulk-forming agents (Psyllium) or low-FODMAP rice. Opioids (Loperamide, Diphenoxylate). *Note: Rifaximin may be used, but restrict strictly to those with confirmed SIBO.*

Past-Paper High Yield

- **Ischemic heart disease masquerading as GI issue**: *Always* rule out cardiac ischemia first in patients presenting with functional chest pain.
- **Differentiating Dyspepsia sub-types**:
  - Pain *related* to meals (early satiety/fullness) = PDS → Treat with prokinetics.
  - Pain *unrelated* to meals (epigastric burning) = EPS → Treat with PPIs.
- **Post-infectious IBS Risk Factors**: The *duration* of the initial gastroenteritis infection is the single strongest predictor of developing post-infectious IBS.
- **IBS Exclusions**: Symptoms awaking the patient from sleep (nocturnal symptoms) are an **alarm symptom** and rule out functional IBS.
- **Rumination Management**: High-yield differentiator—treatment is explicitly behavioral (diaphragmatic breathing), *not* anti-emetics.

Memory Pearls

- **PDS = P**ostprandial → give **P**rokinetics.
- **EPS = E**pigastric pain → give **P**PI**s**.
- **Rome III Timeframes**: **6** and **3** (Onset ≥ **6** months ago, symptomatic for at least the last **3** months).

- **FODMAP**: **F**ermentable **O**ligo-, **D**i-, **M**ono-saccharides **A**nd **P**olyols (sugar-free sweeteners). Avoid beans, apples, cabbage, wheat.

Pancreatitis

Core Concepts

- **Pancreatic Cellular Overview:**
  - **Acinar cells (80%):** Exocrine function.
  - **Ductal cells (10%):** Secretion modification.
  - **Islet cells (10%):** Endocrine function (Insulin, Glucagon, Somatostatin, Pancreatic polypeptides).
- **Pathogenesis of Acute Pancreatitis (AP):** Ductal obstruction, reflux, or increased ductal permeability (due to alcohol, drugs, or infections) leads to disruption of cell membranes and auto-digestion.
- **Pathology Classifications:** Interstitial (mild, lower risk) vs. Necrotizing (severe, high risk of infection and death).

Diagnosis / Clinical Features

- **Acute Pancreatitis Presentation:**
  - Severe abdominal pain, nausea, vomiting, fever, tachycardia.
  - **Hemorrhagic signs (severe disease):** Cullen's sign (periumbilical bruising), Grey-Turner's sign (flank bruising).
- **Etiology of Acute Pancreatitis:**
  - **Major causes:** Gallstones (most common) and Alcohol.
  - **Other causes:** Idiopathic, Drugs, Hyperlipidemia, Infections, Hypercalcemia, Ductal obstruction, Trauma, Ischemia/Hypotension, Post-operative.
- **Drug-Induced Acute Pancreatitis:**
  - *Idiosyncratic:* Azathioprine / 6-Mercaptopurine, Sulfonamides, Pentamidine, Valproic acid, Cimetidine.
  - *Dose-dependent:* Thiazides (high dose).
  - *Secondary to Hypertriglyceridemia:* Estrogens.
- **Recurrent Pancreatitis Etiologies:**
  - **Pancreatic Divisum:** Most common congenital abnormality (5-10% of population). Failure of major and minor duct fusion. *Treatment:* Minor duct sphincterotomy.
  - **Hereditary Pancreatitis:** Autosomal dominant, childhood onset. Calcifications develop by the second decade. High risk of pancreatic carcinoma.
- **Chronic Pancreatitis (CP) Presentation:**
  - Triad/Tetrad: Abdominal pain, Pancreatic calcifications, Steatorrhea, Diabetes.

- *Etiologies:* Alcohol (most common), Idiopathic, Tropical, Hereditary, Hyperparathyroidism, Cystic Fibrosis, Pancreatic divisum.
- **Pancreatogenic Diabetes:** "Brittle" diabetes occurring in severe disease. Involves loss of **both** Insulin and Glucagon. Insulin requirements are low, and Ketoacidosis is notably rare.

Investigations

- **Laboratory Diagnosis of AP:**
  - Leukocytosis, Elevated Amylase, Elevated Lipase.
  - **Predictors of Gallstone Pancreatitis:** Age > 50, Female, Amylase > 4,000 IU/L, AST > 100 U/L, Alkaline Phosphatase > 300 IU/L.
- **Differentiating Causes of Hyperamylasemia:**

CONDITION	AMYLASE	LIPASE
Pancreatitis	High	High
Biliary stones / Intestinal injury / Renal failure	High	High
Parotitis / Tubo-ovarian pathology	High	**Normal**
Macroamylasemia	High	**Normal**

- **Imaging in AP:**
  - **Ultrasound:** Useful for detecting gallstones (normal vs. bulky/inflamed pancreas).
  - **CT Scan Indications:** Ranson's score > 3, refractory hypoxemia/hypotension, persistent leukocytosis/fever, tender abdominal mass, hemodynamic deterioration, or presence of Cullen/Grey-Turner signs.
- **Diagnosing Chronic Pancreatitis:**
  - *Most Sensitive:* Endoscopic Ultrasound (EUS), ERCP (Structure); Secretin test (Function).
  - *Less Sensitive:* CT Scan, Transabdominal US; Bentiromide (PABA), Serum Trypsinogen, Fecal Chemotrypsin.
  - *Least Sensitive:* Abdominal X-Ray (shows calcifications); Fecal Fat.

Management

- **Acute Pancreatitis:**
  - **Essential Supportive Care:** NPO, IV fluid replacement, close clinical surveillance, nutritional support, adequate pain control.
  - **Interventions to reduce inflammation:** ERCP with papillotomy (for impacted gallstones), Peritoneal lavage (to remove toxic ascites).
  - **Unproven/Ineffective therapies:** Routine prophylactic antibiotics, reducing pancreatic secretions (via H2 blockers, NG suction, glucagon, or somatostatin).
- **Antibiotic Selection (if infection is confirmed/suspected):**

- *Excellent Penetration (Use these):* Ciprofloxacin, Ofloxacin, Imipenem, Metronidazole.
- *Poor Penetration (Avoid):* Aminoglycosides, Broad-spectrum penicillins, 3rd-generation cephalosporins.

- **Chronic Pancreatitis Management:** Discontinue alcohol, suppress pancreatic secretion (using oral Pancreatic Enzymes), modify neurotransmission (nerve block for pain), relieve obstruction (surgery, stenting).

Complications / Prognosis

- **Ranson's Criteria for Severity (AP):** Mortality risk correlates directly with the score.
  - **At Admission:** Age > 55, WBC > 16K, Glucose > 200 mg/dL, LDH > 350 IU/L, AST > 250 U/L.
  - **During First 48 Hours:** Hematocrit drop > 10%, BUN rise > 5 mg/dL, Calcium < 8 mg/dL, PaO2 < 60 mmHg, Base deficit > 4 mEq/L, Fluid sequestration > 6L.
- **CT Criteria of Severity (AP):**
  - Grade A: Normal.
  - Grade B: Enlargement.
  - Grade C: Peri-pancreatic inflammation.
  - Grade D: Single fluid collection.
  - Grade E: Multiple fluid collections / Phlegmon (ill-defined mass, sterile or infected).
- **Infection & Mortality by AP Subtype:**
  - *Interstitial:* Infection <1%, Mortality <1%.
  - *Necrotizing:* Infection 30-50%. Mortality is 10% if sterile, and up to 30% if infected.
- **Specific Acute Complications:**
  - **Hypocalcemia:** Loss of non-ionized calcium is common/asymptomatic (no tx needed). Loss of ionized calcium is rare, causes neuromuscular irritability, and requires treatment.
  - **ARDS:** Delayed onset, associated heavily with hyperlipidemia, characterized by progressive hypoxemia unresponsive to O2, increased lung stiffness, and diffuse opacities. Potentially reversible.
  - **Pancreatic Pseudocyst:** Complications include obstruction (CBD/Duodenum), bleeding, infection, leakage, rupture.
    - *Indications for Intervention (Surgical, Percutaneous, or Endoscopic):* Size > 5 cm, duration > 4-6 weeks, severe pain, rapid expansion, or structural complications.
- **Chronic Pancreatitis Complications:** CBD stenosis, duodenal obstruction, **splenic vein thrombosis**, pleural effusion, pseudocyst, pancreatic ascites.

Past-Paper High Yield

- **Drug-induced Pancreatitis culprits:** Differentiate idiosyncratic (Azathioprine, Valproate) from dose-dependent (Thiazides).
- **Amylase vs. Lipase:** Understand that parotitis, tubo-ovarian disease, and macroamylasemia elevate Amylase but leave Lipase *normal*.

- **CP Diabetes unique features:** Distinct from Type 1/Type 2 DM. Low insulin requirement, absence of glucagon, and DKA is very rare.
- **Gallstone Pancreatitis Labs:** Look for an Amylase > 4,000 IU/L combined with elevated liver enzymes (AST > 100, ALP > 300) as highly predictive for a biliary etiology.
- **Antibiotic Choice in Necrotizing Pancreatitis:** Imipenem, Fluoroquinolones, and Metronidazole have good pancreatic penetration; Aminoglycosides and 3rd-gen Cephalosporins do *not*.
- **Pseudocyst intervention thresholds:** Memorize the "5 and 5" rule approximation (Size > 5 cm, Duration > 4-6 weeks).

Memory Pearls

- **Ranson's Criteria Mnemonic:**
  - *Admission ("GA LAW"):* **G**lucose >200, **A**ge >55, **L**DH >350, **A**ST >250, **W**BC >16k.
  - *48 Hours ("C HOBBS"):* **C**alcium <8, **H**ct drop >10%, p**O**2 <60, **B**UN rise >5, **B**ase deficit >4, **S**equestration >6L.
- **Pancreatic Divisum:** "Divided" ducts (major/minor failure to fuse) = treat the minor (minor duct sphincterotomy).

Autoimmune Liver Disease

Core Concepts

Autoimmune liver diseases are divided into three major pathologies based on the primary site of inflammation and the pattern of liver injury:

- **Primary Sclerosing Cholangitis (PSC):** Diffuse inflammation and fibrosis of the intrahepatic and extrahepatic biliary tree. Strongly associated with Inflammatory Bowel Disease (IBD).
- **Primary Biliary Cirrhosis / Cholangitis (PBC):** Non-suppurative destruction of small intrahepatic bile ducts. Primarily affects middle-aged women.
- **Autoimmune Hepatitis (AIH):** Intermittently progressive, cell-mediated inflammatory liver disease targeting hepatocytes, typically responding favorably to immunosuppression.

Diagnosis / Clinical Features

Primary Sclerosing Cholangitis (PSC)

- **Clinical Presentation:** Cholestatic pattern. Mostly asymptomatic initially (15-44%). Symptomatic patients present with fatigue (75%), pruritus (70%), jaundice, and hepatosplenomegaly.
- **Associations: 60-80% of PSC patients have IBD** (Ulcerative Colitis is twice as common as Crohn’s).

Primary Biliary Cirrhosis (PBC)

- **Clinical Presentation:** Insidious onset, heavily female predominant. **Fatigue** is the most common symptom (up to 80%), followed by **pruritus** (20-60%) and jaundice (late).

- **Physical Exam:** Hepatomegaly, hyperpigmentation, and **xanthomata/xanthelasma** (15-50% frequency, associated with high cholesterol).
- **Associations:** High rate of extrahepatic autoimmune diseases: **Sicca syndrome** (70%), autoimmune thyroid disease (40%), and scleroderma/CREST syndrome.

Autoimmune Hepatitis (AIH)

- **Clinical Presentation:** Typically a middle-aged (or teenage) woman presenting with fatigue, arthralgias/myalgias, oligomenorrhea, and jaundice.
- **Classification:**
  - **Type 1:** Any age (usually adults), ANA and SMA positive.
  - **Type 2:** Predominantly children/teens, LKM-1 positive, faster progression to cirrhosis.

Investigations

Laboratory & Serological Profile

FEATURE	PSC	PBC	AIH
Liver Enzyme Pattern	Cholestatic (Elevated ALP)	Cholestatic (Elevated ALP)	Hepatocellular (High AST/ALT, >5x normal)
Key Autoantibodies	**p-ANCA** (80%) ANA (50-60%), SMA (35%)	**AMA** (>90%) ANA, ASMA	**ANA, SMA** (Type 1) **LKM-1** (Type 2)
Other Distinct Labs	AMA is typically negative (<2%)	High IgM, High Cholesterol	High IgG (Gamma globulins)

Imaging & Histology

- **PSC:**
  - **Imaging (Diagnostic): MRCP** is the diagnostic modality of choice (non-invasive, no radiation, cost-effective). Shows typical "beaded" cholangiographic abnormalities (strictures/dilations).
  - **Histology: Onion skin fibrosis** (concentric fibrosis). *Note: Small-duct PSC (5%) has a normal cholangiogram but positive biopsy.*
- **PBC:**
  - **Histology: Florid duct lesion** (non-suppurative destructive cholangitis).
  - *Note:* 5-10% of cases are AMA-negative but have identical histology and prognosis.
- **AIH:**
  - **Diagnosis:** Requires a constellation of findings (International AIH Group Score).
  - **Histology: Interface hepatitis** with a **lymphoplasmacytic infiltrate** and rosetting of liver cells.

Management

Primary Sclerosing Cholangitis (PSC)

- **Medical:** No proven disease-specific medical therapy exists.

- **Intervention: ERCP** is used therapeutically for balloon dilation of dominant, symptomatic biliary strictures (stenting is less preferred due to complications).
- **General Care:** Screen for varices, manage osteoporosis, and treat ascending cholangitis with antibiotics.
- **Surgical:** Liver transplantation (85-88% 5-year survival).

Primary Biliary Cirrhosis (PBC)

- **Disease-Modifying Therapy: Ursodeoxycholic Acid (UDCA)**. It is cytoprotective, modulates HLA expression, stabilizes bile canalicular membranes, and acts as a choleretic.
- **Symptom Management:**
  - *Sicca syndrome:* Increased fluid intake, oral sialogogues, artificial tears.
  - *Xanthomata:* May resolve with UDCA therapy.

Autoimmune Hepatitis (AIH)

- **Indication to treat:** AST ≥ 10x normal, or AST ≥ 5x normal with gamma-globulin ≥ 2x normal, or bridging necrosis on biopsy.
- **Regimens:**
  - **Prednisone Monotherapy:** Used in pregnancy, severe cytopenia, malignancy, or Azathioprine intolerance/TPMT deficiency.
  - **Combination (Prednisone + Azathioprine):** Preferred for maintenance to spare steroids. Ideal for postmenopausal women, diabetics, obese patients, and those with osteoporosis or hypertension.

Management of Chronic Cholestasis (Applicable to PSC & PBC)

- **Metabolic Bone Disease:** Osteoporosis is common (independent of menopause). Manage with Calcium + Vitamin D and Bisphosphonates. (Avoid steroids as they worsen bone disease).
- **Malabsorption:** Steatorrhea requires supplementation of fat-soluble vitamins (A, D, E, K).

Complications / Prognosis

- **PSC Specific Risks:** High risk of **Cholangiocarcinoma** (7-15% lifetime risk) and Colon Cancer (due to concurrent IBD). Annual cancer surveillance is critical.
- **Portal Hypertension:** Common in PBC/PSC as cirrhosis develops. Independent predictors of varices include serum albumin, bilirubin, and platelet count.
- **Transplantation Outcomes:** AIH has an 80-90% 5-year post-transplant survival but a 30-40% recurrence rate in the allograft. PSC also has good survival but recurrent issues with rejection, infection, and colon cancer.

Past-Paper High Yield

- **Differentiating AIH vs. Wilson's Disease:** A patient presenting with extreme transaminitis (ALT/AST > 1500), remarkably low Alkaline Phosphatase, and neurological signs (asterixis, **choreiform movements**) has **fulminant Wilson's disease**, not Autoimmune Hepatitis. AIH lacks choreiform movements.

- **ERCP vs. MRCP Use:** While MRCP is the preferred non-invasive test for *diagnosing* PSC, **ERCP is the most appropriate next step** for therapeutic management of acute biliary obstruction or ascending cholangitis (e.g., patient presenting with fever, highly elevated liver enzymes, and a dilated CBD).
- **PBC Medical Therapy: Ursodeoxycholic acid (UDCA)** is the highest-yield pharmacological intervention for PBC. It delays disease progression and can help resolve secondary signs like xanthomata.

Memory Pearls

- **PSC: P**rimary **S**clerosing **C**holangitis = **P**-ANCA, **S**trictures (beading on MRCP), **C**olitis (Ulcerative Colitis).
- **PBC: P**rimary **B**iliary **C**irrhosis = **P**ruritus, **B**lood tests show **A**MA (Mitochondrial), **C**REST/Sjogren's association.
- **AIH: A**uto**I**mmune **H**epatitis = **A**ST/ALT high, **I**gG high, **H**istology (Interface hepatitis). Types: 1 (ANA/SMA), 2 (LKM-1).

ASH and NASH

Core Concepts

- **Nonalcoholic Fatty Liver Disease (NAFLD):** The most common form of chronic liver disease (20–30% global prevalence) and the hepatic manifestation of metabolic syndrome.
- **Nonalcoholic Steatohepatitis (NASH):** A progressive subtype of NAFLD (~3% of the population) that carries a high risk of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).
- **The Spectrum of NAFLD:**
  - *Simple Steatosis:* Fat accumulation without significant inflammation.
  - *NASH:* Steatosis + lobular inflammation + hepatocellular ballooning injury ± fibrosis.
  - *Cirrhosis:* Fibrosis and nodular regeneration.
- **Metabolic Syndrome (ATP III Criteria):** Requires ≥ 3 of the following 5 features:
  1. Waist circumference ≥ 102 cm (men) or ≥ 88 cm (women)
  2. Triglycerides ≥ 150 mg/dL
  3. HDL < 40 mg/dL (men) or < 50 mg/dL (women)
  4. Blood Pressure ≥ 130/85 mm Hg
  5. Fasting Plasma Glucose ≥ 110 mg/dL
- **Pathogenesis:** Elevated free fatty acids (FFAs) → oxidative stress (ROS) → hepatocyte apoptosis (cytochrome c, caspase 3) → Kupffer cell activation → hepatic stellate cell (HSC) activation and fibrogenesis.

Diagnosis / Clinical Features

- **Presentation:**
  - Usually asymptomatic (45–100%) or presents with non-specific fatigue and RUQ discomfort.

- Frequently an incidental finding (elevated LFTs, fatty liver on ultrasound, or hepatomegaly).
- Hepatomegaly is detected in 60–80% of patients.

- **Diagnostic Exclusions:** Must exclude other causes to diagnose NAFLD:
  - *Alcohol Consumption:* Must be ≤ 1–2 drinks/day (greater amounts suggest Alcoholic Liver Disease/ASH).
  - *Medications:* Corticosteroids, amiodarone, methotrexate, calcium channel blockers, tamoxifen.
  - *Other:* Viral hepatitis, autoimmune hepatitis, Wilson disease, hemochromatosis, altered nutrition (TPN, rapid weight loss, starvation).

Investigations

- **Biochemical Findings:**
  - **AST and ALT:** Mildly elevated (2–5x upper limit of normal). *Note: ALT level is NOT a reliable indicator of disease severity.*
  - **AST/ALT Ratio:** Usually **< 1** in early NAFLD (65–90% of patients).
  - **Alkaline Phosphatase (ALP):** Elevated (2–3x normal) in < 50% of patients.
  - **Serum Ferritin: Elevated in ~50% of patients.**
  - **Liver synthetic function** (Albumin, Bilirubin, INR) remains normal unless cirrhosis has developed.
- **Imaging:**
  - *Ultrasound:* Increased echogenicity ("bright" or radiopaque liver).
  - *CT:* Low attenuation of the liver.
- **Liver Biopsy (Gold Standard):**
  - Required to differentiate simple steatosis from NASH and to stage fibrosis.
  - **Diagnostic Triad for NASH:** Steatosis (≥ 5% of hepatic parenchyma) + Mixed lobular inflammation + Hepatocellular ballooning.

Management

- **Lifestyle Modification (First-line):**
  - *Weight Loss Goal:* ≥ 5% weight loss is required to improve steatosis; **7–10% weight loss** is needed to improve necroinflammation. Aim for 0.5–1.0 kg/week.
  - *Diet:* Caloric restriction (600 kcal deficit), Mediterranean or Atkins diet. Low sodium, simple carbohydrates, and saturated/trans-fats.
  - *Exercise:* 5–7 sessions/week (30–45 mins each); aim for >10,000 steps/day.
- **Pharmacotherapy (For NASH):**
  - **Pioglitazone:** Consider for patients with biopsy-proven NASH and Type 2 Diabetes. (Warn about weight gain, bone loss, potential bladder cancer risk).
  - **Vitamin E (800 IU/day):** Consider for *non-diabetic* adults with biopsy-proven, *non-cirrhotic* NASH.
- **Bariatric Surgery:**

- Indicated for severe obesity (BMI >40, or >35 with comorbidities).
- Improves NASH but is *contraindicated* if portal hypertension or gastroesophageal varices are present.

Complications / Prognosis

- **Fibrosis Progression:** Averages 1 stage per 7 years, but 20% are "fast progressors" who can develop cirrhosis within 10 years.
- **Risk Factors for Rapid Progression:** Central obesity, HTN, T2DM, dyslipidemia, metabolic syndrome, and advancing age.
- **Mortality:** NASH is the 2nd most common reason for liver transplant and 3rd most common cause of HCC in Western countries. Leading cause of death is usually cardiovascular.

Past-Paper High Yield

- **Typical Clinical Vignette:** A middle-aged, obese patient with Type 2 Diabetes presenting with marked hepatomegaly, mildly elevated transaminases (2-5x normal), and an echogenic (radiopaque) liver on ultrasound. **Diagnosis: NASH**.
- **Serum Ferritin:** Know that ferritin is **elevated in ~50%** of NASH patients. (This is frequently tested as a standalone true/false statement).
- **Transaminase Ratios and Levels (The Traps):**
  - *Early NASH:* AST/ALT ratio is < 1.
  - *Advanced Fibrosis in NASH:* AST/ALT ratio flips to **> 1**.
  - *Alcoholic Liver Disease (ASH):* AST/ALT ratio is typically **> 2** (rarely seen in NASH).
  - *Enzyme degree:* LFTs in NASH are usually *only* 2–5x normal. Watch out for distractor options claiming massive elevations (e.g., ALT/AST x10 normal or ALP x5 normal—these are false for NASH).

Memory Pearls

- **Rule of 5s and 10s for NASH weight loss: 5%** loss fixes the **F**at (steatosis), **7–10%** loss fixes the **F**ire (inflammation).
- **NASH Biopsy Triad: F**at (≥5%), **F**ire (lobular inflammation), and **B**alloons (hepatocyte ballooning).
- **AST/ALT Ratios: < 1** = simple NASH; **> 1** = advanced fibrosis/cirrhosis; **> 2** = alcoholic (ASH).

Liver Cirrhosis

Core Concepts

- **Definition:** The irreversible late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules.
- **Pathophysiology of Systemic Findings:**
  - *Loss of Synthetic Function:* Decreased albumin (edema), decreased clotting factors (elevated PT/INR).

- *Impaired Detoxification / Breakdown:* Hyperammonemia (hepatic encephalopathy), impaired estrogen breakdown (gynecomastia, testicular atrophy, spider angiomata, palmar erythema).
- *Portal Hypertension:* Shunting of blood leads to varices, caput medusae, and splenomegaly (causing cytopenias).

- **Definitive Treatment:** Liver transplantation.

Diagnosis / Clinical Features

- **Presentation:** Often asymptomatic (diagnosed incidentally or at autopsy in 30-40% of cases). Can present acutely as decompensated cirrhosis with complications.
- **Stigmata of Chronic Liver Disease (Physical Exam):**
  - **Skin/Nails:** Spider angiomata, palmar erythema, Terry's nails, clubbing, jaundice.
  - **Endocrine:** Gynecomastia, testicular atrophy (due to altered estrogen metabolism).
  - **Abdomen/GI:** Hepatomegaly (or shrunken liver), splenomegaly, caput medusae (distended periumbilical veins), fetor hepaticus (musty breath odor).
  - **Musculoskeletal:** Dupuytren's contracture, hypertrophic osteoarthropathy.

Investigations

- **Liver Enzymes:**
  - AST and ALT moderately elevated (AST > ALT). *Normal aminotransferases do not rule out cirrhosis.*
  - Alkaline Phosphatase (ALP) usually elevated (<2–3x normal limit). Higher elevations suggest Primary Biliary Cirrhosis (PBC) or Primary Sclerosing Cholangitis (PSC).
  - GGT correlates with ALP; disproportionately high in alcohol-induced cirrhosis.
- **Liver Function / Synthetic Tests:**
  - **Bilirubin:** Normal early, progressive rise in advanced disease.
  - **Albumin:** Hypoalbuminemia reflects synthetic decline (though non-specific).
  - **Prothrombin Time (PT/INR):** Highly sensitive for liver synthetic dysfunction.
- **Other Laboratory Findings:**
  - **Hyponatremia:** Common with ascites; due to inability to excrete free water (high ADH secretion).
  - **Thrombocytopenia:** Primarily caused by portal hypertension -> congestive splenomegaly (spleen sequesters up to 90% of circulating platelets).
  - **Anemia & Leukopenia:** Multifactorial (GI loss, folate deficiency, hypersplenism).
  - **Globulins:** Increased due to shunting of bacterial antigens to lymphoid tissue.
    - *Marked IgG elevation:* Autoimmune hepatitis.
    - *Marked IgM elevation:* PBC (present in 90-95% of patients).
- **Radiology:**
  - **Ultrasound (Initial):** Shows small, nodular liver; detects portal hypertension (increased portal vein diameter, collateral veins).

- **Fibroscan:** Uses shear wave propagation to assess tissue stiffness (faster wave = denser fibrosis).

- **Histology:** Liver biopsy (percutaneous, transjugular, laparoscopic) is the **gold standard**, particularly useful for diagnosing metabolic causes.

Management

- **Ascites Management:**
  - Sodium restriction: < 2 grams (88 mEq) daily.
  - Diuretics: **Spironolactone** (100–400 mg daily) +/- **Furosemide** (40–160 mg daily). Monitor kidney function and electrolytes closely.
  - **Large Volume Paracentesis (LVP):** If performing LVP, replace albumin to prevent circulatory dysfunction.
    - *Rule:* Give **8 grams of 25% albumin for each liter** of ascitic fluid removed.
- **Hepatic Encephalopathy (HE):**
  - **Lactulose (First-line):** 30–45 mL PO 2–4 times/day; titrate to achieve 2–3 soft stools daily. Can be given as an enema if the patient cannot take PO.
  - **Rifaximin:** Used as add-on therapy for secondary prophylaxis, or if no improvement within 48 hours of starting lactulose.
  - *Note on Ammonia Labs:* High ammonia does *not* add diagnostic, staging, or prognostic value. However, a **strictly normal ammonia level puts the diagnosis of HE in question**.

Complications / Prognosis

- **Spontaneous Bacterial Peritonitis (SBP):**
  - **Diagnosis:** Ascites + Temp > 37.8°C (100°F), abdominal pain/tenderness, altered mental status, OR **Ascitic fluid PMN count ≥ 250 cells/mm³**.
  - **Management Caveat:** Permanently discontinue non-selective beta-blockers once SBP has developed.
  - **High-Risk for SBP (Prophylaxis Indications):**
    1. Cirrhosis with concurrent GI bleeding.
    2. History of 1+ prior SBP episodes.
    3. Ascitic fluid protein < 1.5 g/dL AND either:
       - Impaired renal function (Cr ≥ 1.2, BUN ≥ 25, or Na ≤ 130).
       - Liver failure (Child-Pugh ≥ 9 and Bilirubin ≥ 3).
- **Child-Pugh Classification:** Use to grade severity (A: <7, B: 7-10, C: >10).
  - Parameters evaluated: **Bilirubin, INR, Albumin, Encephalopathy, Ascites** *(Mnemonic: "Pour Another Beer At Eleven" - PT/INR, Ascites, Bilirubin, Albumin, Encephalopathy)*.

PARAMETER	1 POINT	2 POINTS	3 POINTS
Bilirubin (mg/dL)	< 2.0	2.0 - 3.0	> 3.0

PARAMETER	1 POINT	2 POINTS	3 POINTS
INR	< 1.7	1.7 - 2.3	> 2.3
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
Encephalopathy	None	Grade I - II	Grade III - IV
Ascites	None	Slight	Moderate / Tense

Past-Paper High Yield

- **First Presentation of Tense Ascites:** A patient presenting with new tense ascites and asymptomatic hyponatremia should be treated with **paracentesis, salt restriction, spironolactone, and furosemide**. Do not isolate the hyponatremia and delay fluid offloading with just water restriction.
- **Budd-Chiari Syndrome (Hepatic Vein Thrombosis):** Suspect in young females on oral contraceptives presenting with abdominal pain, ascites, and jaundice. The key distinguishing physical finding from standard decompensated cirrhosis is a **tender enlarged liver** (due to acute hepatic congestion).
- **Primary Biliary Cirrhosis (PBC) Serology:** The most common serologic finding in PBC is the **Anti-mitochondrial antibody (AMA)** (associated with significantly elevated IgM levels).
- **Ascitic Fluid Analysis (SAAG):** Serum Ascites Albumin Gradient (SAAG) = Serum Albumin – Ascitic Albumin.
  - A SAAG **≥ 1.1 g/dL** indicates portal hypertension (e.g., Cirrhosis, Right Heart Failure, Budd-Chiari).
  - *Exam Trap:* Do not diagnose SBP unless the absolute PMN count is ≥ 250 cells/mm³. If given WBCs and a neutrophil percentage, you must multiply them (e.g., WBC 230 x 30% PMNs = 69 PMNs = NOT SBP).

Memory Pearls

- **Albumin Replacement Rule:** 8 grams / 1 Liter removed during large-volume paracentesis.
- **Cytopenia in Cirrhosis:** Thrombocytopenia is usually the earliest and most profound cytopenia, driven directly by splenic sequestration (up to 90% stored).
- **Enzyme Pattern:** AST > ALT in cirrhosis (especially alcohol-related), whereas ALT > AST in most acute viral/toxic liver injuries.

Hereditary Liver Diseases and Wilson's Disease

Core Concepts

- **Inherited Causes of Cirrhosis:** Hemochromatosis, Wilson's disease, Alpha-1-antitrypsin deficiency, Cystic fibrosis, and Familial intrahepatic cholestasis.
- **Hemochromatosis:** An autosomal recessive iron overload disorder. Involves *HFE* gene mutations (most commonly C282Y homozygosity or C282Y/H63D compound heterozygosity) leading to

increased intestinal iron absorption.

- **Wilson's Disease:** An autosomal recessive copper overload disorder (Chromosome 13 defect). A missense mutation in the *ATP7B* gene (a p-type ATPase) impairs copper excretion into bile and prevents incorporation into ceruloplasmin. Copper builds up in the liver, spills into the blood, and deposits in target organs (brain, cornea, kidneys).
- **Iron vs. Copper Balance (Normal):**
  - *Iron:* Ingest 10-20 mg/d; Absorb 1-2 mg/d. Total body iron is ~4g.
  - *Copper:* Ingest 1.5-4.0 mg/d. Excreted primarily in bile, with minimal urine output (<70 µg/day).

Diagnosis / Clinical Features

Hemochromatosis

- **Demographics:** Phenotypic expression is higher in men and increases with age (women are protected pre-menopause due to menstruation/pregnancy). Highly prevalent in Caucasians (Heterozygote 1:12, Homozygote 1:400).
- **Classic Triad (Late):** Cirrhosis, Diabetes Mellitus ("bronze diabetes"), and skin hyperpigmentation.
- **Musculoskeletal:** Arthropathy, arthritis, and **pseudogout** (calcium pyrophosphate deposition).
- **Endocrine:** Hypogonadism (due to pituitary gonadotropin deficiency leading to testicular atrophy), diabetes mellitus.
- **Cardiac:** Cardiomyopathy, conduction disorders.
- **Hepatic:** Hepatomegaly, cirrhosis, markedly increased risk of hepatocellular carcinoma (HCC).
- **Infection:** Increased susceptibility to bacteremia (e.g., *Vibrio vulnificus*, *Listeria*, *Yersinia*).

Wilson's Disease

- **Demographics:** Consider in children, adolescents, or young adults presenting with cryptogenic liver disease, hemolysis, or early-onset atypical neurologic/psychiatric symptoms.
- **Hepatic:** Acute hepatitis, fulminant hepatic failure, chronic hepatitis, cryptogenic cirrhosis.
- **Neurologic/Psychiatric:** Parkinson-like disorders (tremor, gait disturbance), psychosis, personality changes.
- **Ophthalmologic:** Kayser-Fleischer (KF) rings (copper in Descemet's membrane), sunflower cataracts.
- **Hematologic:** Coombs-negative hemolytic anemia (often presenting concurrently with acute liver disease).
- **Renal:** Fanconi syndrome (proximal renal tubular acidosis) with hypouricemia.
- **Musculoskeletal:** Osteoporosis, arthropathy.

Investigations

Hemochromatosis

- **Initial Blood Tests:**
  - **Transferrin Saturation:** Usually the earliest abnormality. **>50%** (often 55-100%).

- **Serum Ferritin:** Markedly elevated (>300 ng/mL in males; >250 ng/mL in females; can be up to 3000).
- *Note on Ferritin Interpretation:* If ferritin is high but iron/transferrin saturation is normal/low, suspect acute liver injury, acute phase reactant, or chronic disease rather than hemochromatosis.

- **Genetic Testing:** Check for *HFE* mutations (C282Y and H63D) in suspected patients or those with appropriate family history.
- **Liver Biopsy:** Used if diagnosis is uncertain or to stage disease/fibrosis.
  - Prussian Blue stain shows extensive iron deposition (3+ to 4+).
  - Hepatic iron index > 1.9 (mmol/g dry weight ÷ age).

Wilson's Disease

- **Serum Labs:**
  - **Ceruloplasmin:** Decreased (<20 mg/dL). *Caveat: 5% of Wilson's patients have normal ceruloplasmin; it can also be low in protein-losing states or hepatic failure.*
  - **Total Serum Copper:** Paradoxically **decreased or normal**. (Because 90% of serum copper is normally bound to ceruloplasmin, low ceruloplasmin drives total serum copper down, even though *free/unbound* serum copper is highly elevated).
- **Urine Labs:**
  - **24-hour Urine Copper:** Markedly **elevated (>100 µg/24 hr)**.
- **Slit Lamp Examination:** Confirms the presence of Kayser-Fleischer rings.
- **Liver Biopsy:** Gold standard/confirmatory. Quantitative hepatic copper > 250 µg/g dry weight.

Management

Hemochromatosis

- **Phlebotomy:** Mainstay of therapy.
  - *Acute phase:* Remove 1 unit (250 mg Fe) weekly or biweekly until mildly anemic.
  - *Maintenance phase:* Continue every 2-3 months. Target Ferritin < 50 ng/mL and Transferrin Saturation < 50%.
  - Improves survival and prevents disease progression.

Wilson's Disease

- **Chelation Therapy:** Penicillamine or Trientine (always give with Pyridoxine/B6 to prevent deficiency).
- **Zinc:** Blocks intestinal absorption of copper.
- **Diet:** Avoid high-copper foods (organ meats, shellfish, nuts, chocolate).
- **Liver Transplantation:** Curative in severe acute liver failure or decompensated cirrhosis.
- **Monitoring:** Follow 24-hour urine copper and non-ceruloplasmin (free) copper. **Do NOT monitor Kayser-Fleischer rings** to guide therapy.
- **Screening:** First-degree relatives must be screened.

Complications / Prognosis

Reversibility of Hemochromatosis with Phlebotomy:

- **Reversible:** Cardiac dysfunction, glucose intolerance (DM), hepatomegaly, skin pigmentation ("bronzing").
- **Irreversible (Permanent):** Cirrhosis, risk of Hepatocellular Carcinoma (HCC), arthropathy/pseudogout, and hypogonadism.

Past-Paper High Yield

- **The Wilson's Disease Lab Trap:** You must know the expected lab pattern in untreated Wilson's disease. Expect **HIGH** urinary copper, **HIGH** free/tissue copper, but **REDUCED/NORMAL** total serum copper (due to low ceruloplasmin). An exam option stating "low urinary copper" in untreated Wilson's is **incorrect**.
- **Hemolysis + Liver Failure:** Co-occurrence of Coombs-negative hemolytic anemia and liver disease strongly points to Wilson's disease.
- **Hemochromatosis Arthropathy:** A young-to-middle-aged male with known hemochromatosis presenting with an acutely swollen, painful joint (especially wrists or 2nd/3rd MCPs) has **Pseudogout** (calcium pyrophosphate crystal deposition disease). Do not confuse this with RA or gout.
- **Irreversible features of Hemochromatosis:** Remember that phlebotomy will not reverse joint pain (arthropathy) or the risk of HCC once cirrhosis has developed.

Memory Pearls

- **Wilson's Labs:** Low Ceruloplasmin, Low Total Serum Copper, HIGH Urine Copper, HIGH Free Serum Copper, HIGH Hepatic Copper.
- **HFE Gene: H**igh **F**erritin **E**xpression.
- **C282Y:** The most important mutation to look for in Hemochromatosis.
- **Kayser-Fleischer Rings:** Required for the diagnosis of Wilson's with neurologic symptoms, but absent in up to 50% of patients with purely hepatic presentations. Never use them to monitor treatment efficacy.

Viral Hepatitis A-E

Core Concepts

- **Enterically Transmitted (Fecal-Oral):** Hepatitis A (HAV) and E (HEV).
  - Primarily cause acute disease; no chronic state in immunocompetent patients.
- **Parenterally Transmitted (Blood/Body Fluids):** Hepatitis B (HBV), C (HCV), and D (HDV).
  - Can progress to chronic infection, cirrhosis, and hepatocellular carcinoma.
- **Genomes:** All hepatitis viruses are **RNA** viruses *except* **HBV**, which is a **DNA** virus (Hepadnaviridae).

FEATURE	HAV	HBV	HCV	HDV	HEV
Transmission	Fecal-oral	Parenteral, Sexual, Perinatal	Parenteral (esp. IVDU), Sexual, Perinatal	Parenteral, Sexual	Fecal-oral
Chronicity	None	Age-dependent (90% neonates; <10% adults)	High (70-85%)	Low (Coinfection); High (Superinfection)	None (except immunosup-pressed)
Vaccine	Yes	Yes	No	Prevents via HBV vaccine	No (globally)

Diagnosis / Clinical Features

- **Hepatitis A (HAV):**
  - Average incubation 21 days.
  - Symptomatic jaundice is age-dependent (<10% in children <6 years; 70–80% in adults >14 years).
  - Associated with contaminated food/water (e.g., raw shellfish, infected food handlers) and child day care centers.
- **Hepatitis B (HBV):**
  - Average incubation 60–90 days.
  - Perinatal transmission is the primary route in highly endemic regions (highest risk if mother is HBeAg+).
- **Hepatitis C (HCV):**
  - Average incubation 6–7 weeks.
  - Most acute infections are asymptomatic (jaundice in only 20–30%).
- **Hepatitis D (HDV):**
  - Requires HBV envelope (HBsAg) to replicate.
  - **Coinfection (HBV + HDV simultaneously):** Severe acute hepatitis, self-limited, low risk of chronicity.
  - **Superinfection (HDV on top of chronic HBV):** Presents as an acute flare/decompensation; *very high* risk of progressing to chronic HDV infection.
- **Hepatitis E (HEV):**
  - Average incubation 40 days.
  - Endemic in regions with poor sanitation; commonly affects travelers.

Investigations

1. Hepatitis B Serology (High-Yield for Exams):

- **HBsAg (Surface Antigen):** General marker of current active infection (acute or chronic).
- **Anti-HBs (Surface Antibody):** Marker of recovery and immunity (vaccination or resolved infection).

- **Anti-HBc IgM (Core IgM):** Marker of *acute* infection. Positive during the "window period" when HBsAg disappears but Anti-HBs has not yet appeared.
- **Anti-HBc IgG (Core IgG):** Marker of *past* or *chronic* infection (positive for life after natural exposure; negative in vaccinated individuals).
- **HBeAg (e Antigen):** Marker of active viral replication and high infectivity.
- **Anti-HBe (e Antibody):** Suggests virus is no longer replicating significantly (though HBsAg may still be positive from integrated HBV).
- **HBV DNA:** Indicates active replication. Most accurate marker, especially in "escape mutants" (where HBeAg is negative despite active replication). Used to monitor therapy.

2. Serology for Other Viruses:

- **HAV:** Acute = HAV-IgM via EIA. Immunity/Past exposure = HAV-IgG (total anti-HAV).
- **HCV:**
  - *Screening:* Anti-HCV (detectable 4–8 weeks post-exposure; remains positive even if cleared).
  - *Confirmation:* HCV RNA (qualitative/quantitative; positive within 1–3 weeks; indicates active viremia).
- **HDV:** Total anti-HDV / IgM anti-HDV + HDV RNA + HBsAg.
- **HEV:** IgM anti-HEV; HEV RNA in stool.

Management

- **HAV & HEV:** Generally self-limited; supportive care.
- **HBV:**
  - *Acute:* Supportive.
  - *Chronic:* Interferon OR Nucleos(t)ide analogs (First-line: **Entecavir** or **Tenofovir**).
- **HCV:** Direct-Acting Antivirals (DAAs).
- **HDV:**
  - **Pegylated Interferon alpha** (for 48–72 weeks).
  - *Exam Trap:* Nucleos(t)ide analogs (like Entecavir/Tenofovir) are **NOT** effective for HDV.
- **Prophylaxis / Prevention:**
  - *HAV:* Post-exposure prophylaxis with HAV vaccine or Immunoglobulin (IG) within 2 weeks of exposure.
  - *HBV:* Post-exposure HBIG (highly effective within 48h) + vaccination (e.g., neonates born to HBsAg+ mothers).
  - *HCV:* No vaccine; relies on blood screening and behavior modification.

Complications / Prognosis

- **HAV:** May cause fulminant hepatitis, cholestatic hepatitis, or relapsing hepatitis. **No** chronic sequelae.
- **HBV Chronicity:** Inversely related to age at infection.

- Neonates (<1 yr): 90% become chronic.
- Older children/Adults: 2–10% become chronic.
- *Complications:* 15–25% premature mortality from chronic liver disease/cirrhosis/HCC.

- **HCV Chronicity:** Extremely high. ~70% develop chronic hepatitis; persistent infection in 85–100%. No protective antibody response is naturally generated.
- **HEV Mortality:** Case fatality is generally 1–3%, but skyrockets to **15–25% in pregnant women**. Chronic sequelae only seen in immunosuppressed patients.

Past-Paper High Yield

- **Diagnosis of Exclusion:** Acute viral hepatitis (especially HAV) often presents with generic acute transaminitis. An exam question may present an acute liver injury patient with **normal** Ceruloplasmin, Iron studies, Alpha-1-antitrypsin, and **negative** Autoimmune markers (Anti-Smooth Muscle Antibody/ANA). In the absence of metabolic or autoimmune causes, select the acute viral etiology (e.g., Hepatitis A) as the most likely diagnosis.
- **Vaccinated vs. Natural Immunity (HBV):**
  - *Vaccinated:* Anti-HBs (+), Anti-HBc (–), HBsAg (–).
  - *Natural Clearance:* Anti-HBs (+), Anti-HBc IgG (+), HBsAg (–).
- **Acute Flare in Chronic HBV:** Differentiate a primary acute HBV infection (Anti-HBc IgM +) from an HDV superinfection (Anti-HDV IgM + with HBsAg + and Anti-HBc IgG +).

Memory Pearls

- **A** and **E** = **A**cute and **E**nteric (Fecal-oral).
- **B**, **C**, **D** = **B**lood-borne, **C**hronic potential, **D**eadly (cirrhosis/HCC).
- **H**epatitis **E** is highly lethal in **E**xpectant (pregnant) mothers.
- HDV **C**oinfection = **C**lears; HDV **S**uperinfection = **S**evere (Chronic).
- HB**V** = DNA **V**irus. All others are RNA.

Hematology

Exam Map

TOPIC CLUSTER	PAST-PAPER WEIGHT	REVISION PRIORITY
Approach to Anemia	21 Questions	⭐⭐⭐⭐⭐ (Absolute Mastery Required)
Bleeding Disorders & Hemostasis	16 Questions	⭐⭐⭐⭐⭐ (Diagnostic algorithms & flowcharts)
Hemoglobinopathies & Hemolytic Anemias	9 Questions	⭐⭐⭐⭐ (Clinical triggers & complications)
Leukemias (Chronic & Acute)	7 Questions	⭐⭐⭐ (Genetic markers & specific therapies)
Transfusion, Lymphoma, Myeloma & Megaloblastic	9 Questions	⭐⭐ (Strict staging & criteria memorization)

High-Yield Exam Themes & Revision Priorities:

- **The Anemia Algorithm:** You must be able to instantly categorize anemia using MCV and Reticulocyte count. Differentiating Iron Deficiency (low ferritin, high RDW) from Thalassemia Trait (normal/high iron, normal RDW, target cells) is heavily tested.
- **The "Aplastic" Traps:** Distinguish strictly between true *Aplastic Anemia* (pancytopenia, hypocellular marrow, no splenomegaly) and a *Parvovirus B19 Aplastic Crisis* (sudden Hb drop and paradoxically low reticulocytes in a patient with a known hemolytic disease like Hereditary Spherocytosis or Sickle Cell).
- **Coagulation Mixing Studies:** A recurring exam favorite. Prolonged PTT that fully corrects with normal plasma = Factor Deficiency (e.g., Hemophilia). Failure to correct = Inhibitor (e.g., Acquired Hemophilia or Antiphospholipid Syndrome).
- **The Thrombocytopenia Grid (ITP vs. TTP vs. HIT vs. DIC):**
  - *ITP:* Isolated low platelets, treat with steroids, avoid transfusions.
  - *TTP:* Normal PT/PTT + schistocytes + severe ADAMTS13 deficiency + requires plasmapheresis.
  - *DIC:* Prolonged PT/PTT + low fibrinogen + high D-dimer.
  - *HIT:* Heparin use + platelet drop + paradoxical new thrombosis.
- **Hemolysis Triggers & Smears:** G6PD deficiency triggers (infections are highly tested, alongside fava beans and antimalarials) associated with bite cells and Heinz bodies. Autoimmune Hemolytic Anemia (Warm) is defined by spherocytes and a positive DAT/Coombs test.
- **Leukemia Distinguishers:**
  - **CML:** t(9;22) Philadelphia chromosome + basophilia.
  - **CLL:** Asymptomatic presentation = "watch and wait" (do not aggressively treat early stage).
  - **AML M3 (APL):** t(15;17) + Auer rods + treat with ATRA + extreme risk of DIC.

- **ALL:** Tumor Lysis Syndrome labs + absolute requirement for CNS prophylaxis.

- **Pharmacology & Bridging:** The physiological requirement to bridge Warfarin with Heparin is a guaranteed exam concept (rapid Protein C/S depletion causes a transient hypercoagulable state, risking skin necrosis). Also, remember NOACs are absolutely contraindicated with mechanical valves.
- **Transfusion Protocols:** Know that returning the bag to the blood bank is the universal first step for any reaction. Differentiate TRALI (multiparous donor antibodies, non-cardiogenic edema, <6 hours) from TACO (fluid overload/hypertension).
- **Multiple Myeloma Staging:** Memorize the "CRAB" features. Elevated β2-microglobulin (> 5.5 mg/dL) is the specific marker for advanced Stage III disease.
- **B12 vs. Folate:** Differentiate purely by neurological symptoms (Subacute Combined Degeneration) and elevated Methylmalonic Acid (MMA) in B12 deficiency. Remember the "folate trap" of treating B12 deficiency with folate.

Approach to Anemia

Core Concepts

- **Definition:** Anemia is defined as a reduction in hemoglobin (Hb) concentration, hematocrit (Hct), or RBC count. The cut-off is typically defined as <-2 SD from the mean or the 2.5th percentile.
- **WHO Hb Thresholds for Anemia:**
  - **Men (>15 years):** < 13 g/dL
  - **Women, non-pregnant (>15 years):** < 12 g/dL
  - **Women, pregnant:** < 11 g/dL
- **Severity Grading (Non-pregnant Women):** Mild (11–11.9 g/dL) | Moderate (8–10.9 g/dL) | Severe (< 8 g/dL).
- **Hepcidin-Ferroportin Axis (Key Iron Regulation):**
  - **Hepcidin:** A 25 kDa peptide hormone that serves as the master iron regulator.
  - **Mechanism:** Hepcidin binds to **ferroportin** (the only cellular iron exporter on enterocytes, macrophages, and hepatocytes), leading to its degradation. This *locks* iron inside the cells, lowering serum iron.
  - **Regulation:**
    - *Hypoxia/Anemia:* Decreases hepcidin → allows iron release.
    - *Inflammation (IL-6):* Increases hepcidin → traps iron (pathophysiology of Anemia of Chronic Disease).
  - **Disease States:** Hepcidin deficiency = Hemochromatosis; Hepcidin excess = Anemia of Chronic Disease.

Diagnosis / Clinical Features

- **The "Anemia Syndrome":** Driven by tissue hypoxia. Symptoms include dizziness, fatigue, exertional shortness of breath, headaches, chest pain/palpitations, and secondary heart failure.

- **Iron Deficiency Anemia (IDA) - Clinical Principles:**
  - **A Crucial Rule:** "Iron deficiency anemia is not a final diagnosis per se." Always establish and document the underlying cause (e.g., "IDA secondary to colon cancer").
  - **Causes to hunt for:**
    - *Nutritional* (poor red meat intake)
    - *Blood loss* (GI/GU malignancies, heavy menses, hemosiderinuria)
    - *Malabsorption* (Celiac disease/gluten enteropathy)
    - *Increased demand* (Repeated pregnancies)

Investigations

- **Kinetic Approach (Reticulocyte Count):**
  - **Corrected Reticulocyte %** = Patient's Retic % × (Patient's Hct / 45)
  - **Reticulocyte Production Index (RPI)** = Corrected Retic / Maturation Time. *(Maturation time: 1 for Hct 45%, 1.5 for 35%, 2 for 25%, 2.5 for 15%).*
- **Morphological Approach (MCV):**
  - **Microcytic (MCV < 78 fL, MCH < 26 pg):** IDA, Thalassemia, Lead toxicity, Sideroblastic anemia, Anemia of chronic disease.
  - **Normocytic:** Acute blood loss, hemolysis, bone marrow failure, anemia of chronic disease.
  - **Macrocytic (MCV > 98 fL):** Megaloblastic anemias, Myelodysplastic Syndrome (MDS).
- **Differentiating Microcytic Anemias:**
  - **Ferritin:** The single best marker for iron deficiency in adults.
  - **RDW (Red Cell Distribution Width):**
    - *IDA:* High RDW (severe hypochromia, anisocytosis, and poikilocytosis).
    - *Thalassemia Trait:* Normal RDW (hypochromia with target cells, but uniform cell size).

Management

- **Oral Iron:** First-line therapy (ferrous gluconate/sulfate). Educate the patient on adherence and side effects.
- **Monitoring Response:** Check CBC monthly. Expected Hb rise is approximately **1 g/dL every 10 days**. Check ferritin at 3 months.
- **IV Iron:** (e.g., iron sucrose, carboxymaltose) is indicated for patients who cannot absorb oral iron (e.g., severe malabsorption, **previous bariatric surgery**), or cannot tolerate oral preparations.

Past-Paper High Yield

Bone Marrow Failure & Aplastic Anemia

- **Aplastic Anemia Diagnosis:** A patient with fatigue, ecchymosis, pancytopenia (e.g., Hb 9, Plt 70K, WBC 2000), hypocellular bone marrow, and *no* fibrosis.
- **Aplastic Anemia Treatment: Bone Marrow Transplant (BMT)** is the definitive treatment for young patients with an HLA-matched family member (10-year survival > 80%).

- **Febrile Neutropenia with Hypoplastic Marrow:** Best initial management for a patient presenting with fever, profound pancytopenia, and hypoplastic marrow is **Packed RBCs, Platelets, and IV Antibiotics**.

Hemolysis & Blood Banking

- **Acute Hemolytic Transfusion Reaction:** The most common presentation in a young adult is **back pain, red urine, and headache**.
- **ABO Incompatibility:** It is *false* to state that ABO system antibodies frequently cross the placenta causing hemolysis. (Unlike Rh IgG antibodies, ABO antibodies are primarily IgM and do not readily cross the placenta).
- **Hemolysis Labs:** In active hemolysis (e.g., patient with anemia and 8% reticulocytes), finding a *normal* LDH is highly unexpected (LDH is typically elevated).

Thrombosis & Coagulation

- **Heparin-Induced Thrombocytopenia (HIT):** Classically presents with **skin necrosis at the site of injection** after ~10 days of heparin use. *Next step in management:* Stop heparin and start a direct thrombin inhibitor.
- **Antiphospholipid Syndrome (APS):** Characterized by a prolonged PTT that **does not correct** with a mixing study (due to an inhibitor, not a factor deficiency).
- **TTP (Thrombotic Thrombocytopenic Purpura):** Fundamentally caused by a lack of **ADAMTS13**.

Malignancy & Bone Marrow Infiltration

- **Primary Myelofibrosis:** Bone marrow findings characteristically show **fibrosis and teardrop cells**.
- **Metastatic Infiltration:** An older male with chronic lower back pain, enlarged prostate, elevated PSA, and pancytopenia with abnormal dysplastic cells in the BM has pancytopenia due to **infiltration of the bone marrow by metastatic prostate cancer**.
- **Non-Hodgkin Lymphoma (NHL):** The vast majority are of **B-cell** origin.
- **Hodgkin Lymphoma Staging:** Involvement of cervical and inguinal lymph nodes (both sides of the diaphragm) + B symptoms (sweating, weight loss, fever) = **Stage IIIB**.
- **Chronic Lymphocytic Leukemia (CLL):** Presents with progressive splenomegaly, treatment-refractory anemia, weight loss, night sweats, and a profoundly elevated lymphocyte count (e.g., 65 x 10^9/L).

Miscellaneous High-Yield Exam Differentiators

- **Bariatric Surgery:** A patient with a history of bariatric surgery presenting with severe microcytic anemia (MCV 69) and deeply low ferritin (e.g., 4) requires an **IV iron transfusion** (oral iron will not be absorbed).
- **Pernicious Anemia Trap:** Pernicious anemia causes pancytopenia/macrocytic anemia and is **not** associated with thrombocytosis.
- **Takayasu Arteritis:** A young Asian woman with syncope, severe fatigue, absent peripheral pulses, elevated ESR, and normocytic anemia. The most accurate diagnostic test is **Aortic Arteriography**.

- **Drug-Drug Interaction:** A patient on statins given antibiotics (e.g., macrolides) developing GI distress, fatigue, and foot drop (inability to plantar flex) is suffering from a **statin-antibiotic drug-drug interaction** (statin toxicity/myopathy).
- **Meningococcal Infection:** A teenager presenting with lethargy, fever, **petechiae on lower limbs**, and purulent CSF (high neutrophils, low glucose, high protein) has a meningococcal infection.
- **Neuro/Exam Trap:** A somnolent patient presenting with right-sided ptosis and a dilated right pupil likely has a **Posterior Communicating Artery (P. comm) aneurysm** compressing the oculomotor nerve.

Megaloblastic Anemia

Core Concepts

- **Pathophysiology:** Characterized by impaired DNA synthesis (arrest in S-phase) leading to delayed nuclear division. Cytoplasmic maturation (dependent on RNA/protein synthesis) remains intact, resulting in **asynchronous maturation** between the nucleus and cytoplasm and the formation of large precursor cells (megaloblasts).
- **Ineffective Erythropoiesis:** DNA replication errors trigger intramedullary apoptosis of hematopoietic precursors. This causes intramedullary hemolysis, manifesting peripherally as macrocytic anemia with a paradoxically **low reticulocyte count**.
- **Etiologies:**
  - **Vitamin B12 (Cobalamin) Deficiency:** Most commonly due to **pernicious anemia** (autoimmune destruction of gastric parietal cells/intrinsic factor). Other causes: gastrectomy, terminal ileum resection/disease (Crohn's), blind loop syndrome, *Diphyllobothrium latum* (fish tapeworm), and strictly vegan diets.
  - **Folate (Folic Acid) Deficiency:** Often due to decreased intake (alcohol use disorder, malnutrition, elderly), increased demand (pregnancy, hemolysis), or malabsorption (celiac, tropical sprue).
  - **Copper Deficiency:** Can cause macrocytic (or micro/normocytic) anemia, neutropenia, myelopathy, and peripheral neuropathy.
  - **Drugs:**
    - *Impaired DNA synthesis:* Methotrexate, Hydroxyurea, 5-Fluorouracil, Azathioprine, Trimethoprim, Zidovudine.
    - *Impaired absorption/metabolism:* Metformin, PPIs/Antacids, Oral Contraceptives, Phenytoin, Valproic acid.
  - **Rare Inherited Syndromes:**
    - *Thiamine-responsive megaloblastic anemia (TRMA):* Autosomal recessive (SLC19A2 mutation) presenting in infancy with megaloblastic anemia, diabetes mellitus, and early-onset sensorineural hearing loss.
    - *Imerslund-Grasbeck syndrome:* Biallelic mutation affecting the ileal receptor for the B12-IF complex; associated with proteinuria.

Diagnosis / Clinical Features

- **General Anemia Symptoms:** Weakness, exertional shortness of breath, palpitations, pallor, tachycardia, flow murmurs.
- **Gastrointestinal:** Hunter glossitis (beefy red, smooth tongue).
- **Hemolysis Signs:** Jaundice/icterus and splenomegaly secondary to intramedullary hemolysis.
- **Neurological Manifestations (Vitamin B12 Deficiency ONLY):**
  - Loss of vibratory sense and proprioception (positive Romberg test).
  - Paresthesias, peripheral neuropathy with lancinating pains.
  - Psychiatric disturbances (dementia-like presentation).
  - *Note:* Babinski reflex, hyporeflexia, clonus, and optic atrophy are less frequent.
  - **Crucial:** Neurological deficits may be incompletely reversible or permanent despite treatment.

Investigations

- **Complete Blood Count & Peripheral Smear:**
  - **MCV > 100 fL** (MCV > 115 fL is highly specific for B12 or Folate deficiency). *Note: A normal MCV does not entirely rule out the disease (e.g., combined with iron deficiency).*
  - **Hypersegmented neutrophils** (highly sensitive and specific).
  - **Macro-ovalocytes** and **teardrop cells**.
  - **Low reticulocyte count** (distinguishes it from hemolytic anemias/bleeding which also cause elevated MCV but have reticulocytosis).
- **Diagnostic Biomarkers:**
  - *Vitamin B12 Level:* < 200 pg/mL is deficient. (Spuriously low in multiple myeloma, HIV, pregnancy, OCPs; falsely elevated in myeloproliferative neoplasms, alcoholic liver disease, renal disease).
  - *Folate Level:* < 2 ng/mL is deficient. (Assay may be falsely negative/normal in patients with Intrinsic Factor autoantibodies).
- **Metabolite Testing (The Definitive Differentiator):**

DEFICIENCY	HOMOCYSTEINE LEVEL	METHYLMALONIC ACID (MMA) LEVEL
Folate (B9)	Elevated	Normal
Cobalamin (B12)	Elevated	**Elevated**

- **Bone Marrow Aspiration (if diagnosis is unclear):** Hypercellular marrow, giant metamyelocytes, megaloblasts. Required primarily to rule out myelodysplastic syndrome (MDS) if vitamins are normal.

Management

- **Rule Out B12 Deficiency First:** B12 and folate levels **must** be checked simultaneously. Replacing folate in a B12-deficient patient will correct the anemia but allow irreversible neurological damage

to rapidly progress.

- **Vitamin B12 Supplementation:**
  - *Indications for Parenteral (IM):* Neurologic symptoms, increased demand (pregnancy/infancy), or severe malabsorption.
  - *Dosing:* 1000 mcg IM weekly until corrected, then monthly.
  - *Oral Alternative:* 1000 mcg PO daily is equally effective if there is no intestinal malabsorption. Sublingual formulations are also available.
  - *Duration:* Indefinite/life-long for non-reversible causes (e.g., pernicious anemia, gastric bypass).
- **Folate Supplementation:**
  - *Dosing:* 1 mg PO daily. Continued indefinitely if the underlying cause is irreversible.
- **Treatment Response Timeline:**
  - Intramedullary hemolysis markers (LDH, bilirubin) improve within **1 week**.
  - Hemoglobin/Hematocrit normalize within **1 to 2 months**.
  - Neurological/psychiatric symptoms take **3 to 12 months** to recover (may transiently worsen, or be permanently irreversible).
  - *Transfusion:* Reserved only for severe, highly symptomatic anemia.

Complications / Prognosis

- **Gastric Malignancy:** Patients with pernicious anemia have a **7-fold relative risk** of gastric cancer (incidence ~0.27% per patient-year) due to chronic atrophic gastritis. Counsel patients to self-monitor and report GI symptoms immediately.
- **Fetal Complications:** Folate deficiency during pregnancy is strongly associated with **neural tube defects** (preventable with 600 mcg/day prenatal supplementation).
- **Neurological Morbidity:** Untreated or mismanaged B12 deficiency leads to permanent subacute combined degeneration of the spinal cord.

Past-Paper High Yield

- **The "Folate Trap":** Giving folate to a B12-deficient patient will improve the hematologic picture but exacerbate/unmask severe neurological deficits. Always check B12 before prescribing folate.
- **Storage Timelines:** Body stores of B12 (liver) last **2 to 4 years** (a strict vegan takes years to develop anemia). Body stores of Folate last only **3 to 4 months** (an alcoholic or malnourished patient develops anemia rapidly).
- **Metabolite differentiation:** The test of choice to confirm borderline B12 vs. Folate deficiency is **Methylmalonic Acid (MMA)**. Elevated MMA = B12 deficiency.
- **Reticulocyte Count:** Megaloblastic anemia features intramedullary hemolysis and ineffective erythropoiesis, hence the reticulocyte count is **low**, contrasting with peripheral hemolytic anemias.

Memory Pearls

- **B12 vs. Folate: B**12 has **B**oth (Hematologic + Neurologic symptoms); Folate just has hematologic.
- **B12 Absorption Pathway:**

1. Salivary R-binder (mouth)
2. Intrinsic Factor (stomach parietal cells)
3. Cleavage of R-binder (pancreatic enzymes in duodenum)
4. Absorption (Terminal Ileum).
   Any pathology along this tract (gastrectomy, pancreatitis, Crohn's in ileum) causes B12 deficiency.

Acquired Hemolytic Anemia

Core Concepts

- **Hemolysis Definition:** Shortened RBC survival leading to RBC destruction, with or without anemia (anemia occurs when destruction exceeds bone marrow compensation).
- **Classification by Site of Destruction:**
  - **Extravascular:** RBCs ingested by reticuloendothelial (RE) cells in the spleen and liver.
  - **Intravascular:** RBC destruction within the blood vessels.
- **Evidence of Increased RBC Production (Compensation):**
  - **Peripheral Blood:** Elevated reticulocytes (corrected/RPI), presence of circulating nucleated RBCs (NRBCs).
  - **Bone Marrow:** Erythroid hyperplasia, reduced myeloid/erythroid (M/E) ratio.
  - **Bone (Chronic):** Frontal bossing (deforming changes in skull/long bones due to marrow expansion).
- **Bone Marrow Failure (Aplastic Anemia - AA):** Life-threatening failure of erythrocyte, WBC, and platelet production. Characterized by peripheral pancytopenia and a hypocellular (empty) bone marrow. Primary defect is depletion/damage of hematopoietic precursor stem cells.

Diagnosis / Clinical Features

- **General Hemolytic Anemia Features:**
  - Anemia syndrome (fatigue, pallor, dyspnea).
  - Jaundice & Splenomegaly (typical of extravascular hemolysis).
  - Dark urine (tea-colored or red) and chronic ankle ulcers.
  - Increased requirement for folic acid.
- **Autoimmune Hemolytic Anemia (Warm, IgG-mediated):**
  - 45% Primary (Idiopathic).
  - 40% Secondary (Lymphoproliferative disease like NHL, Connective tissue disease, Infections).
  - 15% Drug-induced.
- **Intravascular Hemolysis:** Can present due to mechanical damage (MAHA), chemical damage (burns), severe infection (Malaria, Babesiosis), or ABO transfusion reactions.
- **Aplastic Anemia Presentation:**
  - Typically young adults or children (can affect any age).

- Bleeding (thrombocytopenia) and Anemia (fatigue) are the most common presenting combination.
- Infection (neutropenia).
- **Key Distinguisher:** *No splenomegaly* (unlike hemolytic states or myeloproliferative disorders).

Investigations

- **Autoimmune Hemolytic Anemia (AIHA):**
  - **Peripheral Smear:** Normocytic/macrocytic anemia with **densely hemoglobinated spherocytes** and polychromasia (reticulocytes).
  - **Hemolysis Labs:** Elevated LDH, elevated unconjugated (indirect) bilirubin, elevated reticulocyte count.
  - **Coombs Testing:**
    - **Direct Antiglobulin Test (DAT/Direct Coombs):** Positive (detects IgG or C3d bound *directly* to the patient's RBCs).
    - **Indirect Antiglobulin Test:** Detects circulating anti-RBC antibodies in the patient's serum.
  - **Bone Marrow:** Erythroid hyperplasia with megaloblastoid changes (due to relative folate depletion from high turnover).
- **Microangiopathic Hemolytic Anemia (MAHA):**
  - **Peripheral Smear:** Schistocytes (fragmented RBCs).
  - **Differential Diagnosis:** TTP, HUS, DIC, Vasculitis, Malignant HTN, HELLP/Preeclampsia, Metastatic neoplasm with vascular invasion.
- **Aplastic Anemia:**
  - **Peripheral Blood:** Pancytopenia with reticulocytopenia (retics near 0%).
  - **Bone Marrow Aspirate/Biopsy:** Hypocellular/aplastic marrow.
  - **Myelophthisic anemia (DDx):** Peripheral pancytopenia but marrow is normocellular, hypercellular, or infiltrated (fibrotic, granulomatous, or neoplastic cells).

Management

- **Warm Autoimmune Hemolytic Anemia (IgG):**
  - **1st Line:** Corticosteroids (Prednisone 1 mg/kg/day for 2 weeks, then taper) + Folic acid supplementation.
  - **Treat underlying cause:** (e.g., manage the lymphoproliferative disorder if secondary).
  - **2nd Line / Refractory:** Splenectomy, Immunosuppressive agents, IVIG.
- **Aplastic Anemia:**
  - Remove causative agent (drugs, toxins) and provide supportive care (RBC transfusions, treat infections/bleeding).
  - **Young patients (<40) + HLA-identical sibling:** Bone Marrow Transplant (BMT) is the best first-line therapy.

- **Older adults or no sibling donor:** Immunosuppressive therapy (IST) with Anti-thymocyte globulin (ATG) + Cyclosporine A (CSA).

Complications / Prognosis

- **Aplastic Crisis:** Triggered by **Parvovirus B19** infection. The virus lyses RBC precursors causing a 7-10 day cessation of erythropoiesis. Normal patients tolerate this, but hemolytic patients (who rely on high reticulocyte production to compensate for shortened RBC lifespan) will acutely drop their hemoglobin and reticulocytes.
- **Gallstones:** Chronic hemolysis leads to high bilirubin excretion, causing pigment (biliary) stones.
- **Secondary Malignancy:** AIHA can precede or be the initial presentation of lymphoproliferative disorders like Non-Hodgkin Lymphoma (NHL).

Past-Paper High Yield

- **Classic Presentation of Warm AIHA:** A case featuring anemia, **high LDH**, high indirect bilirubin, and **spherocytes** on the peripheral blood smear should immediately point to Autoimmune Hemolytic Anemia.
- **Diagnostic Peripheral Cell:** The characteristic cell seen in the peripheral blood in patients with warm antibody AIHA is the **densely hemoglobinated spherocyte**.

Memory Pearls

- **Spherocytes + Positive DAT (Coombs)** = Autoimmune Hemolytic Anemia.
- **Schistocytes + Negative DAT** = Microangiopathic Hemolytic Anemia (think TTP, DIC, HUS).
- **High Retics + Splenomegaly** = Hemolysis (Marrow is working).
- **Zero Retics + Pancytopenia + NO Splenomegaly** = Aplastic Anemia (Marrow is empty).
- **Hemolysis + Sudden drop in Retics** = Parvovirus B19 Aplastic Crisis.

Congenital Hemolytic Anemia and Hemoglobinopathies

Core Concepts

- **Classification of Congenital Hemolytic Anemias:**
  - **Membrane Defects:** Hereditary Spherocytosis (HS).
  - **Enzymopathies:** G6PD Deficiency, Pyruvate Kinase (PK) Deficiency.
  - **Hemoglobinopathies:** Beta-Thalassemia, Sickle Cell Disease (SCD).
- **Aplastic Crisis:** A universal risk in chronic hemolytic anemias (especially tested in HS and SCD). It is triggered by **Parvovirus B19** infection, which halts red blood cell production, leading to a sudden, severe drop in hemoglobin accompanied by a paradoxically **low reticulocyte count**.

Diagnosis / Clinical Features

- **G6PD Deficiency:**

    - **Genetics:** X-linked recessive (Xq28 mutation). *G6PD Med* (Mediterranean/Kurdish) is a severe variant (563 C->T mutation).
    - **Pathophysiology:** Defect in the Pentose Phosphate Pathway impairs NADPH production, leaving RBCs vulnerable to oxidative stress.
    - **Clinical Syndromes:** Ranges from asymptomatic to severe acute intravascular hemolysis (red urine, loin pain, jaundice).
    - **Neonatal Jaundice:** Occurs 1-3 days after birth; high risk for kernicterus.
    - **Hemolytic Triggers:**
        - **Infections:** A very common trigger (neutrophil/macrophage oxygen burst generates H_2O_2).
        - **Favism:** Exposure to fava (broad) beans; divicine produces free oxygen radicals.
        - **Drugs:** Antimalarials (Primaquine), Sulpha drugs, Dapsone, Nitrofurantoin, Methylene Blue, Nalidixic Acid, Pyridium.
        - **Other:** Diabetic Ketoacidosis (DKA), Henna (in infants).
- **Hereditary Spherocytosis (HS):**
    - **Genetics:** Mostly autosomal dominant.
    - **Molecular Defect:** Most commonly **ankyrin mutations**. Also spectrin, band 3, or protein 4.2 (Japanese) deficiency.
    - **Clinical:** "Anemia syndrome", splenomegaly, jaundice, pigment gallstones.
- **Sickle Cell Disease (SCD):**
    - **Genetics:** Autosomal recessive; point mutation in beta-globin gene (**β6 Glu → Val**).
    - **Vaso-Occlusive Manifestations:** Acute chest syndrome (ACS), hepatic/splenic crisis, priapism, stroke, avascular necrosis of the bone (e.g., hip).
    - **Infectious Complications:** Functional asplenia (auto-splenectomy) increases susceptibility to encapsulated organisms (*Pneumococcus, H. influenzae*). Tissue infarction predisposes to *Staphylococcus* osteomyelitis.
- **Sickle Cell Trait:**
    - Protective against malaria.
    - Genitourinary complications: Hyposthenuria (inability to concentrate urine), papillary sloughing, painless hematuria, and UTIs during pregnancy.
    - Other risks: Splenic infarction at high altitudes (hypoxia), rhabdomyolysis, sudden death.
- **Beta-Thalassemia:**
    - **Clinical Effects:** Severe anemia leading to extramedullary hematopoiesis (causes "tumor effect", skeletal changes, stunted growth), massive splenomegaly, and osteoporosis. Dilated cardiomyopathy can occur secondary to severe anemia.

Investigations

- **G6PD Deficiency:** Blood film shows **Bite cells** and **Heinz bodies**. High LDH, high indirect bilirubin, hemoglobinuria (intravascular hemolysis).
- **Hereditary Spherocytosis:** High reticulocytes, **Negative DAT** (Direct Antiglobulin Test, differentiates from autoimmune hemolysis), abnormal **Osmotic Fragility Test**.

- **Sickle Cell Disease:** Smear shows sickle cells and Howell-Jolly bodies (due to auto-splenectomy).
- **Beta-Thalassemia Major:** Severe microcytic hypochromic anemia (e.g., Hb 6, MCV 55), highly elevated serum ferritin (iron overload).

Management

- **G6PD Deficiency:**
  - Avoid precipitating factors (drugs, fava beans).
  - Supportive care during crisis: Folate, maintain good urine output, blood transfusion if severe. Exchange transfusion for severe neonatal jaundice.
- **Sickle Cell Disease:**
  - **Painful Crisis:** Correct fluid/electrolytes (use **hypotonic fluid** and avoid overhydration), treat underlying illness, use opioid analgesics (**avoid meperidine**), and use incentive spirometry. Transfusion is *not* indicated for uncomplicated pain.
  - **Disease Modification: Hydroxyurea** (increases HbF, reduces pain crises, ACS, and transfusion needs). Prophylactic penicillin in childhood prevents encapsulated infections.
  - **Transfusion Indications:** Stroke (decreases recurrence by 90%), Acute Chest Syndrome, Aplastic Crisis, Pre-operative optimization, symptomatic anemia, and splenic/hepatic sequestration.
- **Beta-Thalassemia Major:**
  - Chronic blood transfusions.
  - **Iron Chelation Therapy:** Required to prevent end-organ iron overload (skin, heart, liver, endocrine).
    - **Oral Deferasirox:** First-line, once-daily tridentate chelator, highly specific for iron, excreted mainly in feces.
    - *Deferoxamine:* Parenteral alternative.
  - **Curative Therapy:** Allogeneic Bone Marrow Transplantation (Allo-BMT).

Complications / Prognosis

- **Acute Chest Syndrome (SCD):** Indistinguishable from pneumonia (pleuritic chest pain, fever, cough, hypoxia, worsening anemia, new infiltrate). Multifactorial etiology (rib infarct causing splinting, fat embolism, atypical/viral infections). Treated with incentive spirometry, bronchodilators, O_2, and RBC transfusions.
- **Iron Overload (Beta-Thalassemia):** Constant transfusions lead to fatal iron deposition in the heart (cardiomyopathy), liver, and endocrine organs without chelation therapy.

Past-Paper High Yield

- **Parvovirus B19 & HS:** A patient with known hereditary spherocytosis presenting with a sudden drop in Hemoglobin AND a **low reticulocyte count** is experiencing an aplastic crisis caused by Parvovirus B19. (Tested multiple times as the key differentiator from a standard hemolytic crisis, which would have *high* reticulocytes).

- **G6PD Triggers: Infections** are a very common and highly tested trigger of hemolysis in G6PD deficiency, alongside classic triggers like antimalarials and fava beans.
- **Heinz Bodies = G6PD:** If a patient is given anti-malarial prophylaxis and develops anemia with Heinz bodies on the smear, the diagnosis is G6PD deficiency (not Hereditary Spherocytosis).
- **Thalassemia Cure:** The definitive, curative treatment for transfusion-dependent Beta-Thalassemia is **Bone Marrow Transplantation (BMT)**.
- **Thalassemia Chelation: Oral deferasirox** is a primary, first-line treatment for iron chelation.
- **SCD Complications:** Stroke, Priapism, and Acute Chest Syndrome are classic complications of SCD. **AML (Acute Myeloid Leukemia) is NOT** associated with sickle cell disease.

Memory Pearls

- **Bite & Heinz:** Think **G6PD**. (The spleen *bites* out the *Heinz* bodies).
- **Low Retics + Hemolytic Anemia = Parvovirus B19.**
- **Hyposthenuria & Hematuria:** Think **Sickle Cell Trait** (sickling in the renal medulla due to hypoxia/hypertonicity).
- **Glu → Val at position 6:** The exact mutation for **Sickle Cell**.
- **No Meperidine in SCD:** Metabolite normeperidine causes seizures. Use other opioids.

Bleeding Disorders 1

Core Concepts

- **Primary vs. Secondary Hemostasis:**
  - **Primary Hemostasis (Platelets/Vessel Wall):** Characterized by mucocutaneous bleeding (epistaxis, GI/vaginal bleeding, gums), petechiae, superficial small ecchymoses. Bleeding after cuts/scratches is immediate and usually mild.
  - **Secondary Hemostasis (Coagulation Factors):** Characterized by deep soft tissue bleeding (joints, muscles/hemarthrosis), large/deep ecchymoses. Bleeding after cuts/scratches is rare. Bleeding after surgery/trauma is delayed (1–2 days) and often severe.
- **Coagulation Screening:**
  - **Prothrombin Time (PT):** Assesses the Extrinsic and Common pathways.
  - **Activated Partial Thromboplastin Time (aPTT):** Assesses the Intrinsic and Common pathways.
  - **Thrombin Time (TT):** Assesses the conversion of fibrinogen to fibrin.
  - **Bleeding Time (BT):** Assesses platelet function (platelet count must be normal for this to be valid).
- **Mixing Studies:** Differentiates factor deficiency from the presence of an inhibitor (e.g., autoantibodies).
  - **Correction** of prolonged aPTT/PT when patient plasma is mixed 1:1 with normal plasma = **Factor Deficiency**.
  - **Failure to correct** = **Inhibitor** (e.g., acquired hemophilia, lupus anticoagulant).

Diagnosis / Clinical Features

- **Hemophilia A and B:**
  - Inherited X-linked recessive bleeding disorders. Factor VIII deficiency (Hemophilia A; 1/10,000) and Factor IX deficiency (Hemophilia B; 1/50,000).
  - Severity depends on factor levels:
    - **Severe (<1%):** Spontaneous bleeding, hemarthrosis.
    - **Moderate (1–5%):** Bleeding with mild injury.
    - **Mild (>5–25%):** Bleeding with surgery or major trauma.
  - **Genetics:** The F8 gene is on Xq28. An **intron 22 inversion** is the most common mutation causing *severe* Hemophilia A (responsible for ~45% of cases).
- **Von Willebrand Disease (VWD):**
  - Most common inherited bleeding disorder (Autosomal Dominant).
  - vWF anchors platelets to the subendothelium and acts as a carrier protein for Factor VIII (prolonging its half-life).
  - Features primary hemostasis bleeding (mucocutaneous, prolonged bleeding from minor cuts).
- **Disseminated Intravascular Coagulation (DIC):**
  - Systemic activation of coagulation leading to intravascular fibrin deposition, causing both microvascular thrombosis (organ failure) and depletion of platelets/factors (severe bleeding).
  - **Triggers:** Sepsis (most common), major trauma (head injury, fat embolism), obstetric emergencies (amniotic fluid embolism, abruption), malignancies, severe allergic reactions, or snake venom.
- **Immune Thrombocytopenia (ITP):**
  - Autoimmune destruction of platelets. Presents with isolated thrombocytopenia, easy bruising, and petechiae in an otherwise healthy patient.
  - **Key Negative Findings:** No hepatosplenomegaly, no systemic symptoms, normal coagulation profile.
- **Hemolytic Uremic Syndrome (HUS):**
  - Characterized by the triad of Microangiopathic Hemolytic Anemia (MAHA), Thrombocytopenia, and Acute Kidney Injury (hematuria). Frequently preceded by bloody diarrhea (e.g., post-party/gathering infection).

Investigations

- **VWD Laboratory Findings:**
  - **Type 1 (Partial quantitative):** ↓ vWF antigen, ↓ vWF activity, Normal multimers.
  - **Type 2 (Qualitative):** ↓ vWF activity (out of proportion to antigen), Abnormal multimers.
  - **Type 3 (Total quantitative):** ↓↓ vWF antigen (absent), ↓↓ vWF activity, Absent multimers.
  - *Note:* aPTT may be normal or slightly prolonged (due to secondary FVIII clearance).
- **DIC Laboratory Findings:**
  - ↑ PT, ↑ aPTT, ↑ TT (consumption of coagulation factors).

- ↓ Fibrinogen, ↓ Platelets.
- ↑ Fibrin Degradation Products (FDPs) and ↑ D-Dimer (due to plasmin cleaving fibrin).
- Peripheral smear: Schistocytes (fragmented RBCs due to intravascular fibrin strands).

- **ITP vs. Aplastic Anemia (Bone Marrow differentiation):**
  - **ITP:** Peripheral smear shows large platelets. Bone marrow shows **normal or HIGH megakaryocytes** (compensatory production).
  - **Aplastic Anemia:** Presents with pancytopenia (e.g., Hb 7, Plt 10k, WBC 1000). Bone marrow is **severely hypocellular**.
- **Myeloproliferative Neoplasms (MPNs):**
  - Patients with massively elevated cell lines require differentiation.
  - A pan-myelosis (↑ Hb, ↑ WBC, ↑ Platelets >800k) with increased neutrophils and basophils points to **Polycythemia Vera (Rubra Vera)**, not just Essential Thrombocytosis.

Management

- **Hemophilia:**
  - **Acute Bleeding:** Replace missing factor (FVIII or FIX). Mild/Moderate bleeding target is 30% (25-40 U/kg). Major bleeding target is 80-100% (50 U/kg).
  - **Prophylaxis:** Scheduled factor replacement (e.g., 20 U/kg twice weekly) to prevent target joints.
  - **Mild Hemophilia A Adjuncts: DDAVP** (releases stored vWF and FVIII from endothelium) and Tranexamic Acid (stabilizes fibrin clot).
  - **Inhibitor Management:** Recombinant FVIIa, By-passing agents, high-dose FVIII (if low titer), or Immune Tolerance Induction (ITT).
  - **Novel Therapies: Emicizumab** (a bispecific antibody that bridges FIXa and FX, mimicking FVIII function).
- **Von Willebrand Disease:**
  - **Type 1:** DDAVP (Deamino-8-arginine vasopressin) 0.3 µg/kg IV.
  - **Type 2 and 3:** Factor VIII concentrate containing vWF (e.g., Humate-P). Cryoprecipitate can also be used as it contains vWF, FVIII, and fibrinogen.
- **DIC:**
  - *First step:* Treat the underlying cause vigorously (e.g., IV antibiotics for sepsis).
  - *Supportive:* FFP (replaces factors), Platelet transfusion, Coagulation inhibitor concentrates (ATIII).
- **ITP:**
  - **First-line: Steroids** (e.g., Prednisolone).
  - **Contraindicated:** Platelet transfusions are generally *not used* because the transfused platelets will just be rapidly destroyed by circulating autoantibodies.
- **Aplastic Anemia (Severe):**

- Immediate priority in young, severe cases is to look for an **HLA-matched sibling for Bone Marrow Transplant (BMT)**.

Complications / Prognosis

- **Hemophilia Inhibitors:** 10-15% of severe Hemophilia A patients develop alloantibodies (inhibitors) against exogenous FVIII, rendering standard replacement therapy ineffective.
- **Transfusion-transmitted infections:** Historically, plasma-derived factors caused Hepatitis B, Hepatitis C, and HIV infections. Modern recombinant products eliminate this risk.

Past-Paper High Yield

- **Mixing Study Trap:** A patient (e.g., 25 y/o male) presenting with acute hemarthrosis and a massively prolonged aPTT (e.g., 112 sec) that *does NOT improve* with a mixing study has **Acquired Hemophilia with Inhibitor Development**, not an inherited factor deficiency.
- **ITP Presentation & Management:**
  - *Classic stem:* Young female, easy bruising, petechiae, isolated severe thrombocytopenia (e.g., 12k), large platelets on smear, *no splenomegaly*.
  - *Exam focus:* **Steroids** are the best first-line treatment. Platelet transfusion is explicitly *not used*.
  - *Pathology core:* Bone marrow will have **normal or HIGH megakaryocytes**. Primary ITP has *no association* with systemic disorders.
- **Aplastic Anemia differentiation:** A young patient with acute bleeding (menorrhagia), fever, NO splenomegaly, and pancytopenia. The definitive diagnostic finding is a **severely hypocellular bone marrow**, and the primary curative step is **HLA-matched BMT**.
- **HUS Diagnosis:** A patient with a recent history of bloody diarrhea (e.g., "went to a party 3 days ago") presenting with acute renal failure (hematuria) and thrombocytopenia. The best next step to confirm the diagnosis is to **look for schistocytes in the blood film**.
- **Polycythemia Vera:** A patient with elevated Hb (>14.5), extremely high platelets (>800,000), leukocytosis, and basophilia is diagnosed with **Polycythemia Rubra Vera**, distinguishing it from Essential Thrombocytosis (which features isolated platelet elevation).

Memory Pearls

- **DIC vs. Liver Disease:** Both have high PT/aPTT and low platelets, but **DIC has low fibrinogen and high D-dimers**, whereas factor VIII is *normal or high* in liver disease (it is made in endothelial cells, not just the liver) but consumed in DIC.
- **DDAVP works on the Endothelium:** Releases stored vWF (and therefore FVIII). Useful in mild Hemophilia A and Type 1 VWD, but useless in severe cases where stores are absent.
- **Type 3 VWD mimics Hemophilia A:** Because vWF is entirely absent, FVIII has no carrier and gets degraded rapidly, leading to prolonged aPTT and deep tissue bleeding.

Bleeding Disorders 2

Core Concepts

- **Platelet Physiology:** Lifespan is 7–10 days. The adult body produces 10^11 platelets/day (3000 platelets per megakaryocyte). 20–30% are pooled in the spleen.
- **Classification of Platelet Disorders:**
  - **Quantitative:** Abnormal distribution (splenomegaly), dilution effect, decreased production, increased destruction (immune vs. non-immune).
  - **Qualitative:** Inherited (rare, e.g., Glanzmann Thrombasthenia) vs. Acquired (medications, chronic renal failure, cardiopulmonary bypass).
- **Platelet Destruction Syndromes:**
  - *Immune:* ITP, Drug-induced, HIT.
  - *Non-immune / Consumptive:* DIC, TTP, Sepsis.
- **Clinical Bleeding Pattern:** Cutaneous/mucosal (petechiae, ecchymoses, epistaxis, menorrhagia, GI, intracranial) is characteristic of platelet-type bleeding. Bleeding manifestations generally correlate with the platelet count (e.g., life-threatening if <10k, minor trauma bleeds if 10k–30k).

Diagnosis / Clinical Features

- **Glanzmann Thrombasthenia (GT):** Inherited qualitative platelet disorder. Presents with life-long mucosal bleeding, prolonged bleeding from cuts, purpura, and menorrhagia. Parents are often consanguineous (e.g., 1st-degree relatives).
- **Immune Thrombocytopenia (ITP):** Autoimmune destruction of platelets mediated by autoantibodies against major platelet membrane glycoproteins. Megakaryocytes in the bone marrow are increased, but production remains decreased. Presents with isolated sudden-onset purpura, petechiae, and mucosal bleeding in an otherwise healthy patient without splenomegaly or lymphadenopathy.
- **Heparin-Induced Thrombocytopenia (HIT):** Typically occurs 4–14 days after heparin exposure (or rapidly if previously exposed). Suspect if platelet count drops >50% or falls <100k. Characterized by paradoxical **thrombosis** (arterial or venous limb gangrene) and skin necrosis at the injection site.
- **Thrombotic Thrombocytopenic Purpura (TTP):** Caused by severely deficient ADAMTS13 (VWF-cleaving protease), leading to ultra-large VWF multimers that cause microvascular thrombosis.
  - **Classic Pentad:**
    1. Microangiopathic hemolytic anemia (MAHA)
    2. Thrombocytopenia
    3. Neurologic dysfunction (confusion, seizures, leukoencephalopathy on MRI)
    4. Renal disease
    5. Fever.
- **Acquired Hemophilia:** Sudden onset of severe, unprovoked bleeding (e.g., joint effusion, soft tissue bleeding) in a patient with no prior bleeding history. Due to the development of

autoantibodies (inhibitors) against clotting factors (most commonly Factor VIII).

Investigations

- **Glanzmann Thrombasthenia:**
  - *Platelet count and morphology:* Normal.
  - *PT/PTT/TT:* Normal.
  - *Hallmarks:* Prolonged bleeding time (>15 mins), **absent or impaired clot retraction**, absent/reduced platelet fibrinogen.
  - *Flow cytometry:* Absent or reduced GPIIb-IIIa receptors. No aggregation with physiological aggregating agents.
- **Immune Thrombocytopenia (ITP):** Isolated severe thrombocytopenia. PT, PTT, TT are normal. Rule out secondary immune causes (DAT, ANA, anti-DNA).
- **Thrombotic Thrombocytopenic Purpura (TTP):**
  - *Hallmark:* High LDH, indirect hyperbilirubinemia, reticulocytosis, and schistocytes on blood smear.
  - *Coagulation:* **PT, PTT, and TT are normal** (differentiates TTP from DIC).
  - *Specific testing:* Severely deficient ADAMTS13.
- **Evaluating Prolonged PTT (Mixing Study):**
  - If a patient has a prolonged PTT, mix their plasma 1:1 with normal plasma.
  - *Full correction:* Indicates a factor deficiency (e.g., Hemophilia).
  - *Partial / No correction:* Indicates the presence of an inhibitor (e.g., Acquired hemophilia with inhibitor, or Antiphospholipid antibody/Lupus anticoagulant).

Management

- **Glanzmann Thrombasthenia:** Supportive care.
- **Immune Thrombocytopenia (ITP):**
  - *Observation:* If PLT >50k and no bleeding.
  - *Initial Therapy:* If PLT <30k or bleeding -> Oral Prednisolone (1 mg/kg/day for ~4 weeks, then taper).
  - *Curative/2nd line:* Splenectomy, Rituximab.
  - *Rescue Therapy:* IVIG, High-dose glucocorticoids.
  - *Chronic Therapy:* Thrombopoietin (TPO) receptor agonists (see comparison below).
- **Thrombotic Thrombocytopenic Purpura (TTP):**
  - *Primary:* **Daily plasma exchange (plasmapheresis)** until recovery (reduces mortality from >90% to <20%). Monitor LDH and PLT count.
  - *Relapsed/Refractory:* Rituximab, Vincristine, Splenectomy.
  - *Note:* Glucocorticoids and aspirin have an unproven adjunctive role.
- **Heparin-Induced Thrombocytopenia (HIT):**
  - **Two Do's:** STOP heparin immediately, START an alternative anticoagulant.

    - **Two Don'ts:** NO warfarin until substantial platelet recovery (prevents venous limb gangrene); NO platelet transfusions (worsens thrombosis).
    - **Two Diagnostics:** Send HIT functional testing, order bilateral lower limb duplex ultrasounds.
- **Platelet Transfusion Complications:**
    - *Transfusion Reactions:* Higher incidence than RBCs; related to storage length, leukocytes, and especially bacterial contamination.
    - *Refractoriness:* Alloimmune destruction (HLA antigens) or Non-immune (MAHA, DIC, fever, sepsis, splenomegaly, medications like Amphotericin, Vancomycin).

TPO RECEPTOR AGONIST	ROMIPLOSTIM	ELTROMBOPAG
Mechanism	Binds TPOR active site	Binds TPOR transmembrane domain
Route	Subcutaneous (SQ)	Oral (PO)
Hepatic Toxicity	No	**Yes**
Immunogenicity	Yes	No
Response overall	~80% (works in splenectomized pts)	~80% (works in splenectomized pts)

Complications / Prognosis

- **HIT Complications:** High risk of new thrombosis (up to 50%), amputation (~10%) due to arterial thrombosis or venous limb gangrene, and death (10–20%).
- **TTP Prognosis:** Untreated mortality >90%; treated with plasma exchange mortality <20%. Monitor ADAMTS13 post-recovery for relapse.
- **ITP in Pregnancy:** Requires careful monitoring during pregnancy and post-delivery care of the newborn due to maternal IgG crossing the placenta.

Past-Paper High Yield

- **Prolonged PTT + Venous Thrombosis:** A patient with bilateral lower limb swelling (DVT), PE, and prolonged PTT most likely has Antiphospholipid Syndrome (Lupus Anticoagulant).
- **Hemophilia A vs B Diagnosis:** The definitive test to distinguish Hemophilia A from B is a **Factor Assay**.
- **Hemophilia A Genetics:** The most common cause of severe Hemophilia A in Jordan is the **Intron 22 inversion**.
- **Mixing Studies & Acquired Hemophilia:** A middle-aged/elderly patient with new-onset severe bleeding (e.g., joint effusion, large joints) and prolonged PTT that only *partially corrects* on a mixing study is diagnostic of **Acquired hemophilia with an inhibitor**.
- **Cirrhotic Variceal Bleed Prophylaxis:** (General clinical crossover) A patient presenting with an upper GI bleed and stigmata of cirrhosis (telangiectasias, ascites) should receive prophylactic antibiotics; the preferred agent is **Ceftriaxone**.

Memory Pearls

- **HIT Management Rules:** 2 Do's (Stop Heparin, Start Non-Heparin AC), 2 Don'ts (No Warfarin yet, No Platelets), 2 Diagnostics (HIT assay, Venous Dopplers).
- **TTP vs DIC:** TTP has normal coagulation times (PT/PTT), while DIC has prolonged PT/PTT and elevated D-dimers. Both have thrombocytopenia and schistocytes.
- **ITP Treatment Thresholds:** PLT >50k = None; PLT <30k or bleeding = Glucocorticoids.

Acute Leukemia

Core Concepts

- **Pathogenesis of AML:** A disease strongly associated with aging. Hematopoietic stem cells acquire mutations over their lifetime → clonal hematopoiesis → subclonal evolution → MPD / MDS / AML.
- **Mechanisms of Clinical Manifestations:**
  - *Bone Marrow Replacement:* Anemia, thrombocytopenia, neutropenia.
  - *Extramedullary Infiltration:* Lymph nodes, gums (gingival hyperplasia), skin (leukemia cutis), and CNS.
  - *Release of Granules/Metabolites:* DIC, Tumor Lysis Syndrome (hyperuricemia/gout, acute renal failure).
  - *Hyperviscosity:* Due to extreme leukocytosis (e.g., WBC > 50,000–100,000).

Diagnosis / Clinical Features

- **AML Presentations:**
  - Bleeding diathesis (easy bruising, hemorrhagic spots) and systemic infections (fever).
  - *Promyelocytic (M3):* High risk of DIC (elevated PT/PTT, active bleeding).
  - *Myelomonocytic (M4):* Associated with painful gums (gingival hyperplasia), leukemia cutis, and potential CNS disease.
- **ALL Presentations:**
  - More common in younger patients (e.g., teens/young adults).
  - Fatigue, joint pain, bone pain, high fever, severe tonsillar/throat infections.
  - Prominent generalized lymphadenopathy and hepatosplenomegaly.
  - Frequent baseline presentation with Tumor Lysis Syndrome (TLS).

Investigations

- **Laboratory Findings:**
  - Pancytopenia or extreme leukocytosis with circulating blasts.
  - *Tumor Lysis Labs (classic in ALL):* ↑ LDH, ↑ Uric Acid, ↑ Potassium, ↑ Phosphate, ↓ Calcium.
  - *Coagulation:* Prolonged PT/PTT (evaluate for DIC, especially in AML M3).
- **Morphology & Staining:**

- *AML:* Prominent **Auer rods** (especially in M3).
- *ALL:* **PAS strongly positive (+++)**.

- **ALL FAB Morphologic Subtypes:**
  - **L1 (75%):** Small round blasts, clumped chromatin.
  - **L2 (20%):** Pleomorphic, larger blasts, clefted nuclei, fine chromatin.
  - **L3 (5%):** Large blasts, prominent nucleoli, vacuolated cytoplasm.
- **ALL Immunophenotyping:**
  - *B-Lineage (80%):* CD19(+), Tdt(+).
    - Pro-B: CD10(–), CyIg(–)
    - Common: CD10(+), CyIg(–)
    - Pre-B: CD10(+), CyIg(+), SmIg(–)
    - Mature-B: SmIg(+)
  - *T-Lineage (20%):* CD7(+), Tdt(+).
    - Pre-T: CD2(–)
    - Mature-T: CD2(+)

Management

- **AML M3 (APL):**
  - Treated with **ATRA (all-trans retinoic acid)** to induce differentiation of leukemic cells.
  - Responsive to cytarabine/daunorubicin, but chemotherapy causes rapid tumor lysis; ~10% die from DIC induced by granule release from dying cells.
- **ALL Treatment Phasing:** Choice depends on risk, immunophenotype, age, and biological condition.
  - **Induction (1 month):** Goal is rapid restoration of normal marrow. Regimen includes Anthracycline, Vincristine, Cyclophosphamide, L-asparaginase, MTX, Ara-C, Steroids.
  - **Consolidation (4-8 months):** Goal is to prevent resistant clones and eliminate residual disease. Options: Chemotherapy or Allogeneic Stem Cell Transplant.
  - **Maintenance (2-3 years):** 6-MP, Methotrexate, Vincristine, Steroids.
  - **CNS Prophylaxis (Crucial):** Intrathecal Methotrexate, Ara-C, Steroids, or Craniospinal irradiation.
- **Allogeneic BMT Indications in ALL:** High-risk disease, unacceptable minimal residual disease, good performance status, and donor availability. Curative intent.

Complications / Prognosis

- **ATRA Syndrome (Retinoic Acid Syndrome):**
  - *Timing/Cause:* Occurs within the first 3 weeks of ATRA therapy. Caused by adhesion of newly differentiated neoplastic cells to the pulmonary vasculature endothelium.
  - *Features:* Fever, dyspnea, chest pain, pulmonary infiltrates, pleural/pericardial effusions, and hypoxia. Does *not* cause DIC.

- *Treatment:* Glucocorticoids, chemotherapy, supportive care. Mortality is ~10%.

- **Prognostic Categories in ALL (Cytogenetics):**
  - *Better:* Normal karyotype, Hyperdiploidy.
  - *Poor:* t(8;14), t(4;11).
  - *Very Poor:* t(9;22) → BCR/ABL(+).
- **High/Very High-Risk Features in ALL:**
  - Pre-T or Pro-B immunophenotypes.
  - Age > 35 years.
  - WBC > 30k (B-ALL) or > 100k (T-ALL).
  - No remission after 4 weeks of induction therapy.
  - Philadelphia chromosome positive / BCR-ABL(+).
- **Prognostic Categories in AML:**
  - *Good Prognosis:* t(15;17) [M3], inv(16) [M4].

Past-Paper High Yield

- **Polycythemia Vera to AML Transformation Trap:** Exam questions often test the natural history of myeloproliferative disorders. It is **false** to state that 50% of Polycythemia Vera cases transform into AML. (The actual transformation rate is much lower, typically <10%).
- **CNS Staging and Prophylaxis (ALL vs. Lymphoma):** Unlike typical Hodgkin Lymphoma (where brain CT is not routine for staging unless symptomatic), **ALL has a high propensity for CNS involvement**. CNS prophylaxis (intrathecal chemo/radiation) is a mandatory component of ALL management.
- **Tumor Lysis Syndrome Labs:** Be prepared to identify TLS in ALL case vignettes: markedly elevated LDH and Uric Acid, hyperkalemia, hyperphosphatemia, and *hypocalcemia*.
- **M4 AML Distinguishers:** Look for an inverted 16 chromosome, eosinophilia, painful/swollen gums, and leukemia cutis (skin infiltration).

Memory Pearls

- **M3 / APL Triad:** t(15;17) + prominent Auer rods + high DIC risk. Treatment = ATRA.
- **ATRA Syndrome vs. DIC:** ATRA causes *pulmonary infiltrates/effusions* (ATRA syndrome) but does *not* cause DIC. Traditional chemotherapy in M3 *does* cause DIC due to granule release.
- **B-cell ALL progression (Surface markers):** Starts with CD19+/CD10- (Pro-B) → gains CD10+ (Common) → gains Cytoplasmic Ig (Pre-B) → gains Surface Ig (Mature-B).

Chronic Leukemia

Core Concepts

- **Chronic Lymphocytic Leukemia (CLL):** Accumulation of morphologically mature but immunologically immature B-lymphocytes in peripheral blood, bone marrow, and lymphatic tissues.

- **Chronic Myeloid Leukemia (CML):** Clonal expansion of a hematopoietic stem cell driven by a reciprocal translocation between chromosomes 9 and 22, resulting in the BCR-ABL fusion gene. Accounts for 20% of adult leukemias; primarily affects middle-aged individuals.

Diagnosis / Clinical Features

Chronic Lymphocytic Leukemia (CLL)

- **Presentation:** Often asymptomatic. May present with recurrent infections (due to hypogammaglobulinemia), fever, pallor.
- **Physical Exam:** Lymphadenopathy (cervical, axillary) and Splenomegaly.
- **Key Distinction:** Recurrent infections and bulky lymphadenopathy are prominent.

Chronic Myeloid Leukemia (CML)

- **Presentation:** Insidious onset (often accidental discovery). Hypermetabolic symptoms (fatigue, malaise, sweating, weight loss).
- **Physical Exam:** Minimal to massive splenomegaly (causes LUQ pain, early satiety, mass effect). Mild hepatomegaly.
- **Key Distinction:** Lymphadenopathy is **rare** in CML unless in terminal stages.

Investigations

Chronic Lymphocytic Leukemia (CLL)

- **CBC:** Lymphocytosis. May show anemia and thrombocytopenia.
- **Immunophenotyping (Flow Cytometry):** CD5(+), CD19(++), CD20(++), surface Ig(+).
- **Hemolysis markers:** Direct Antiglobulin Test (DAT) may be strongly positive, indicating secondary Autoimmune Hemolytic Anemia (AIHA), with elevated reticulocytes and LDH.
- **Cytogenetics:** +12 (Trisomy 12) is a noted abnormality.

Chronic Myeloid Leukemia (CML)

- **CBC & Smear:** Elevated WBC count (<5% blasts in chronic phase). Elevated platelets. Normochromic normocytic anemia. **Basophilia** is a hallmark finding.
- **Uric Acid:** Often elevated (hyperuricemia/gout risk) due to high cell turnover.
- **Diagnostic Confirmation (Gold Standard):**
  - **Cytogenetics/Karyotyping:** Identifies t(9;22)(q34;q11.2) — the Philadelphia chromosome.
  - **FISH (Fluorescence In Situ Hybridization):** Locates the BCR-ABL translocation (Locus Specific Identifier).

Management

Chronic Lymphocytic Leukemia (CLL)

- **Indications for Treatment:** Symptoms, decline in Hb or platelets, massive/progressive lymphadenopathy or hepatosplenomegaly, recurrent infections.
- **Asymptomatic/Early Stage:** Watchful waiting.

- **Pharmacologic Options:**
  - *Alkylating Agents:* Chlorambucil, Cyclophosphamide.
  - *Purine Nucleosides:* Fludarabine, Pentostatin, Cladribine.
  - *Chemoimmunotherapy.*

Chronic Myeloid Leukemia (CML)

- **Primary Therapy: Imatinib mesylate** (Tyrosine Kinase Inhibitor).
  - *Mechanism:* Competitive inhibition at the ATP binding site of the Abl kinase.
  - *Side Effects:* Fluid retention, nausea, muscle cramps, diarrhea, skin rashes. Myelosuppression is the most common hematologic side effect.
- **Resistance to Imatinib:** Caused by kinase site mutations, gene amplification, alternative signaling pathways, or multi-drug efflux proteins (manage with 2nd generation TKIs).
- **Definitive Therapy:** Allogeneic Stem Cell Transplant (SCT). Recommended for selected patients or in blast crisis.

Complications / Prognosis

CLL Prognostic Markers

- **Clinical Staging:** Rai (Stage 0-IV) and Binet (Stage A-C). Median survival ranges from >10 years (Early) to 1-3 years (Advanced).
- **IgHV Mutation Status:**
  - *Mutated (Post-germinal center):* Slow progression, better prognosis.
  - *Unmutated (Pre-germinal center):* Rapid progression, worse prognosis.
- **Surrogate Markers:** ZAP 70 and CD38 presence indicates poorer prognosis.

CML Disease Phases

1. **Chronic Phase:** <5% blasts. 95% of patients achieve complete hematologic remission with Imatinib in this phase.
2. **Accelerated Phase:** Blasts 10–20% in blood/marrow, Basophils ≥20%, Platelets <100k, cytogenetic clonal evolution.
3. **Blastic Phase (Crisis):** Acute leukemia presentation. Blasts ≥20% in blood/marrow. Hyposegmented neutrophils (Pelger-Huet anomaly) may appear. Blasts can be myeloid, lymphoid, or erythroid.

Past-Paper High Yield

- **CLL vs. CML differentiating feature:** The **t(9;22)** translocation is exclusively a hallmark of CML and is **never** expected in a patient with CLL.
- **CML Genetic Abnormality:** Always identify **t(9;22)** (Philadelphia chromosome) for CML.
- **Next step for suspected CML:** Order **FISH looking for BCR-ABL translocation**.
- **Best diagnostic indicator for CML:** The presence of **t(9;22) alongside basophilia** confirms the diagnosis (better and more specific than relying solely on a bone marrow biopsy).

- **CLL Prognosis & Management:** A patient diagnosed with CLL in the early/chronic phase will generally **live for a long time without treatment** (watchful waiting is the correct approach for asymptomatic early-stage disease).

Memory Pearls

- **CML Triad:** Middle-aged + Massive Spleen + Basophilia = think CML. Confirm with FISH for t(9;22).
- **CLL Flow:** B-cell disease that aberrantly expresses T-cell marker **CD5**.
- **CLL = Watch and Wait:** Do not treat CLL just for an elevated WBC; wait for cytopenias, bulky lymphadenopathy, or B-symptoms.

Chronic Myeloproliferative Disorders and VTE

Core Concepts

Venous Thromboembolism (VTE)

- **Multifactorial Disease:** Caused by combined inherited and acquired risk factors (Virchow's Triad: Stasis, Hypercoagulability, Endothelial Damage).
- **Burden of Disease:** Preventable, highly common in hospitalized patients (most have ≥1 risk factor), and carries significant mortality and morbidity.
- **Important Genetic Factors (Thrombophilias):** Protein C deficiency, Protein S deficiency, Antithrombin III (ATIII) deficiency, Factor V Leiden mutation, Prothrombin (Factor II) mutation.

Myeloproliferative Neoplasms (MPNs)

- **Definition:** Clonal bone marrow stem cell disorders causing hyperproliferation of one or more myeloid lineages *without* dysplasia.
- **Key Pathogenesis:** Gain-of-function **JAK2-V617F mutation**. Present in:
  - **~95%** of Polycythemia Vera (PV)
  - **43–57%** of Primary Myelofibrosis (MF)
  - **23–57%** of Essential Thrombocythemia (ET)
- **Common MPN Features:** Splenomegaly, hypercatabolism (weight loss, acute gouty arthritis), unusual thromboses (e.g., Budd-Chiari syndrome), and generalized pruritus (classically aquagenic/after bathing).

Diagnosis / Clinical Features

- **VTE Presentation:**
  - *DVT:* Painful, swollen, hot limb.
  - *PE:* Repeated attacks of cough, hemoptysis, shortness of breath.
- **Polycythemia Vera (PV):** Often presents with plethoric "hot" face, severe aquagenic pruritus, gout (due to high cell turnover/hyperuricemia), and unusual thrombosis. Labs show polycythemia (high Hb/RBC mass) alongside normal O2 saturation, leukocytosis, thrombocytosis, and notably **low serum erythropoietin (EPO)**.

Investigations

WHO Diagnostic Criteria for Polycythemia Vera (PV) *Requires BOTH Major criteria OR 1 Major + 2 Minor criteria:*

- **Major Criteria:**
  1. Elevated RBC mass >25% above mean normal OR Hemoglobin >18.5 g/dL (male) / >16.5 g/dL (female).
  2. Presence of JAK2 V617F mutation.
- **Minor Criteria:**
  1. Bone marrow showing trilineage myeloproliferation (panmyelosis).
  2. Low serum erythropoietin (EPO) levels.
  3. Endogenous erythroid colony formation in vitro.

WHO Diagnostic Criteria for Essential Thrombocythemia (ET) *Requires ALL FOUR criteria:*

1. Platelet count ≥ 450,000/µL.
2. JAK2 V617F positive OR no evidence of reactive thrombocytosis.
3. Does not meet WHO criteria for other MPNs (e.g., PV, CML, MF).
4. Bone marrow shows marked megakaryocytic hyperplasia (large, mature morphology) with little to no granulocytic or erythroid proliferation.

Management

VTE Treatment Modalities

- **Initial:** Thrombolytic therapy, Heparin (UFH or LMWH), Oral Anticoagulant Therapy (Warfarin/NOACs). Overlap required if starting Warfarin.
- **Other Modalities:** Venous thrombectomy, IVC filters, Pulmonary embolectomy (for severe/refractory cases).

Anticoagulant Pharmacology Overview

DRUG CLASS	MECHANISM & KINETICS	DOSING & MONITORING	KEY COMPLICATIONS / NOTES
Unfractionated Heparin (UFH)	Thrombin inhibition (needs >18 monosaccharide units) & Xa inhibition.	80 U/kg load → >18 U/kg/hr. Goal PTT 1.5–2.5.	Risk of HIT. Requires continuous IV and PTT monitoring.
LMWH (Enoxaparin, Tinzaparin)	Factor Xa inhibition (>5 monosaccharide units).	Enox: 1 mg/kg BID. Tinz: 175 U/kg daily.	Subcutaneous. Preferred in malignancy and pregnancy.
Warfarin	Inhibits Vit K synthesis of II, VII, IX, X, Protein C & S. Peak 72–96h; t½ 36–42h.	Start 5 mg once. Target INR 2–3.	**Contraindicated in pregnancy.** Bleeding, skin necrosis.
NOACs - Xa Blockers	Direct Factor Xa inhibitors (Apixaban, Rivaroxaban).	Fixed dosing. No routine monitoring.	GI bleed (Rivaroxaban), dyspepsia, liver enzyme ↑.
NOACs - IIa Blocker	Direct Thrombin (Factor II) inhibitor (Dabigatran).	Fixed dosing. No routine monitoring.	Dyspepsia, gastritis.

NOAC Contraindications: Prosthetic heart valves, severe renal impairment (requires dose reduction in moderate impairment), significant active bleeding/haemostasis disorders, liver disease, pregnant/breastfeeding women, children <18 years.

MPN Management

- **Ruxolitinib:** Selective JAK1 & JAK2 inhibitor.
  - *Indication:* Second-line treatment for MPNs (after hydroxyurea).
  - *Efficacy:* Improves systemic symptoms (pruritus, constitutional symptoms) and reduces transfusion requirements/splenomegaly.
  - *Limitation:* No demonstrated survival benefit as yet.

Complications / Prognosis

- **VTE Complications:**
  - Post-thrombotic syndrome (venous stasis/ulceration) occurs in ~40% of DVT patients.
  - Pulmonary hypertension develops in ~5% of PE patients.
  - Death occurs in 3% (DVT) to 30% (PE) of cases.
- **Warfarin-Induced Skin Necrosis / Microvascular Thrombosis:** Occurs due to the rapid depletion of Protein C (an endogenous anticoagulant with a short half-life) before procoagulant factors (II, IX, X) deplete. Risk is highest in patients with heterozygous Protein C or S deficiency, high initial Warfarin doses, or inadequate heparin overlap.
- **MPN Progression:** MPNs carry a significant predisposition to evolve into acute leukemias or fibrosis.
  - *PRV:* ~70% progress to Myelofibrosis (MF); ~10% transform to Acute Myeloid Leukemia (AML).
  - *ET:* ~10% transform to AML.
  - *CML:* ~30% transform to AML.

Past-Paper High Yield

- **Warfarin + Heparin Overlap:** Always tested. Warfarin causes a transient prothrombotic state due to the rapid clearance of Protein C and S (short half-lives compared to Factor II and X). You *must* bridge with Heparin until INR is therapeutic.
- **Diagnostic Trap (PV vs. Secondary Polycythemia):** Suspect PV in a patient with high Hemoglobin/RBC mass, splenomegaly, gout, and aquagenic pruritus. The differentiator is **low EPO levels** and **JAK2+ status** (Secondary causes like COPD or high altitude will have *high* EPO).
- **NOACs vs. Warfarin:** NOACs are absolutely contraindicated in patients with mechanical/prosthetic heart valves, moderate/severe liver disease, and pregnancy. Use Warfarin for mechanical valves; use LMWH in pregnancy.
- **MPN Classic Triad of Complications:** Expect questions linking MPNs to 1) Gout (hyperuricemia from cell turnover), 2) Budd-Chiari syndrome (hepatic vein thrombosis), and 3) Progression to Myelofibrosis or AML.

Memory Pearls

- **Virchow's Triad for VTE: SHE** (Stasis, Hypercoagulability, Endothelial damage).
- **Warfarin targets:** "DiXon" factors (IX, X, VII, II).
- **NOAC targets:** "Xa" is in the name for Factor Xa inhibitors (Api**xa**ban, Rivaro**xa**ban). Dabiga**tr**an targets **ThR**ombin (IIa).
- **MPN Mutations: JAK2** = "Just A Kinase 2". Present in almost all **PV** (95%), half of **E**T and **M**F. (Mnemonic: **PV** is the **P**rincipal **V**ictim of JAK2).

Lymphoma and Myeloma

Core Concepts

- **Lymphoma (NHL & Hodgkin's):** Malignancies arising from lymphocytes. 85% of Non-Hodgkin Lymphomas (NHL) are of B-cell origin; the rest are T-cell or null cell. Each type reflects a lymphocyte arrested at a specific developmental stage.
- **Multiple Myeloma (MM):** A plasma cell dyscrasia characterized by bone marrow infiltration, secretion of abnormal monoclonal proteins, and end-organ damage.
- **Key Etiological Associations (NHL):**
  - *Viral:* EBV (Burkitt's), HTLV-I (T-cell leukemia-lymphoma), Hepatitis C.
  - *Chronic Inflammation: Helicobacter pylori* (Gastric MALT lymphoma), *Chlamydia psittaci* (Ocular adnexal lymphoma), Sjögren's syndrome.
  - *Immunosuppression:* AIDS, Organ transplant (cyclosporine), Congenital (Wiskott-Aldrich).
  - *DNA Repair Defects:* Ataxia telangiectasia, Xeroderma pigmentosum.

Diagnosis / Clinical Features

Lymphomas (General):

- **Lymphadenopathy:** Painless enlargement (extent dictates the stage).
- **B-Symptoms:** Fever, night sweats, significant weight loss.
- **Other features:** Extra-nodal involvement, local compression symptoms.

Multiple Myeloma: Clinical presentation is driven by bone marrow infiltration and abnormal protein secretion.

- **Bone pain:** Especially in the back; osteolytic lesions and pathological fractures (driven by *osteoclast* activation, not osteoblasts).
- **Renal impairment:** Due to light chain toxicity to renal tubules (occurs in ~50% of patients).
- **Infections:** Recurrent bacterial infections (>2 episodes) due to hypogammaglobulinemia of normal functioning antibodies.
- **Hyperviscosity syndrome:** Especially common in rare IgM-secreting myeloma.
- **Amyloidosis:** Deposition of light chains.

Investigations

Lymphomas:

- **Excisional LN Biopsy:** Absolute requirement for definitive diagnosis and subtyping (FNA is insufficient).
- **Ann Arbor Staging:**
  - Stage I: 1 lymph node region.
  - Stage II: >1 lymph node region, *same* side of diaphragm.
  - Stage III: Lymph node regions on *both* sides of diaphragm.
  - Stage IV: Diffuse extra-nodal sites.

Multiple Myeloma:

- **Diagnosis of Active MM requires BOTH:**
  1. Clonal bone marrow plasma cells ≥10% *OR* biopsy-proven bony/extramedullary plasmacytoma.
  2. ≥1 **CRAB** feature (Calcium ↑, Renal failure, Anemia, Bone lesions).
- **Smouldering MM:** Serum monoclonal protein ≥3 g/dL OR urinary monoclonal protein ≥500 mg/24h AND/OR bone marrow plasma cells 10%–60%. *Crucially, there is an absence of CRAB criteria (no end-organ damage).*
- **Imaging: Plain X-rays (Skeletal Survey)**, MRI, or PET scan. *Trap:* Lytic lesions do not show up well on standard radionuclide bone scans because there is no osteoblastic activity.
- **Labs:** Serum protein electrophoresis (SPEP) and immunofixation, Quantitative immunoglobulins, Serum β2-microglobulin.

Management

Lymphoma:

- **Indolent NHL (e.g., Follicular, CLL/SLL, MALT):** Observation only until symptomatic (constitutional symptoms, anatomical obstruction, painful LNs, cytopenias). Treatments include Oral/IV chemo (chlorambucil, CHOP), Rituximab (anti-CD20).
- **Aggressive NHL (e.g., DLBCL):** Disseminates via bloodstream early. **Must use systemic chemotherapy** (CHOP-R x 8 cycles, or CHOP-R x 3 + radiotherapy). *Note: Highly responsive to chemo and potentially curable.*
- **Very Aggressive (e.g., Burkitt's):** Multidrug pediatric leukemia regimens + BMT.
- **Hodgkin's Lymphoma:** ~85% curable. Regimens include ABVD, MOPP, BEACOPP.

Multiple Myeloma:

- Standard chemotherapy combos: Dexamethasone + Thalidomide OR Bortezomib/Lenalidomide; Melphalan + Prednisone.
- High-Dose Chemotherapy with Autologous Bone Marrow Transplant.

Complications / Prognosis

Multiple Myeloma - International Staging System (ISS):

- **Stage I:** Serum albumin > 3.5 g/dL AND serum β2-microglobulin < 3.5 mg/dL.
- **Stage II:** Fits neither I nor III.
- **Stage III:** Serum **β2-microglobulin > 5.5 mg/dL** (Indicates poor prognosis).
- *Adverse Prognostic Genetics:* Deletion 13, t(4;14).

Lymphoma Adverse Prognostic Factors:

- Age > 60 years.
- Stage III or IV (advanced disease).
- High serum Lactate Dehydrogenase (LDH).
- Performance status (ECOG ≥ 2).
- > 1 extranodal site involved.

Past-Paper High Yield

- **Myeloma Staging Marker:** A patient with multiple myeloma is categorized as **Stage 3** if their **β2-microglobulin is > 5.5 mg/dL**.
- **Advanced Myeloma Labs:** An elevated **β2-microglobulin** is a hallmark laboratory finding specifically indicating advanced, extensive multiple myeloma. *(Note: Past papers may contain a typo referring to "B2 macroglobulin"; recognize this as β2-microglobulin)*.
- **Curability of Lymphomas: Diffuse Large B-Cell Lymphoma (DLBCL)** is the classic example of an aggressive, yet **highly curable** non-Hodgkin lymphoma. Contrast this with Follicular lymphoma, which is indolent (patients live a long time) but generally *incurable* with standard therapy.
- **Myeloma Clinical Traps:** For questions asking "Which of the following is NOT seen in multiple myeloma," you must rely on standard inclusion criteria. **Expect to see:** CRAB features (Hypercalcemia, Renal failure, Anemia, Bone *lytic* lesions), elevated total protein/globulin gap, elevated ESR, hyperviscosity, amyloidosis, and recurrent infections. Look for an option that clearly violates these (e.g., *osteoblastic* lesions, normal ESR, or a feature of a completely different disease like prominent painless lymphadenopathy, which points to lymphoma instead).

Memory Pearls

- **Myeloma End-Organ Damage (Buy CAVIAR):**
  - **Buy** = Lytic bone lesions (visible on plain x-ray)
  - **C** = hyper**C**alcemia
  - **A** = **A**nemia
  - **V** = Hyper**V**iscosity
  - **I** = Bacterial **I**nfections
  - **A** = **A**myloidosis
  - **R** = **R**enal failure (light chain cast nephropathy)
- **Lymphoma Translocations (Must Know for Exams):**
  - **t(14;18):** Follicular Lymphoma (*bcl-2* oncogene)
  - **t(8;14):** Burkitt's Lymphoma (*c-myc* oncogene)

- **t(11;14):** Mantle Cell Lymphoma (*cyclin D1* gene)

Blood Transfusion

Core Concepts

- **Blood Component Shelf Life & Storage:**
  - **Packed Red Blood Cells (pRBCs):** Shelf life 35–42 days at 1–6°C.
  - **Platelets:** Shelf life 5 days at 20–24°C (room temperature). *Because they are kept at room temperature, platelets have the highest risk of bacterial contamination (1 in 250 transfusions).*
  - **Fresh Frozen Plasma (FFP):** Shelf life 1 year at -18°C. Must be ABO compatible. Dose: 10–15 mL/kg. Indicated for multiple coagulation factor deficiencies (liver disease, trauma, DIC) and rapid warfarin reversal.
- **Special Red Blood Cell Preparations:**

MODIFICATION	INDICATION	MECHANISM / BENEFIT
Leukodepleted (Leukopoor)	Previous non-hemolytic febrile reactions	Prevents febrile reactions, CMV transmission, and reduces alloimmunization/vCJD risk.
Irradiated	Immunocompromised / immunodeficient patients	Inactivates donor lymphocytes, preventing Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD).
Washed	IgA deficiency, Paroxysmal Nocturnal Hemoglobinuria (PNH)	Removes plasma proteins, preventing severe anaphylaxis.
CMV-negative	CMV-negative recipients (e.g., transplant, neonates)	Prevents initial CMV infection (Note: ~50% of donors are naturally seropositive).

Diagnosis / Clinical Features

- **Categories of Acute Transfusion Reactions (< 24 hours):**
  - *Immunologic:* Hemolytic (ABO incompatibility), Febrile non-hemolytic, Allergic, Anaphylactic, TRALI.
  - *Non-immunologic:* Transfusion-Associated Circulatory Overload (TACO), Bacterial contamination, Air embolus, Metabolic reactions.
- **Categories of Delayed Transfusion Reactions (> 24 hours):**
  - *Immunologic:* Alloimmunization (HLA, RBC), Delayed hemolytic, GVHD, Post-transfusion purpura.
  - *Non-immunologic:* Iron overload, Viral transmission (HCV, HBV, HIV).
- **Transfusion-Related Acute Lung Injury (TRALI):**
  - **Onset:** Typically occurs within 1–4 hours (and strictly within the first 6 hours) of starting the transfusion.
  - **Pathophysiology:**

        - *Immune (Classical) Theory:* Donor anti-leukocyte/HLA antibodies (often from multiparous female donors who were alloimmunized during pregnancy) react with recipient neutrophils.
        - Neutrophils sequester in the pulmonary vasculature → release cytokines/complement → endothelial damage and capillary leak.
    - **Clinical Presentation:** Rapid onset of non-cardiogenic pulmonary edema, acute respiratory distress (ARDS), fever with chills, non-productive cough, cyanosis, and hypotension.
    - **Prevention:** Avoid using multiparous women as plasma/blood donors.

Investigations

- **Acute Transfusion Reaction Workup:**
    - Send the remaining blood unit and post-transfusion patient blood/urine samples back to the blood bank for Coombs testing, hemolysis check, and potential bacterial culture.
- **TRALI Imaging:**
    - **Chest X-ray:** Bilateral pulmonary infiltrates classically in the hilar region.
    - *Key Differentiator:* Physiologic/radiographic features will show *no* clinical evidence of left atrial hypertension (PAWP < 18 mm Hg), differentiating TRALI from TACO.

Management

- **Universal Protocol for ALL Acute Transfusion Reactions:**
    1. **STOP THE TRANSFUSION IMMEDIATELY.**
    2. Maintain IV access with 0.9% Normal Saline (NaCl).
    3. Check blood component label and patient ID for mismatch.
    4. Monitor patient vitals, blood pressure, and urine output closely.
    5. Notify the Blood Bank.
    6. **Do NOT discard the transfused unit**; keep it and send it to the blood bank along with fresh patient blood/urine samples for investigation.
    7. Provide necessary supportive care.
- **TRALI Management:**
    - No specific targeted treatment; care is largely supportive.
    - Provide respiratory support with supplemental O2. Most cases require mechanical ventilation.
    - Steroids may be used in some cases.
- **Iron Overload Management (Frequent Transfusions):**
    - Oral **deferasirox** is the first-line treatment for iron chelation in patients undergoing frequent transfusions (e.g., thalassemia). Note: Organ damage from iron overload *can* often be halted or partially reversed with effective chelation.

Complications / Prognosis

- **Metabolic Complications of Massive Transfusion:**

- **Hypocalcemia:** Due to systemic chelation of calcium by the *citrate* anticoagulant used in stored blood bags.
- **Hyperkalemia:** Due to progressive RBC lysis and leakage of intracellular potassium during storage. (*Hypo*kalemia is not a complication of transfusion).

- **Platelet Transfusion Refractoriness:**
  - Failure to achieve the expected platelet bump.
  - *Immune causes:* HLA alloimmunization (most common).
  - *Non-immune causes:* Splenic sequestration, DIC / microangiopathic hemolytic anemia, active bleeding, severe infection/fever, or medications (Amphotericin, Vancomycin, ATG, Interferons).

Past-Paper High Yield

- **Suspected Reaction Protocol Trap:** In a suspected transfusion reaction, it is fundamentally **WRONG** to discard the transfused units. You must stop the transfusion, secure the IV with saline, check vitals, and *return the bag to the blood bank*.
- **TRALI Timing:** Classic exam presentation specifies that TRALI occurs strictly within the **first 6 hours** following a transfusion.
- **Metabolic Derangements:** Blood transfusions do **NOT** cause *hypokalemia*. Stored blood actually causes *hyperkalemia* (RBC lysis) and *hypocalcemia* (citrate toxicity).
- **Iron Chelation:** With advancements in care for patients requiring frequent transfusions, **oral deferasirox** is now the first-line treatment for iron overload. It is a misconception that established organ damage can never be improved.

Memory Pearls

- **"Washed prevents Washout" (Anaphylaxis):** Use washed RBCs for IgA deficiency to prevent severe anaphylactic shock.
- **"Irradiation kills the Invaders":** Irradiated RBCs destroy donor T-cells, preventing Graft-Versus-Host Disease (GVHD).
- **"Leuko-poor stops the fever":** Leukodepletion removes donor WBCs, heavily reducing febrile non-hemolytic reactions.
- **TRALI vs. TACO:**
  - **TRALI:** Multiparous donor antibodies → *Hypo*tension, *Normal* left atrial pressure (non-cardiogenic).
  - **TACO:** Fluid overload → *Hyper*tension, *Elevated* left atrial pressure, BNP elevation.

Megaloblastic Anemia and Pernicious Anemia

Core Concepts

- **Macrocytic Anemias:** Defined by an elevated MCV (>100 fL). Major causes include:
  - **Megaloblastic:** Vitamin B12 (cobalamin) deficiency, Folate deficiency, Drugs (methotrexate, azathioprine, 6-mercaptopurine).

    - **Non-megaloblastic:** Liver disease (alcohol, cirrhosis), increased erythropoiesis (hemolysis, hemorrhage response), hypothyroidism.
    - **Bone Marrow Disorders:** Myelodysplastic Syndrome (MDS), hypoplastic anemia.
- **Pernicious Anemia (PA):** An autoimmune disorder and the end-stage of Atrophic Body Gastritis (ABG).
    - Pathophysiology: Autoimmune destruction of the oxyntic gastric mucosa leads to **achlorhydria** and **lack of Intrinsic Factor (IF)**, preventing B12 absorption in the terminal ileum.
    - Associations: Highly associated with other autoimmune diseases (Autoimmune thyroid disease, Type 1 Diabetes, Vitiligo).
- **Myelodysplastic Syndrome (MDS):** A heterogeneous group of clonal malignant hematopoietic stem cell disorders characterized by ineffective, dysplastic hematopoiesis.
    - Results in variable cytopenias and carries a high risk of transformation to Acute Myeloid Leukemia (AML).

Diagnosis / Clinical Features

Vitamin B12 Deficiency

- **Neurological symptoms (Hallmark):** Subacute Combined Degeneration of the Spinal Cord (degeneration of the **posterior and lateral columns**).
    - Presents with loss of vibration and proprioception in lower limbs, imbalanced gait, paresthesia in hands/feet.
    - Psychiatric features: "Odd" behavior, irritability, psychosis.
- **Physical Exam:** Beefy red tongue (glossitis), vitiligo (if autoimmune PA).

Folate Deficiency

- **Presentation:** "Anemia syndrome" (fatigue, pallor, weight loss) **without** neurological symptoms.
- **Causes:**
    - *Inadequate intake:* Lack of fresh/uncooked food, chronic alcoholism, TPN.
    - *Malabsorption:* Celiac disease, sprue, alcoholism.
    - *Increased requirement:* Pregnancy/lactation, chronic hemolysis, malignancy.
    - *Defective utilization:* Folate antagonists (methotrexate, trimethoprim), purine/pyrimidine analogs.

Myelodysplastic Syndrome (MDS)

- **Epidemiology:** Typical patient is elderly (60–90 years old) with a slight male preponderance.
- **Clinical:** >80% present with anemia (chronic low Hb leading to cardiac remodeling/heart failure). 50–70% have granulocytopenia (frequent infections), 30% have thrombocytopenia.

Investigations

- **Peripheral Blood Smear:**

    - **B12/Folate Deficiency:** Shows **Macro-ovalocytes** and **Hypersegmented neutrophils** (>5 lobes).
    - *Note on Nucleated RBCs/Blasts:* Nucleated RBCs can occasionally be seen in the periphery in severe anemia. **Blasts** are *not* seen in simple B12/folate deficiency; their presence strongly suggests MDS or leukemia.
- **Bone Marrow:**
    - *B12/Folate:* Hypercellular with **Megaloblasts** (these reside in the marrow, *not* the peripheral blood).
    - *MDS:* Dysmorphic cells, ringed sideroblasts (e.g., ≥15% in RARS), and varying percentages of blasts (<20%; if ≥20%, it is AML).
- **Laboratory Tests (Megaloblastic Anemia):**
    - Elevated LDH (often dramatically high, e.g., >1000) due to ineffective erythropoiesis (intramedullary hemolysis).
    - Low corrected reticulocyte count.
    - **PA specific:** Anti-Intrinsic Factor (IF) antibodies and Anti-Parietal Cell (PCA) antibodies.
- **MDS Diagnostics:**
    - Diagnosis requires bone marrow aspirate (with iron stain for sideroblasts) + biopsy + cytogenetics.
    - Common cytogenetic anomalies: del(5q), -7/del(7q), +8.
    - Prognosis scoring (WPSS) incorporates WHO category, karyotype, and transfusion requirement.

Management

Vitamin B12 Deficiency (Pernicious Anemia)

- **Avoid Blood Transfusions:** Generally not required, even with very low Hb.
- **Replacement:** Vitamin B12 IM injections daily for 7–10 days, followed by monthly lifelong injections.
- **Monitoring Timeline:**
    - **2 days:** LDH falls; bone marrow megaloblastic changes disappear.
    - **3–4 days:** Reticulocytosis begins (peaks at 5–10 days).
    - **10–14 days:** Rise in Hb begins; hypersegmented PMNs disappear.
    - **8–10 weeks:** Hb and MCV normalize.
- **Treatment Risk:** Watch closely for **severe hypokalemia** during the early response (due to massive cellular uptake of potassium during new RBC synthesis).

Folate Deficiency

- Treat the underlying cause.
- Administer oral folic acid (5 mg twice daily for 3 months, then maintenance if necessary).
- *Pregnancy:* Adequate folate is critical for neural tube closure in the fetus.

Myelodysplastic Syndrome (MDS)

- **Low-Risk:** Best supportive care (transfusions, iron chelation), hematopoietic growth factors (EPO/G-CSF), Lenalidomide (specifically for isolated del(5q)), Azacitidine (hypomethylating agent).
- **High-Risk:** Intensive chemotherapy or Allogeneic Stem Cell Transplantation (SCT) – the only curative option.

Past-Paper High Yield

- **Peripheral Smear vs. Bone Marrow Trap:** Be hyper-vigilant when asked about *peripheral blood* findings in B12 deficiency. The peripheral blood features **macro-ovalocytes** and **hypersegmented neutrophils**. **Megaloblasts** are found exclusively in the *bone marrow*. If an exam question asks to identify peripheral cells and includes distractors like "macrospheres" (not a real hematologic term) or "blasts" (indicative of leukemia/MDS), recognize that severe dyserythropoiesis in B12 deficiency can occasionally push **nucleated RBCs** into the periphery, but *blasts* are incorrect for nutritional megaloblastic anemia.
- **Neurological Manifestations:** B12 deficiency causes subacute combined degeneration (loss of vibration/proprioception). Folate deficiency does *not*. This is the classic differentiator in clinical vignettes.
- **Hypokalemia Warning:** You must monitor potassium levels closely in the first few days of B12 replacement therapy, as rapid reticulocytosis can cause fatal hypokalemia.
- **MDS Chromosome:** Isolated del(5q) is a specific WHO subtype of MDS that presents with anemia, normal/increased platelets, and has a targeted treatment (Lenalidomide).

Memory Pearls

- **B**12 deficiency = **B**ad nerves (subacute combined degeneration).
- **B**12 peripheral smear = **B**ig oval cells (macro-ovalocytes) and **B**ig PMNs (hypersegmented).
- **Subacute Combined Degeneration: P**osterior (Proprioception) and **L**ateral (Leg weakness/motor) columns.
- **MDS Hallmark:** Elderly patient + refractory pancytopenia + ringed sideroblasts + rule out B12/folate first.

Venous Thromboembolism (VTE)

Core Concepts

- **Pathogenesis (Virchow's Triad):** Thrombosis is a multifactorial "accident" occurring when genetic and acquired risk factors compound to tip the hemostatic balance. Most hospitalized patients have at least one risk factor.
  - **Venous Stasis:** Immobility, age > 40, CHF, stroke, paralysis/spinal cord injury, anesthesia, obesity, varicose veins, hyperviscosity (polycythemia), severe COPD.
  - **Hypercoagulability:** Cancer, high estrogen states, pregnancy, inflammatory bowel disease (IBD), nephrotic syndrome, sepsis, smoking, thrombophilias.
  - **Endothelial Damage:** Surgery, trauma, central venous lines, prior VTE.
- **Inherited Thrombophilias:**

1. Factor V Leiden mutation (most common inherited)
2. Prothrombin (Factor II) G20210A mutation
3. Protein C deficiency
4. Protein S deficiency
5. Antithrombin III (ATIII) deficiency

- **Importance of VTE:** It is a common, costly, and largely *preventable* disease. Left unprophylaxed, it carries a high risk of life-threatening events (PE) and severe long-term morbidity (Post-Thrombotic Syndrome).

Diagnosis / Clinical Features

- **Deep Vein Thrombosis (DVT):** Presents classically with unilateral, painful swelling, erythema ("hotness"), and edema of the affected extremity (e.g., following long-distance travel).
- **Pulmonary Embolism (PE):** Presents with shortness of breath, repeated attacks of cough, hemoptysis, and pleuritic chest pain.

Investigations

- **Imaging:** Duplex Ultrasound is the primary modality for confirming DVT (e.g., in the common femoral vein).
- **Coagulation Monitoring:**
  - **aPTT:** Used to monitor Unfractionated Heparin (Target: 1.5–2.5x normal).
  - **PT/INR:** Used to monitor Warfarin (Target INR: 2.0–3.0). *INR = (Patient PT / Control PT)^ISI*.

Management

- **Acute Anticoagulation (Parenteral):**
  - **Unfractionated Heparin (UFH):** Requires >18 monosaccharide units to inhibit thrombin. Given as 80 units/kg loading dose → 18 units/kg/hr infusion.
  - **Low Molecular Weight Heparin (LMWH):** <18 monosaccharide units; preferentially inhibits Factor Xa. E.g., Enoxaparin (1 mg/kg BID) or Tinzaparin (175 units/kg once daily).
  - **Pentasaccharide:** Pure Factor Xa inhibition.
- **Long-term Anticoagulation (Oral):**
  - **Warfarin (Vitamin K Antagonist):** Inhibits synthesis of Factors II, VII, IX, X, and Proteins C & S.
    - *Kinetics:* Highly protein-bound (99% to albumin). Half-life is 25–60 hours. Peak plasma concentration in 2–8 hours, but *antithrombotic effect takes days* because pre-formed factors must clear.
    - *Bridging:* Must overlap with Heparin for at least 5 days and until INR is therapeutic (2.0–3.0). Factor VII and Protein C deplete rapidly, creating a transient prothrombotic state before Prothrombin (Factor II) and Factor X deplete.
  - **Direct Oral Anticoagulants (NOACs/DOACs):**
    - *Factor Xa Inhibitors:* Apixaban, Rivaroxaban.
    - *Direct Thrombin (IIa) Inhibitors:* Dabigatran.

    - *Indications:* Treatment/prevention of VTE, stroke prevention in non-valvular AF, VTE prophylaxis post-hip/knee replacement.
    - *Contraindications:* Prosthetic heart valves, clinically significant active bleeding, severe renal impairment (dose adjustment required for moderate), liver disease, pregnancy/breastfeeding, age < 18.
- **Other Modalities (Severe/Refractory Cases):** Thrombolytic therapy, venous thrombectomy, pulmonary embolectomy, IVC filters.
- **Myeloproliferative Neoplasms (MPNs):** Patients with MPNs (e.g., polycythemia) are at high risk for VTE. *Ruxolitinib* (selective JAK 1/2 inhibitor) is used 2nd-line after hydroxyurea to improve systemic symptoms, though it currently shows no distinct survival benefit.

Complications / Prognosis

- **High Early Mortality:** Cumulative mortality for PE is ~17.5% within the first 90 days, with the majority of deaths occurring very early (within 7–14 days). Untreated PE mortality can be up to 30%.
- **Post-Thrombotic Syndrome (PTS):** Occurs in ~40% of patients following a DVT. Characterized by chronic venous stasis, pain, edema, and skin ulceration.
- **Pulmonary Hypertension (CTEPH):** Develops in ~5% of patients post-PE.
- **Warfarin-Specific Complications:**
    - **Bleeding:** Most common complication.
    - **Teratogenicity:** Contraindicated in pregnancy (causes birth defects and abortion).
    - **Skin Necrosis / Microvascular Thrombosis:** Occurs typically in the first few days of therapy, especially in patients with unrecognized *heterozygous Protein C or S deficiency*, if given a large initial dose without adequate heparin overlap.

Past-Paper High Yield

- **The Rationale for Heparin Bridging:** You will be tested on the timeline of Vitamin K-dependent factor clearance. Protein C (an anticoagulant) has a short half-life and clears quickly, alongside Factor VII. Prothrombin (Factor II) takes the longest to clear. Starting Warfarin alone causes a rapid drop in Protein C, leading to a temporary hypercoagulable state and risking *Warfarin-induced skin necrosis*.
- **Heparin Chain Lengths:** UFH inhibits *both* Thrombin (IIa) and Xa because its long chain (>18 units) can physically wrap around both Antithrombin and Thrombin. LMWH is too short to wrap around Thrombin, making it selectively target Factor Xa.
- **Prosthetic Valves & NOACs:** NOACs (Apixaban, Rivaroxaban, Dabigatran) are strictly *contraindicated* in patients with mechanical/prosthetic heart valves (Warfarin is required).

Memory Pearls

- **NOAC Targets:** "Xa-bans" (Api**xa**ban, Rivaro**xa**ban) block Factor **Xa**. Dabiga**t**ran blocks **T**hrombin (Factor IIa).
- **Virchow's Triad: SHE** (Stasis, Hypercoagulability, Endothelial damage).

- **Warfarin Factors: SNTCS** (Seven, Nine, Ten, C, S) – ordered roughly by clearance speed. Prothrombin (II) is the ultimate target for full anticoagulation.

Disorders of Hemostasis

Core Concepts

Disorders of hemostasis are broadly classified into three major categories based on their clinical presentation: **Bleeding disorders**, **Thrombotic disorders**, and **Mixed disorders**.

1. Bleeding Disorders Bleeding disorders are subdivided by the phase of hemostasis affected (Primary vs. Secondary) and the underlying mechanism (Quantitative vs. Qualitative; Congenital vs. Acquired).

DEFECT TYPE	SUB-CATEGORY	CONGENITAL / INHERITED	ACQUIRED
Primary Hemostasis *(Platelet/vWF defects)*	**Quantitative** *(Thrombocytopenia)*		• **Immune-mediated:** Idiopathic, infections, drugs, autoimmune disease • **Decreased production:** Bone marrow depression (aplastic anemia, chemotherapy, infiltration, infections) • **Increased destruction/consumption:** TMAs, DIC, prosthetic heart valves, hypersplenism
	Qualitative *(Platelet dysfunction)*	• von Willebrand Disease (vWD) • Congenital platelet disorders (e.g., Glanzmann's thrombasthenia)	• Uremia • Medications • Acquired vWD
Secondary Hemostasis *(Coagulation factor defects)*	**Factor Deficiencies / Inhibitors**	• Hemophilia A • Hemophilia B • Other rare bleeding disorders	• Liver disease • Vitamin K deficiency • Medications • Severe vWD (results in low Factor VIII) • Acquired hemophilia

2. Thrombotic Disorders Thrombotic disorders (thrombophilias) arise from an imbalance favoring clot formation and can be inherited or acquired.

CONGENITAL (INHERITED)	ACQUIRED
• **Factor V Leiden mutation** • **Prothrombin gene mutation** • **Antithrombin III (ATIII) deficiency** • **Protein C deficiency** • **Protein S deficiency** • **Homocysteinemia**	• Aging & Immobilization • Malignancy • Pregnancy and estrogen use • Antiphospholipid Syndrome (APS) • Nephrotic syndrome • Liver disease • DIC • Heparin-Induced Thrombocytopenia (HIT)

3. Mixed Disorders (Bleeding & Thrombosis) Certain systemic conditions severely dysregulate the entire hemostatic cascade, resulting in a paradoxical combination of both bleeding and thrombotic tendencies:

- **Liver Disease:** Impaired synthesis of both procoagulant factors and natural anticoagulants.
- **DIC (Disseminated Intravascular Coagulation):** Widespread microvascular thrombosis leading to the consumption of platelets and clotting factors, resulting in severe bleeding.
- **HIT (Heparin-Induced Thrombocytopenia):** Immune-mediated platelet activation causing thrombosis, with concurrent drop in platelet count.
- **TTP (Thrombotic Thrombocytopenic Purpura):** Formation of platelet-rich microthrombi causing ischemia, while simultaneously consuming platelets leading to bleeding risk.

Memory Pearls

- **The "Mixed" Quartet:** Always group **Liver disease, DIC, HIT, and TTP** together as conditions that can simultaneously present with thrombocytopenia/bleeding and life-threatening thrombosis.
- **vWD crosses categories:** While classic vWD is a *qualitative primary hemostatic defect* (impaired platelet adhesion), **severe vWD** acts as a *secondary hemostatic defect* because vWF acts as the carrier protein for Factor VIII; without vWF, Factor VIII is rapidly degraded.
- **Nephrotic syndrome as a pro-thrombotic state:** Due to the urinary loss of Antithrombin III (ATIII) and other anticoagulant proteins, it creates an acquired thrombophilia.
- **Uremia equals qualitative platelet dysfunction:** In chronic kidney disease, platelet counts are often normal (no quantitative defect), but platelet function is severely impaired due to uremic toxins.

Infectious diseases

Exam Map

TOPIC	PAST-PAPER WEIGHT	REVISION PRIORITY
Antibiotic Therapy	50 questions	🔴 Absolute Must-Know
HIV	11 questions	🟡 High Yield
Infection Control	11 questions	🟡 High Yield
Tuberculosis	10 questions	🟡 High Yield
Brucellosis	5 questions	🟢 Moderate Yield
Antibiotic Resistance	2 questions	⚪ Low Yield
Typhoid Fever & Salmonella	1 questions	⚪ Low Yield

Recurring Exam Patterns & Practical Revision Priorities:

- **Pharmacology completely dominates:** With 50 questions dedicated to antibiotics, memorizing adverse effect profiles is non-negotiable. Expect recurring "drug traps" separating Vancomycin (Red man, nephro/ototoxicity) from Metronidazole/Isoniazid (neuropathy, seizures), as well as strict contraindications in pregnancy and G6PD deficiency.
- **The Needle-Stick "Rule of 3s":** Transmission probabilities for occupational exposures are heavily tested. You must instantly recall HBV (30%), HCV (3%), and HIV (0.3%), alongside the post-exposure protocols (e.g., HBIG + Vaccine for non-immune HBV exposures; combination ART for HIV).
- **Absolute rules of HIV management:** Exam questions consistently test the principle that Antiretroviral Therapy (ART) is started *immediately* upon diagnosis—never delay for CD4 counts or symptoms. Conversely, recognize CD4 < 200 as the strict trigger for TMP/SMX prophylaxis.
- **PPD Induration Cut-offs for TB:** You will be forced to categorize patients into 5 mm (HIV/immunosuppressed/contacts), 10 mm (healthcare workers/renal failure/DM), and 15 mm (healthy) groups. Also, know that cavitary TB has the highest transmission risk.
- **Vaccine Safety:** Differentiating live-attenuated vaccines (strictly contraindicated in pregnancy and immunocompromised states like HIV) from inactivated vaccines (safe and strongly recommended) is a highly repeated theme.
- **Brucellosis Pearls:** Exam scenarios frequently feature raw milk ingestion, relative bradycardia, and the necessity of prolonged, multidrug therapy (Doxycycline + Rifampin for 6 weeks) due to the organism's intracellular nature and high relapse rate.
- **Isolation Precautions:** Memorize the strict infection control categories: Airborne (TB, Measles, VZV), Droplet (Influenza, Meningitis), and Contact (MRSA, *C. difficile*). Remember that *C. diff* spores require soap and water, not alcohol rubs.

- **Diagnostic Modality Timelines:** Distinguishing *when* to use specific tests is critical. For instance, diagnosing acute "window period" HIV requires a PCR (viral load), not an ELISA (antibodies). Similarly, differentiating food poisoning relies heavily on incubation timelines (preformed toxins in <6 hours vs. Salmonella in 6–72 hours).

Antibiotic Therapy

Core Concepts

- **Bactericidal vs. Bacteriostatic**: Choice depends on host immune status, specific pathogen, and site of infection.
- **Pharmacodynamics**:
  - **Concentration-Dependent**: Increasing the concentration increases the rate of bacterial death. Usually requires large doses at longer intervals.
    - *Examples*: Fluoroquinolones, Aminoglycosides.
  - **Time-Dependent**: Reduction in bacterial density is proportional to the time the serum concentration remains above the Minimum Inhibitory Concentration (MIC). Requires sufficient dosing at appropriate intervals to maintain levels > MIC.
    - *Examples*: β-lactams, Vancomycin.
- **Therapeutic Combinations**:
  - *Indications*: Prevention of resistance (e.g., Tuberculosis, Staphylococcal endocarditis), empiric therapy for severe/polymicrobial intra-abdominal sepsis, and achieving synergistic bacterial killing.
  - *Synergism*: Penicillin + Aminoglycoside (Enterococcal endocarditis); Oxacillin + Aminoglycoside (Staph endocarditis); Antipseudomonal β-lactam + Aminoglycoside (Pseudomonas bacteremia).
  - *Antagonism*: Penicillin + Tetracyclines; or two β-lactams together (can induce β-lactamases).

Host Factors & Adverse Effects

- **Pregnancy Considerations**:
  - *Safe*: Penicillins, Cephalosporins, Erythromycin base.
  - *Contraindicated/Dangerous*: Tetracyclines (hepatic toxicity, fetal dental discoloration), Fluoroquinolones, Clarithromycin. Metronidazole is potentially teratogenic.
- **Genetic/Metabolic Factors**:
  - **G6PD Deficiency**: Avoid **Dapsone**, Sulfonamides, and Nitrofurantoin, as they trigger acute hemolytic anemia.
  - **Diabetes Mellitus**: Intramuscular absorption is poor; use IV route for serious infections. Note that sulfa drugs can potentiate sulfonylurea hypoglycemic agents.
- **Key Adverse Effects (Highly Tested)**:
  - **Vancomycin**: Red man syndrome, nephrotoxicity, ototoxicity, neutropenia, phlebitis. *(Note: Seizures and neuropathy are NOT typical adverse effects)*.

- **Metronidazole**: Metallic taste, GI upset, neuropathy, seizures. *(Note: Red man syndrome is NOT an adverse effect)*.
- **Fluoroquinolones (Ciprofloxacin, Levofloxacin)**: Tendinitis (especially Achilles and rotator cuff), arthropathy.
- **Isoniazid (INH)**: Hepatotoxicity, peripheral neuropathy, and drug-induced lupus.
- **Aminoglycosides**: Nephrotoxicity and cochlear/vestibular toxicity.

Diagnosis / Clinical Features

- **Infection Identification**:
  - **Microbiology**: Gram stain from sterile sites (CSF, pleura, synovium) provides rapid initial guidance. Blood cultures must ideally be drawn *before* administering antibiotics.
  - **Procalcitonin**: The best biomarker to evaluate the severity of pneumonia associated with sepsis.
- **Specific Clinical Associations**:
  - **Malignant Otitis Externa**: A diabetic patient presenting with severe external ear pain, purulent discharge, and an edematous external canal is highly suspicious for *Pseudomonas aeruginosa*.
  - **Infective Endocarditis Organisms**:
    - Acute endocarditis: *Staphylococcus aureus*.
    - Post-dental extraction: Alpha-hemolytic streptococci (*Strep viridans*).
    - *Clostridium septicum* endocarditis/bacteremia is strongly associated with underlying colon cancer.
  - **E. coli O157:H7**: Causes bloody diarrhea, primarily in children, and can progress to Hemolytic Uremic Syndrome (HUS).

Investigations

- **Antimicrobial Susceptibility Testing**: Includes disk diffusion, E-test, MIC, and MBC (Minimum Bactericidal Concentration).
- **Specific Diagnostic Modalities**:
  - **Syphilis**: Darkfield microscopy (active chancre), VDRL/RPR (screening), FTA-ABS/TPHA (confirmatory diagnosis).
  - **COVID-19**: Nasopharyngeal PCR is the definitive test.
  - **H1N1 Influenza**: Diagnosed via nasopharyngeal swab for PCR.
  - **Ascaris lumbricoides**: Diagnosed by detection of eggs in the stool.
  - **C. difficile**: Diagnosed by detection of stool toxins A and B (toxin-mediated disease, NOT immune complex-mediated).

Management

- **General Rules**:
  - The oral route is for stable, mild infections; the IV route is essential for severe infections, sepsis, and conditions impairing absorption (e.g., DM).

    - Neutropenic patients (e.g., absolute neutrophil count critically low) require immediate **protective isolation** and aggressive empiric IV antibiotic therapy.
- **Specific Pathogen Management**:
    - **Brucellosis**: Requires at least 6 weeks of therapy.
        - *Adults*: Doxycycline + Rifampin.
        - *Children (<8 years)*: Rifampin + TMP-SMX (Doxycycline is contraindicated).
    - **Pseudomonas**: Antipseudomonal agents include Ceftazidime.
    - **ADPKD with an infected cyst**: **Ciprofloxacin** is the most appropriate antibiotic due to its superior penetration into renal cysts.
    - **H1N1 Influenza**: Treat the patient and contacts with **Oseltamivir**. Droplet precautions are required. *Do not give antibiotics unless there is a secondary bacterial complication.*
    - **E. coli O157:H7**: **Antibiotics are contraindicated** in both mild and severe cases, as they increase the risk of HUS.
    - **Shingles (Herpes Zoster)**: Oral antivirals (e.g., acyclovir or valacyclovir) are the best initial treatment. *Topical acyclovir is incorrect.*
    - **Hepatitis B (Immune Tolerant Phase)**: A patient with vertically transmitted Hep B, positive HBeAg, normal transaminases (ALT/AST), and high HBV DNA is asymptomatic and should be managed with **observation and monitoring** (no immediate antivirals).
    - **Tuberculosis**: Standard initial therapy utilizes INH, Rifampin, Ethambutol, and Pyrazinamide for 2 months, followed by INH and Rifampin for 4 months.

Complications / Prognosis

- **Secondary Infections**: H1N1 influenza is most commonly complicated by secondary bacterial pneumonia caused by *Streptococcus pneumoniae*.
- **Endocarditis**: The most common cause of death in severe *Brucellosis*.
- **C. difficile Infection**: Recurrence rates can reach up to 20%. It is treated using oral vancomycin, fidaxomicin, or metronidazole.
- **Sepsis**: Associated with Acute Respiratory Distress Syndrome (ARDS), metabolic acidosis, altered reflexes, and hypotension. *It is NOT associated with glove-and-stocking dysesthesias* (a feature of peripheral neuropathy).

Past-Paper High Yield

- **Drug Trap Differentiators**:
    - **Red man syndrome** belongs to Vancomycin, not Metronidazole.
    - **Seizures and neuropathy** belong to Metronidazole/Carbapenems/Isoniazid, not Vancomycin.
    - **Hemolysis in G6PD** is triggered by Dapsone and Sulfonamides.
    - **Drug-induced lupus** is classically linked to Isoniazid (and hydralazine/procainamide).
- **Immunodeficiency Quick Hits**:
    - **IgA deficiency**: Most common congenital immunodeficiency.
    - **Chronic Granulomatous Disease (CGD)**: Characterized by a defect in phagocytosis.

    - **Hyper IgE Syndrome (Job Syndrome)**: Associated with extremely high IgE levels and defective chemotaxis.
    - **Common Variable Immunodeficiency (CVID)**: Characterized by low IgA and IgG levels.
- **Parasitology Quick Hits**:
    - **Enterobius vermicularis (Pinworm)**: Intense anal itching, treated with mebendazole, transmitted via egg ingestion. *Does NOT cause anemia* (Hookworms do).
    - **Ascaris lumbricoides**: Presents as 40 cm smooth brown worms exiting the anus; may cause Loeffler syndrome.
    - **Schistosoma haematobium**: Specifically associated with urinary bladder cancer.
    - **Taenia solium**: The intermediate host is the pig; strictly associated with neurocysticercosis. (*Taenia saginata* is found in cattle).
- **Miscellaneous ID Pearls**:
    - **Hepatitis A**: Transmitted via the feco-oral route, does not cause chronic liver disease, and is vaccine-preventable. *The virus is excreted in feces BEFORE the onset of symptoms, not at the time of onset.*
    - **S. aureus food poisoning**: Preformed exotoxin causes nausea, vomiting, and diarrhea in less than 24 hours. *Fever is typically absent.*
    - **Viral Encephalitis**: HSV is the most common viral etiology.
    - **Norovirus**: Most common cause of diarrhea in adults.
    - **Erysipelas**: Almost exclusively caused by Group A Streptococcus.
    - **Ramsay Hunt Syndrome** (Herpes zoster of the geniculate ganglion): Features lower motor neuron facial weakness, hyperacusis, and altered taste/smell. *(Upper motor neuron weakness is an incorrect distractor).*

Memory Pearls

- **"Vanc is for Veins, Kidneys, and Ears"**: Vancomycin toxicity includes Phlebitis, Nephrotoxicity, and Ototoxicity (along with Red man syndrome).
- **"Quinolones cut cords"**: Fluoroquinolones cause tendon inflammation and rupture (e.g., rotator cuff, Achilles).
- **Septicum = Screen**: Growth of *Clostridium septicum* in blood cultures demands a screening colonoscopy.
- **"Dapsone Damages Deficient RBCs"**: Major trigger for G6PD hemolytic crisis.

Antibiotic Resistance

Core Concepts

- **Definition:** Resistant bacteria are organisms that are not inhibited by the usually achievable systemic concentrations of an antibiotic given at normal dosages.
- **Origins & Biology of Resistance:**
    - **Genetic mechanisms:** Arises via spontaneous mutation or acquired resistance genes.

    - **Gene transfer:** Occurs within or between species via plasmids, chromosomal alterations, or transposons.
    - **Spread mechanisms:** Clonal spread of the resistant organism, plasmid transfer, or transposon mobilization (jumping from plasmid to chromosome).
- **Resistance Selection (Antibiotic Pressure):** Prolonged or repeated antibiotic exposure acts as a selective pressure, allowing resistant strains to survive and proliferate.
    - *Example:* VRSA (Vancomycin-resistant *S. aureus*) can emerge in patients co-infected with MRSA and VRE. The *vanA* resistance gene transfers from VRE to MRSA via plasmids.
- **Ecological Drivers:** Massive non-therapeutic use of antimicrobials in agriculture (historically allowed in the US, restricted in Europe) acts as a major reservoir for resistance, which transfers to humans directly or via the food supply.

Investigations

- **Susceptibility Testing Methods:**
    - **Disk Diffusion:** Qualitative assessment categorizing isolates as Sensitive (S), Intermediate (I), or Resistant (R) based on zone diameter.
    - **Etest:** Both quantitative and qualitative; provides the Minimum Inhibitory Concentration (MIC).
- **Interpreting Results (CLSI Standards):**
    - **Intermediate strains:** The organism's MIC approaches attainable blood levels of the drug. Clinical response rates may be lower than those seen with fully susceptible bacteria.
    - ***In vitro* vs. *in vivo* dilemma:* In vitro* growth inhibition by an agent does not uniformly guarantee clinical cure in the patient.
- **Global & National Surveillance Systems:**
    - Used to track epidemiologic trends (e.g., higher Gram-positive resistance in the US, higher Gram-negative in Europe; highest pneumococcal resistance in the Mediterranean).
    - Major programs: SENTRY (International), EARSS (Europe), NNIS (US Nosocomial/ICU), SCOPE, ICARE.

Management

- **Infection Control Precautions:**
    - **Contact isolation** is mandatory for multidrug-resistant organisms like **MRSA** and **VRE** to prevent horizontal transmission.
- **Antimicrobial Stewardship:**
    - **Restricted Formularies:** Hospitals often restrict broad-spectrum or high-risk antibiotics (e.g., carbapenems, specific 3rd generation cephalosporins, fluoroquinolones) to limit resistance selection.
    - Appropriate de-escalation based on susceptibility testing.

Complications / Prognosis

- **Clinical Impact:** Emergence of resistance during treatment (e.g., in *P. aeruginosa* or *S. pneumoniae* infections) leads to higher rates of suppurative complications, shock, and respiratory failure.
- **Healthcare Burden:** Antimicrobial resistance approximately **doubles** the length of hospital stays, morbidity, and mortality, while adding billions in financial costs annually.

Past-Paper High Yield

- **Extended-Spectrum Beta-Lactamases (ESBL):**
  - **Defining feature:** ESBL-producing bacteria (like *E. coli* or *Klebsiella*) confer resistance to most beta-lactam antibiotics, most importantly **3rd-generation cephalosporins (e.g., Ceftriaxone, Cefotaxime, Ceftazidime)** and monobactams (Aztreonam).
  - *Exam Trap:* ESBL organisms typically remain *susceptible* to carbapenems (Imipenem, Meropenem), making carbapenems the treatment of choice. Do not confuse ESBLs with Carbapenem-Resistant Enterobacteriaceae (CRE).
- **Isolation Precautions:**
  - **MRSA** requires **Contact Precautions** only.
  - *Differentiators:* Tuberculosis (TB) and Measles require Airborne precautions; Influenza requires Droplet precautions.

Memory Pearls

- **VRSA origins:** Think ***vanA* gene transfer**. Co-infection with VRE + MRSA + vancomycin pressure = VRSA via plasmid transfer.
- **ESBL treatment rule: Resistant to Ceftriaxone → Treat with Carbapenems** (Imipenem/Meropenem).
- **Resistance geography:** Nosocomial/ICU settings universally harbor significantly higher resistance rates than community settings.

Typhoid Fever and Salmonella Enterocolitis

Core Concepts

- **The Organism:** Gram-negative, motile, non-sporulating, straight-rod bacteria; obligate intracellular facultative pathogens.
- **Two Major Clinical Syndromes:**
  - **Typhoid (Enteric) Fever:** Caused by *Salmonella enterica* serovars Typhi and Paratyphi (A, B, C).
    - *Reservoir:* **Humans only** (feces is the major portal of exit; urine is minor).
    - *Pathogenesis:* The **Vi antigen** prevents antibody-mediated opsonization and complement-mediated lysis. Bacteria spread via the reticuloendothelial system (macrophages) to the liver, spleen, and bone marrow.

    - **Nontyphoidal Salmonella (Enterocolitis):** Caused by serotypes like Typhimurium, Enteritidis, Newport, Heidelberg, and Choleraesuis.
        - *Reservoir:* Humans and animals (including livestock).
- **Infective Dose (Inoculum):** Infection occurs via the fecal-oral route.
    - *Standard dose:* ~10^6 bacterial cells.
    - *Low gastric acidity:* Decreases the required infective dose significantly (to 10^3 cells).
    - *Prior vaccination:* Increases the required infective dose (to 10^9 cells).
- **Carrier Status:**
    - *Convalescent:* Sheds for 3–12 months post-illness.
    - *Chronic:* Sheds for >12 months (major source of infection in low-incidence countries).

Diagnosis / Clinical Features

FEATURE	NONTYPHOIDAL ENTEROCOLITIS	TYPHOID FEVER
Incubation	**6–72 hours** (usually 12–36 hours)	**10–14 days**
Duration	2–7 days	Up to 4 weeks (if untreated)
Presentation	Acute fever, acute abdominal pain, acute diarrhea, nausea, and vomiting.	Weakness, fatigue, loss of appetite, weight loss.
Key Signs	Gastroenteritis signs.	**Relative bradycardia**, splenomegaly.
Fever Pattern	Acute onset.	**Stepwise progression:** First 9 days no fever but widening daily fluctuations → fever starts day 10 → persistent high-grade by end of week 2.

Investigations

- **Microbiology:** Blood, stool, and urine cultures. (In Typhoid, bacteria typically appear in the bloodstream within 14 days, facilitating secondary metastatic foci).
- **Serology:** Widal test.
- **Adjuncts:** PCR, imaging (to locate abscesses or focal disease), endoscopy.

Management

- **Medical (Typhoid Fever):**
    - Ciprofloxacin, Azithromycin, or Ceftriaxone.
    - *Note:* Extensively Drug-Resistant (XDR) Typhoid Fever is highly prevalent in certain global regions.
    - Antibiotics dramatically reduce the case fatality risk from 10–30% to <1%.
- **Surgical Management:** Indicated for severe complications including gallbladder disease, bowel perforation, splenic/soft-tissue abscesses, and bone/heart involvement.
- **Prevention:**

- **Hygiene:** Hand hygiene and safe food/water practices are the most crucial preventative measures.
- **Vaccines** (Not 100% effective):
  - **Oral (Ty21a / Vivotif):** Live vaccine. 4 capsules (1 every other day). Finish 1 week before travel. Minimum age: **6 years**. Booster: Every 5 years.
  - **Injectable (ViCPS / Typhim Vi):** Polysaccharide vaccine. 1 dose. Give 2 weeks before travel. Minimum age: **2 years**. Booster: Every 2 years.

Complications / Prognosis

Complications occur in 10–15% of hospitalized patients and up to 27% of blood-culture-confirmed cases.

- **Gastrointestinal:** Intestinal perforation, GI hemorrhage, paralytic ileus, hepatitis.
- **Secondary Metastatic Foci:** Splenic abscess, osteomyelitis, endocarditis, infective aortitis (high morbidity/mortality), meningitis.
- **Systemic / Neurological:** Sepsis syndrome, AKI, bone marrow suppression, severe anemia, encephalopathy, psychosis, stupor/coma, seizures, SIADH.
- **Long-term Sequelae:** Persistent *Salmonella* infection is linked to the development of inflammatory bowel disease (IBD) and cancer.

Past-Paper High Yield

- **Incubation Period Rule-Outs:** You must be able to use onset timelines to deduce the pathogen. A patient developing severe nausea, vomiting, and abdominal pain **5 hours** after eating restaurant food is suffering from preformed toxin ingestion (e.g., *Staphylococcus aureus* or *Bacillus cereus*). *Salmonella* enterocolitis has an incubation of **6 to 72 hours** and is an incorrect diagnosis for ultra-rapid onset presentations.
- **Gastric Acid as a Barrier:** Remember that patients on proton pump inhibitors (PPIs) or with achlorhydria require a massively reduced inoculum (10^3) to develop *Salmonella* infection due to the loss of the protective acidic barrier.

Memory Pearls

- **The "Typhoid Triad":** Stepwise fever, relative bradycardia, and splenomegaly.
- **Vi for Virulence:** The **Vi** antigen acts as a shield, preventing opsonization and MAC (complement) lysis, allowing the bacteria to use macrophages as a trojan horse to reach the reticuloendothelial system.
- **Reservoir Rule:** S. **T**yphi is **T**wo-legged only (Human reservoir). Enterocolitis serotypes (e.g., Typhimurium) have animal reservoirs.

Brucellosis

Core Concepts

- **Microbiology:** Gram-negative bacilli or coccobacilli.

- **Pathophysiology:**
  - **Intracellular pathogen:** Possesses a unique ability to invade phagocytic cells.
  - Macrophages transport the bacteria to the reticuloendothelial system (lymph nodes, spleen, liver, bone marrow), as well as mammary glands and sex organs.
  - **Highly infectious:** Only 100 to 1,000 organisms are needed to cause infection.
- **Transmission:**
  - **Zoonotic (No human-to-human transmission).**
  - **Ingestion:** Unpasteurized dairy products (main route for *B. melitensis*).
  - **Occupational exposure:** Slaughterhouse workers, veterinarians (via accidental inoculation of *B. abortus* and *B. melitensis* animal vaccines), and laboratory microbiologists (via aerosol processing without special precautions).
  - *Note:* Infected animals (sheep, cattle, pigs) are often asymptomatic or suffer abortions; they shed Brucella in urine, milk, and placental fluid.
- **Pathogenic Species:**
  - ***B. melitensis*: **The most prevalent worldwide and the** most virulent** (causes the most severe/acute cases). Main source is sheep/goats.
  - ***B. suis*: **Associated with a prolonged illness course and** suppurative destructive lesions**.
  - ***B. abortus*:** Tends to cause mild and self-limited disease.
  - ***B. canis*:** Infects dogs.
  - *Species does NOT alter the treatment regimen.*
- **Epidemiology:** More common in males (5:2 ratio in endemic areas).

Diagnosis / Clinical Features

- **Acute/Subacute Presentation:**
  - Symptoms can develop 2–12 months prior to diagnosis.
  - **Fever:** The most common symptom (80–100%); classically associated with **relative bradycardia**.
  - **Constitutional:** Anorexia, asthenia, fatigue, weakness, and malaise (>90%).
  - **GI:** Abdominal pain, constipation, diarrhea, vomiting.
  - **Respiratory:** Dry cough and shortness of breath (20%), though active pulmonary involvement is rare.
- **Chronic Brucellosis:**
  - Diagnosis made after symptoms persist for > 1 year.
  - Characterized by low-grade fevers and **neuropsychiatric symptoms**.
  - Often due to inadequate initial therapy or underlying localized disease.
  - *Caveat:* Serology and cultures are often negative in this phase.
- **Subclinical Brucellosis:** Asymptomatic; discovered incidentally via serologic screening in high-risk groups. Culture is usually negative.

Complications / Prognosis

- **Prognosis:** Low mortality rate (<5%), but causes chronic debilitating illness with extensive morbidity.
- **Osteoarticular (Most Common):** Occurs in 20–60% of patients. **Sacroiliitis** is the most common focal complication.
- **Cardiovascular: Endocarditis** is very rare (2%) but is the principal cause of mortality.
- **Genitourinary:** Epididymo-orchitis.
- **Neurological (Neurobrucellosis):** Can present with progressive headache, ataxia, and blurred vision. Causes meningitis with CSF findings that closely mimic tuberculosis (elevated protein, low glucose, and lymphocytic pleocytosis).
- **Hepatosplenic:** Splenomegaly and hepatomegaly due to reticuloendothelial seeding.

Investigations

- **Hematology:** Leukopenia with **relative lymphocytosis**, and pancytopenia.
- **Biochemistry:** Elevated liver enzymes.
- **Culture:** The definitive test (highest diagnostic yield for confirming the organism). Can be drawn from blood or bone marrow.
- **Serology: Standard tube agglutination** is the diagnostic mainstay (e.g., Titer ≥ 1/160 indicates infection).
- **PCR:** Not yet in routine clinical practice.

Management

- **Core Principle:** Multidrug regimens and prolonged treatment (several weeks) are required due to **high relapse rates** with monotherapy.
- **Standard Adult Regimens:**
  - *Option 1:* **Doxycycline + Rifampin** for **6 weeks**.
  - *Option 2 (More effective):* **Doxycycline (6 weeks) + Streptomycin (2–3 weeks)**.
- **Special Populations:**
  - **Children < 8 years: Rifampin + TMP-SMX** for 6 weeks. (Doxycycline is contraindicated due to tooth discoloration).
  - **Pregnancy:** Challenging with limited studies. Use **Rifampin alone** or **Rifampin + TMP-SMX**.

Past-Paper High Yield

- **Most virulent & prevalent species:** *Brucella melitensis* (NOT *B. abortus*).
- **Suppurative destructive lesions:** Uniquely characteristic of ***Brucella suis***.
- **Transmission trap:** Brucellosis is heavily tested as a zoonotic disease—it is **NOT** transmitted from human to human.
- **Diagnostic tests:** Standard tube agglutination and Culture are the highest yield/most appropriate diagnostic modalities. PCR is historically incorrect/not standard practice.

- **CSF profile differentiation:** Neurobrucellosis presents with lymphocytic pleocytosis, high protein, and **low glucose** (hypoglycorrhachia). This mimics TB, Sarcoidosis, and Carcinomatous meningitis. (Viral/Herpetic encephalitis typically has *normal* glucose and was the "unlikely" diagnosis in past exams).
- **Raw milk pathogens:** *Brucella*, *Listeria monocytogenes*, and *Mycobacterium bovis* are classic unpasteurized milk pathogens. (*Bacillus anthracis* is NOT acquired this way).
- **Treatment duration:** Must be treated for **several weeks** (typically 6 weeks) to prevent relapse.
- **Demographics/Species Trap:** It is more common in males (not females), and *B. canis* infects dogs (not goats/sheep).

Memory Pearls

- **"Brucella is an intracellular fella"**: Needs prolonged, intracellular-penetrating multidrug therapy (Doxycycline + Rifampin) to avoid relapse.
- **"MELitensis is the Most Malevolent (virulent)"**
- **"SUis causes SUppuration"**
- **Fever + Relative Bradycardia:** Think Brucella, Salmonella (Typhoid), or Legionella.

Tuberculosis

Core Concepts

- **Microbiology:** *Mycobacterium tuberculosis* (MTB) is an acid-fast bacillus (AFB). It is a slow-growing organism (takes 4–8 weeks for visible growth on solid medium).
- **Other Mycobacteria:** *M. bovis* (cattle), *M. microti* (rodents), *M. africanum*, *M. canetti*.
- **Epidemiology:** The second leading infectious cause of mortality worldwide (after COVID; HIV is third). It is a disease of poverty and predominantly affects young adults.
- **Latent vs. Active:** 2 billion people globally have latent TB. HIV-positive patients are **>15 times more likely** to develop active TB from a latent infection.
- **Pathophysiology:** Humans are the only known reservoir for MTB.
  - **Transmission:** Airborne droplet nuclei.
  - Inhaled droplets deposit in terminal airspaces → ingested by macrophages → transported to regional lymph nodes.
  - Outcomes: Eradication, primary active TB, dormant (latent), or reactivation disease (often triggered by immunosuppression).
- **Histology:** Classic finding is **caseous necrotic granuloma**.

Diagnosis / Clinical Features

- **Pulmonary TB:** Cough, fever, weight loss, hemoptysis, chest pain, anorexia, fatigue, and night sweats.
  - *Transmission Risk:* **Cavitary pulmonary TB** carries the highest bacterial load and poses the **highest risk for transmission** to others (higher than miliary, pleural, or extrapulmonary sites).

- **TB Meningitis:** Intermittent or persistent headache for 2–3 weeks, subtle mental status changes progressing to coma over days/weeks. Fever is often low-grade or absent.
- **Skeletal TB:**
  - *Spine (Pott Disease):* Back pain/stiffness; lower-extremity paralysis occurs in 50% of cases.
  - *TB Arthritis:* Monoarthritis. Hips and knees most commonly affected (> ankle > elbow > wrist > shoulder).
- **Gastrointestinal TB:** Mimics peptic ulcer disease or inflammatory bowel disease. Features include oral/anal non-healing ulcers, dysphagia, malabsorption, diarrhea, and hematochezia.
  - Laparoscopy may show extensive yellow-white nodules on the peritoneal surface.
- **Other Sites:** Lymphadenitis (Scrofula), genitourinary TB, cutaneous TB.
- **Associated Skin Findings:** TB is a classic, highly tested cause of **Erythema nodosum** (alongside Streptococcal infection, Sarcoidosis, and IBD).

Investigations

- **Active TB Diagnosis:**
  - **First-line: 3 early-morning sputum samples** (smear + culture + PCR). In hospitalized patients, collected every 8 hours. Children require early-morning gastric aspirates.
  - **Bronchoscopy:** If there is high clinical suspicion (e.g., upper lobe cavity, hemoptysis, weight loss) but sputum AFB smears are negative x3, the **best next step is bronchoscopy** with biopsy/bronchial washing.
  - Other biopsies (bone marrow, liver) ± blood cultures can be used if indicated.
- **Imaging (CXR):**
  - Patchy or nodular infiltrates. **Upper-lobe** involvement is most common.
  - *Cavity:* Indicates advanced infection with a high bacterial load.
  - *Miliary TB:* Numerous small nodular lesions resembling millet seeds.
- **Latent TB Diagnosis (PPD / TST):**
  - Purified Protein Derivative (Mantoux test) is injected intradermally. Read at 48–72 hours by measuring the **size of induration** (not erythema).
  - Identifies latent TB in asymptomatic patients; *not* a diagnostic test for active TB.
- **Mandatory Co-testing:** Obtain an **HIV test** in *all* patients diagnosed with TB.

Management

- **Active TB:** Start an initial **4-drug empiric regimen (RIPE)** for a prolonged course (> 6 months):
  - **R**ifampin
  - **I**soniazid (INH)
  - **P**yrazinamide
  - **E**thambutol (or Streptomycin)
- **Latent TB & Immunosuppression:**

- Patients with latent TB on steroids, with diabetes, renal insufficiency, silicosis, or on **Tumor Necrosis Factor-alpha inhibitors (TNFi)** are at massive risk for reactivation.
- Latent TB *must* be treated (e.g., with Isoniazid) before starting biologic medications like TNFi.

- **Infection Control:** Hospitalized patients require **respiratory isolation** in a **negative pressure room** with staff wearing **N95 masks**.

Complications / Prognosis

- **Prognosis:** Historically, untreated smear-positive TB had a 10-year mortality of ~70%. With proper 4-drug treatment, mortality drops to 3%.
- **HIV/AIDS:** TB is an **AIDS-defining illness**. (Note: Prophylactic TMP/SMX in HIV is given to protect against *Pneumocystis pneumonia*, not TB).

Past-Paper High Yield

- **PPD Cut-offs (Highly Tested!):** Know the thresholds for a positive induration:
  - **≥ 5 mm:** HIV/AIDS patients, close household contacts of a TB case, immunosuppressed (e.g., TNFi use), fibrotic changes on CXR. *(Trap: A 3 mm induration in an AIDS patient is NEGATIVE).*
  - **≥ 10 mm:** Chronic diseases (e.g., **renal failure**, DM), HCWs, IV drug users, high-risk congregate settings, children <4. *(Tested: 12 mm in renal failure = Positive).*
  - **≥ 15 mm:** Healthy individuals with no known risk factors. *(Tested: 17 mm in a healthy person = Positive).*
- **Diagnostic Modality Distinctions:** To diagnose *active* TB, you must use **3 Sputum samples**. PPD and Interferon-γ release assays (IGRA) are for *latent* TB and do not confirm active disease.
- **Transmission Hierarchy: Cavitary pulmonary TB** imposes the absolute highest risk for airborne transmission. Do not select miliary, pleural, or laryngeal TB if cavitary is an option.
- **TNFi Contraindications:** Untreated active or latent TB is an absolute contraindication for starting a TNFi. However, *latent TB treated with isoniazid* is safe and NOT a contraindication.
- **Negative AFB Workup:** If a patient has classic active pulmonary TB symptoms and a cavity on CXR but 3x sputum AFB are negative, the next best step is **bronchoscopy** (do not just repeat AFB in a month or treat empirically without further sampling).
- **AIDS-Defining Illnesses: TB is an AIDS-defining illness.** (Traps: Oral candidiasis and CD4 <300 are *not* AIDS-defining; esophageal candidiasis and CD4 <200 are).

Memory Pearls

- **RIPE: R**ifampin, **I**soniazid, **P**yrazinamide, **E**thambutol (4-drug initial regimen).
- **PPD induration, not erythema:** 5 (HIV/Contacts) - 10 (HCWs/Renal/DM) - 15 (Healthy).
- **Cavity = Contagious:** Cavitary lesions mean high bacterial load and maximum transmission risk.

Infection Control

Core Concepts

Standard Precautions

- Applied universally to reduce transmission risk from recognized and unrecognized sources.
- Applies to blood, all body fluids, non-intact skin, mucous membranes, and all secretions/excretions **except sweat**.
- Includes hand hygiene, barrier precautions, safe sharps handling, and environment/equipment cleaning.

Types of Isolation Precautions

- **Airborne** (Negative pressure room, N95 respirator): Tuberculosis, Measles, Varicella-Zoster Virus (VZV).
- **Droplet** (Private room, surgical mask): Meningitis (for the first 24 hours of therapy), non-H1N1 Influenza.
- **Contact** (Gown, gloves): MRSA, *Clostridium difficile*.
- **Protective** (Private room, mask, gown, gloves): Severely immunocompromised/neutropenic patients.

Vaccinology & Special Populations

- **Live Attenuated Vaccines:** MMR, Oral Polio, Varicella, Intranasal Influenza, Rotavirus.
  - **Absolute Contraindications:** Pregnancy and Immunocompromised states.
- **Inactivated/Subunit Vaccines:** Injectable Influenza, Hepatitis B, Tetanus, Pneumococcal Polysaccharide.
  - **Indications:** Safe (and highly recommended) in both pregnancy and immunocompromised patients.
- **Hepatitis B Vaccine:**
  - Standard series for healthcare workers: 3 doses (0, 1, and 6 months). Check HBsAb titer 1–2 months after the *last* dose.
  - Indirectly **protective against Hepatitis D** virus (HDV requires the HBV surface antigen envelope to infect cells).
- **Influenza Vaccine (Injectable/Inactivated):**
  - Given annually. Contains 3 or 4 strains.
  - **Contraindication:** History of Guillain-Barré Syndrome (GBS) within 6 weeks of a prior influenza vaccination.

Diagnosis / Clinical Features

***Clostridium difficile* Infection**

- **Microbiology:** Gram-**positive**, spore-forming bacillus.

- **Risk Factors:** Recent broad-spectrum antibiotic use (especially clindamycin, cephalosporins, fluoroquinolones) and Proton Pump Inhibitors (PPIs).
- **Clinical Features:** Hospital-associated diarrhea, pseudomembranous colitis, and potential progression to toxic megacolon.

Rubella (German Measles)

- Patients are highly infectious *before* the appearance of the skin rash.
- **Congenital Rubella Syndrome:** A pregnant woman infected during the first month of pregnancy has a **90% probability** of fetal transmission/syndrome.

Investigations

Post-Needle Stick Baseline Testing

- If an injury occurs, immediately test the source patient and the healthcare worker for: **HIV, HCV, HBsAg, and HBsAb titer**.

***C. difficile* Diagnosis**

- Diagnosed via stool toxin assays or PCR.
- **Trap:** Diagnosis is *not* made by routine stool culture (it takes too long and does not differentiate between toxigenic and non-toxigenic strains).

Management

Needle Stick Injuries & Post-Exposure Prophylaxis (PEP)

- **Sharps Management:** Never recap a needle; if absolutely necessary, use a single-handed scoop technique. Pick up dropped needles with forceps. Sharps containers must be closed and puncture-resistant.
- **Hepatitis B (HBV):**
  - If a healthcare worker is exposed to an HBsAg-positive source and their baseline HBsAb titer is negative or low (e.g., vaccinated years ago with no booster/titer check), the next best step is **HBV Vaccine + Hepatitis B Immunoglobulin (HBIG)**.
- **HIV:**
  - If the source is HIV positive, give combination PEP (e.g., 3TC + AZT) for 1 month.
  - Recheck HIV, HCV, and HBV titers at 1, 3, and 6 months.
- **Hepatitis C (HCV):**
  - **No PEP available.** (Neither vaccine nor immunoglobulin exists).

Management of Hospital-Acquired Infections (HAIs)

- **Central Line-Associated Bloodstream Infection (CLABSI):**
  - *Pathogenesis:* Extra-luminal route (common for non-tunneled lines left < 10 days) vs. Intra-luminal route (common for tunneled lines left > 3 weeks).

    - *Prevention:* Use **maximum sterile barrier precautions** for insertion (head cap, mask, sterile gown, sterile gloves, large sterile drape).
    - *Trap:* **Avoid** prophylactic vancomycin use during insertion to prevent VRE emergence.
- **Ventilator-Associated Pneumonia (VAP):**
    - *Major Risk Factor:* Leakage of contaminated subglottic secretions around the endotracheal tube cuff.
- **_C. difficile_ Management:**
    - Stop the offending antibiotic.
    - Administer oral metronidazole (or oral vancomycin/fidaxomicin per modern guidelines).
    - **Infection Control:** Hand hygiene must be performed with **soap and water**. Alcohol-based hand rubs are ineffective against *C. difficile* spores.

Past-Paper High Yield

- **Vaccines in Immunocompromised/Pregnancy:** Be able to instantly recognize MMR, oral polio, and varicella as live vaccines that are absolutely contraindicated in immunocompromised patients and pregnant women. Injectable influenza and pneumococcal vaccines are safe.
- **The Needle-Stick Scenario:** An exposed HCW who received the HBV vaccine decades ago but currently has negative HBsAb and HBsAg requires **both** the HBV vaccine series and HBIG.
- **Hepatitis B Vaccine Fact:** Providing the HBV vaccine directly protects against Hepatitis D (a common distractor/true statement in multiple-choice questions).
- **_C. diff_ Traps: It is a Gram-positive* *(not negative) bacillus, alcohol rubs do* not* work (must use soap and water), and routine stool cultures are incorrect for diagnosis.
- **Rubella:** Pregnant women cannot take the MMR vaccine safely, and the highest risk of congenital rubella syndrome is early in the first trimester (up to 90%).

Memory Pearls

- **Needle Stick Transmission Risk Rule of 3s: HBV ~30%** (highest), **HCV ~3%**, **HIV ~0.3%** (lowest).
- **C. diff hygiene:** "Spores ignore the pour (of alcohol)" – Always use **soap and water**.
- **Standard precautions exception:** Everything is contagious **except sweat**.

Human Immunodeficiency Virus (HIV)

Core Concepts

- **Virology:** HIV is an RNA retrovirus that binds to host cells via the **CD4 receptor** and a **chemokine co-receptor (CCR5)**.
- **Transmission:** Sexual intercourse, vertical (mother-to-child), IV drug use, blood transfusions, and needle-stick injuries.
- **Needle-Stick Injury Risk:** A highly tested concept comparing occupational exposure transmission rates:

    - **Hepatitis B (HBV):** Highest risk at **30%** (if HBeAg positive).
    - **Hepatitis C (HCV):** ~3%.
    - **HIV:** Lowest risk at **0.3%**.
- **Epidemiology in Jordan:** The peak age of HIV incidence in Jordan is **25–35 years**.
- **Universal Precautions:** The most effective way for healthcare workers to prevent transmission (e.g., hand washing, avoiding needle recapping / using one-hand technique, gloves).

Diagnosis / Clinical Features

- **Acute HIV Infection:**
    - Typically occurs **2 weeks to 3 months** after exposure.
    - Presents with a **mononucleosis-like picture** (fever, fatigue, pharyngitis, lymphadenopathy, myalgia, rash). Can also cause aseptic meningitis or Guillain-Barré syndrome.
    - Characterized by **high viremia** (≈10^8 copies/mL) and being **highly infectious**.
- **CDC Classification (1993):**
    - **Category A:** Asymptomatic, acute HIV, or persistent generalized lymphadenopathy (PGL).
    - **Category B (Symptomatic):** Conditions not in A or C (e.g., oral thrush, hairy leukoplakia, VZV/shingles, bacillary angiomatosis, ITP, peripheral neuropathy).
    - **Category C (AIDS-Defining Illnesses):** Typically occurs when **CD4 < 200 cells/mL**.
- **AIDS-Defining Illnesses (High Yield):**
    - *Included:* Invasive candidiasis (esophageal), Brain Toxoplasmosis, Kaposi sarcoma, PCP (Pneumocystis pneumonia), CMV, Cryptococcosis, MAC, Lymphoma, recurrent pneumonia, Wasting syndrome.
    - *Not included:* Mononucleosis syndrome (this is a feature of acute primary HIV, not late-stage AIDS).

Investigations

- **Diagnostic Sequence & Modalities:**
    - **Viral Load (HIV PCR):** Becomes positive as early as 7–10 days. This is the test of choice to **diagnose primary/acute HIV disease** before antibodies form.
    - **4th Generation Ag/Ab Test:** Detects infection in 10–14 days.
    - **ELISA:** Becomes positive 3 weeks to 3 months after infection. *Note: ELISA can be falsely negative in severely immunocompromised patients.*
    - **Western Blot:** The classic confirmatory test for a positive ELISA.
- **CD4 Count vs. Viral Load:**
    - **CD4 Count:** Indicates the state of the immune system and determines the risk of opportunistic infections. Normal range is 430–1690 cells/mL. **It is NOT used to diagnose HIV.**
    - **Viral Load:** Measures the magnitude of viral replication, used to monitor response to therapy and diagnose acute/window-period infections.

Management

- **Antiretroviral Therapy (ART / HAART):**
  - **When to start:** Treatment must be started **immediately once the patient is diagnosed with HIV**. *Do not wait for the CD4 count to drop, viral load to rise, or opportunistic infections to appear.*
  - **Regimen Structure:** Classically involves a "cocktail" of 3 active drugs (e.g., 2 NRTIs + 1 Protease Inhibitor or Integrase Inhibitor).
  - **Aims:** Suppress viral load (to undetectable levels) and increase CD4 count.
- **Prophylaxis against Opportunistic Infections:**
  - If **CD4 < 200 cells/mL**, the patient must be given **TMP/SMX** as prophylaxis for Pneumocystis jirovecii pneumonia (PCP).
- **Opportunistic Infection Management:**
  - **VZV (Shingles):** Treat with **acyclovir**. If a patient presents with *bilateral* or multi-dermatomal shingles, strongly suspect immunosuppression and **perform an HIV test**.

Past-Paper High Yield

- **ART Initiation Trap:** You will be tested on the threshold to start ART. The answer is *always* **"Treatment is started once the patient is diagnosed with HIV."** Any answer choices suggesting waiting for CD4 <250/300, VL >50,000, or symptom onset are incorrect.
- **Diagnostic Trap:** CD4 count is a staging marker, **not** a diagnostic marker. To diagnose early/acute HIV, look for **Viral Load (PCR)**.
- **Needle-Stick Injury Statistics:** Know the exact percentages: HBV = **30%**, HCV = **3%**, HIV = **0.3%**.
- **CD4 = 150 scenario:** If an HIV patient has a CD4 of 150 cells/mL and a high viral load, the immediate priority (alongside HAART) is **TMP/SMX for PCP prophylaxis**.
- **HCV positive screening:** (Applied viral load concept): If a healthcare worker is found to be HCV antibody-positive on screening, the immediate next step is to **do an HCV viral load PCR** to differentiate active infection from cleared past infection.
- **AIDS-Defining vs. Non-Defining:** Mononucleosis syndrome is NOT an AIDS-defining illness; Toxoplasmosis, Kaposi sarcoma, and invasive candidiasis are.

Memory Pearls

- **The 3 rules of 3 for Needle Sticks:** HBV is **3**0%, HCV is **3**%, HIV is 0.**3**%.
- **Acute HIV = PCR:** If the question describes a patient with recent risky behavior + "mono-like" symptoms (fever, rash, lymphadenopathy), antibodies (ELISA) might still be negative. Viral load (PCR) is the answer.
- **CD4 < 200 = PCP Prophylaxis:** Always pair CD4 dropping below 200 with the initiation of TMP/SMX.

Nephrology

Exam Map

TOPIC	PAST-PAPER QUESTIONS	FOCUS AREA
Introduction to Nephrology	36	Urinalysis, cast interpretation, basic renal physiology
Hypertension	23	Secondary HTN screening, drug management, resistant HTN
Chronic Kidney Disease	13	Progression factors, anemia targets, when *not* to start dialysis
Sodium and Water Disorders	13	SIADH criteria, diagnostic flowcharts (U-Osm/U-Na), safe correction
Acid-Base & ABGs	14	Formula application (Winters, Delta gap), mixed disorders
Potassium Disorders	11	ECG changes, emergency management, transcellular shifts
Primary Glomerulonephritis	8	Nephritic vs. nephrotic, timelines, complement levels
Secondary Glomerulonephritis	7	Diabetic progression factors, Lupus classes, biopsy indications
Acute Kidney Injury	5	Prerenal vs. Intrinsic (ATN/AIN) differentiation via labs
Renal Replacement Therapy	5	AEIOU indications, peritonitis criteria, catheter infections

Recurring Exam Patterns & Revision Priorities

- **Master the Urinalysis:** The most fundamental exam skill. Know that standard dipsticks only detect albumin (use SSA for Bence-Jones). Immediately associate RBC casts with Glomerulonephritis, WBC casts with AIN/Pyelonephritis, and Muddy Brown casts with ATN.
- **The Acid-Base Math is Mandatory:** Do not guess mixed disorders. Always calculate the Anion Gap, use Winters Formula to check respiratory compensation, and calculate the Delta Gap for hidden triple disorders (e.g., severe vomiting + DKA/sepsis).
- **Classic "Mixed" Acid-Base Vignettes:** Salicylate toxicity (Primary Respiratory Alkalosis + HAGMA) and severe vomiting with dehydration (Primary Metabolic Alkalosis + HAGMA) are the most highly tested mixed disorders.
- **Sodium Diagnostic Flowchart:** You must use Urine Osmolality and Urine Sodium to solve hyponatremia questions. Appropriately suppressed U-Osm (<100) is Psychogenic Polydipsia. High U-Osm (>100) + High U-Na (>20) in a euvolemic patient (often on an SSRI) is SIADH.

- **Electrolyte Emergencies:** In hyperkalemia with EKG changes, the *only* correct first step is IV Calcium Gluconate. In severe symptomatic hyponatremia (e.g., seizures), the immediate step is 3% Hypertonic Saline.
- **Glomerulonephritis Differentiators:** Focus on timeline and complements. IgA Nephropathy occurs *concurrently* with an infection and has normal complements. PSGN occurs *weeks later* and has low complements.
- **Secondary Hypertension Traps:** Suspect secondary causes based on specific lab/exam pairings: Young + Hypokalemia = Hyperaldosteronism (Conn's). AKI + Raynaud's = Scleroderma Renal Crisis. Remember that high K+ alongside high BP does *not* indicate hyperaldosteronism.
- **Dialysis Initiation Traps:** An asymptomatic patient with an eGFR < 15 does *not* need immediate dialysis. Wait for absolute indications like uremic encephalopathy, pericarditis, refractory hyperkalemia, or refractory acidosis.
- **AKI Subtypes:** Rapidly differentiate prerenal AKI (BUN/Cr > 20:1, FeNa < 1%, bland sediment) from ATN (BUN/Cr < 15:1, FeNa > 2%, muddy brown casts). Remember that AIN frequently presents with fever, rash, and urinary WBCs/eosinophils after antibiotic use.
- **Diabetic Nephropathy Rules:** Microalbuminuria is the earliest and strongest predictor of progression. If a Type 1 Diabetic has heavy proteinuria but *no* diabetic retinopathy, suspect an alternative primary GN and biopsy.

Introduction to Nephrology

Core Concepts

- **Kidney Structure:** Retroperitoneal organs weighing ~150 g each. The nephron is the functional unit (~1 million per kidney), segmented into the proximal tubule, loop of Henle, distal tubule, and collecting duct.
- **Renal Circulation:** Receives 20% of cardiac output, representing the highest tissue-specific blood flow in the body (~350 mL/min/100 g).
    - Features two capillary beds in series: **Glomerular** (high pressure: 40–50 mmHg) draining into the efferent arteriole, followed by **Peritubular** (low pressure: 5–10 mmHg).
    - **Afferent arteriole:** Constricted by NSAIDs (can cause pre-renal AKI).
    - **Efferent arteriole:** Dilated by ACE inhibitors (mechanism by which ACEi decreases intraglomerular pressure).
- **Diuretic Sites of Action:** Thiazide diuretics act on the **distal tubule**.
- **Endocrine Functions:**
    - **Renin:** Produced by granular cells of the juxtaglomerular apparatus.
    - **Erythropoietin (EPO):** Produced by renal cortical interstitial cells.
    - **1-alpha-hydroxylase:** Located in proximal tubule cells; converts inactive Vitamin D to active 1,25-Dihydroxyvitamin D3. *(Note: Renal failure causes hypocalcemia primarily due to decreased hydroxylation of Vitamin D)*.

Diagnosis / Clinical Features

- **Glomerular Filtration Rate (GFR):** Normal is ~130 mL/min (males) and ~120 mL/min (females). Estimated clinically using endogenous creatinine via Cockcroft-Gault, MDRD, or CKD-EPI equations.
- **Hematuria:** Defined as ≥ 5 RBCs/hpf in 3 consecutive centrifuged specimens, at least 1 week apart.
  - **Glomerular Hematuria:** Characterized by dysmorphic RBCs and RBC casts.
  - **Non-Glomerular Hematuria:** Characterized by monomorphic RBCs.
- **Proteinuria Definitions:**
  - **Normal total protein:** < 150 mg/day (Albumin < 30 mg/day).
  - **Moderately increased albuminuria (Microalbuminuria):** 30–300 mg/day.
  - **Severely increased albuminuria (Macroalbuminuria):** > 300 mg/day. This is the threshold at which the standard urine dipstick becomes positive.
- **Hypertension Screening:** Isolated elevated office blood pressure readings (e.g., 150/95) in an asymptomatic patient should be confirmed with **Ambulatory BP monitoring** before initiating therapy.

Investigations

- **Urinalysis (Dipstick vs. SSA):**
  - **Standard dipstick:** Primarily detects albumin.
  - **Sulfosalicylic Acid (SSA) test:** Detects *all* proteins in the urine. Crucial for identifying Bence-Jones proteins in Multiple Myeloma when dipstick is negative or disproportionately low.
  - **False-positive dipstick blood:** A dipstick positive for heme with *no RBCs* on microscopy indicates either myoglobinuria (e.g., rhabdomyolysis post-crush injury) or hemoglobinuria (e.g., hemolysis from a mechanical heart valve).
- **Urine Microscopy (Casts & Crystals):**
  - **RBC casts:** Glomerulonephritis (e.g., PSGN, IgA nephropathy).
  - **WBC casts:** Acute pyelonephritis (diagnostic differentiator from lower UTI/cystitis).
  - **Muddy brown casts:** Acute Tubular Necrosis (ATN).
  - **Struvite crystals (Magnesium ammonium phosphate):** Form in alkaline urine (pH > 7.0) due to urease-positive organisms like *Proteus vulgaris*.
- **Spot Urine Protein-to-Creatinine Ratio (UPCR):** Estimates 24-hour proteinuria in grams by dividing urine protein (mg/dL) by urine creatinine (mg/dL).
- **Renal Imaging:**
  - **Unenhanced CT:** The gold standard test with the highest sensitivity for detecting renal stones (fine calcifications).
  - **Renal Ultrasound:** Evaluates size, cortical thickness, cysts, hydronephrosis, and identifies stones > 3–5 mm.
  - **Contrast-enhanced multiphase CT:** Optimal for evaluating kidney masses.

Management

- **Asymptomatic Bacteriuria:** Observation is the best next step. Do not treat with antibiotics, even in elderly or diabetic patients.
- **Acute Pyelonephritis:** Loin pain, fever, and WBC casts require a urine culture and initiation of empiric antibiotics.
- **Painless Hematuria in the Elderly:** Suspect urological malignancy; best next step is renal imaging combined with cystoscopy.
- **Severe Symptomatic Hyponatremia:** (e.g., SIADH secondary to small cell lung cancer presenting with confusion/lethargy) requires treatment with **Hypertonic saline (3%)**.
- **Beta-Blocker Toxicity Exacerbated by AKI:** Profound bradycardia and hypotension in an oliguric patient on beta-blockers is managed with **Intravenous glucagon**.

Past-Paper High Yield

- **Nephritic Syndromes:**
  - **Post-Streptococcal GN (PSGN):** Young patient, edema, high blood pressure, RBC casts, and **low C3**.
  - **IgA Nephropathy:** Young patient presenting with dark urine concurrently or immediately following a viral URI ("tired for 5 days then dark urine"); biopsy shows **IgA deposits in glomerular capillaries**.
  - **IgA Vasculitis (Henoch-Schönlein Purpura):** Classic triad of colicky abdominal pain, palpable purpura on legs, and hematuria.
- **Nephrotic Syndromes:**
  - **Minimal Change Disease (MCD):** Highly tested association with **Hodgkin Lymphoma**.
  - **Diabetic Nephropathy:** Biopsy characteristically shows **Kimmelstiel-Wilson nodules**.
  - **Amyloidosis: AA amyloid** is driven by chronic inflammatory states (e.g., Rheumatoid arthritis); **AL amyloid** is linked to Multiple Myeloma.
- **Acute Kidney Injury (AKI) Subtypes:**
  - **Acute Tubular Necrosis (ATN):** Classic presentation is post-surgical oliguria and elevated BUN/Cr followed by a return to normal urination.
  - **Acute Interstitial Nephritis (AIN):** Patient developing fever, rash, elevated Cr, and urinary WBCs/eosinophils 1–3 weeks after starting antibiotics (e.g., cephalosporins, amoxicillin).
  - **Cholesterol Embolization:** AKI developing after a cardiac catheterization, accompanied by **livedo reticularis**. (Distinguishes it from contrast-induced nephropathy).
  - **Hemolytic Uremic Syndrome (HUS):** Hemorrhagic diarrhea (E. coli) followed by AKI, thrombocytopenia, and hemolytic anemia. The best next step to confirm is a **blood film** to visualize schistocytes.
- **Multiple Myeloma (MM) Nephropathy:**
  - Suspect in an older adult with back pain, anemia, hypercalcemia, an elevated UPCR, but only 1+ protein on dipstick. Next best step is **Serum Protein Electrophoresis (SPEP)**.

- Renal damage mechanisms include hypercalcemia, hyperuricemia (tumor lysis), and Bence-Jones cast nephropathy. *Recurrent infections due to decreased immunity do NOT cause direct tubulointerstitial damage.*

- **Renal Stones: Hypercitraturia** is a protective factor against stone formation, NOT a risk factor.
- **Orthostatic Proteinuria:** Young patient with proteinuria during daytime activity but a normal early morning UPCR. The correct action is to reassure the patient.
- **Diabetes Insipidus (DI):** Polydipsia, polyuria, and low urine osmolarity without a family history of renal disease. Next step in evaluation is a **water deprivation test**.
- **ADPKD:** Strongly associated with the development of **cerebral (berry) aneurysms**.

Memory Pearls

- **Dipstick vs. SSA:** Dipstick detects *Albumin*; SSA detects *All* proteins (key for Bence-Jones).
- **Heme (+) but 0 RBCs:** Think Myoglobinuria (crush injury/rhabdo) or Hemoglobinuria (mechanical valve hemolysis).
- **Casts point to the location:**
  - RBCs = Glomerulus
  - WBCs = Tubulointerstitium / Pyelonephritis
  - Muddy Brown = Tubules (ATN)
- **Vascular Pharmacology:** NSAIDs constrict the **A**fferent arteriole; **A**CE inhibitors dilate the **E**fferent arteriole.

Hypertension

Core Concepts

- **Blood Pressure (BP) Physiology:** BP = Cardiac Output (CO) × Systemic Vascular Resistance (SVR).
- **Pulse Pressure (PP):** SBP - DBP. It is a surrogate marker for stiffness in large conduit arteries (e.g., thoracic aorta) and is a better independent marker of cardiovascular risk in older patients than SBP or DBP alone.
- **Cardiovascular Risk Scaling:** The risk of cardiovascular mortality **doubles** with each 20/10 mmHg increase in BP, starting from a baseline of 115/75 mmHg.
- **Primary vs. Secondary HTN:** Primary (essential) HTN accounts for 90-95% of cases and is associated with salt sensitivity and RAAS activity.
- **Resistant Hypertension:** Defined as uncontrolled BP despite the concurrent use of 3 antihypertensive agents of different classes (must include a diuretic) at optimal doses, or BP that requires ≥4 drugs to be controlled.

Diagnosis / Clinical Features

- **Classification (ACC/AHA 2017):**
  - **Normal:** < 120 / < 80 mmHg

    - **Elevated:** 120-129 / < 80 mmHg
    - **Stage 1:** 130-139 / 80-89 mmHg
    - **Stage 2:** ≥ 140 / ≥ 90 mmHg
- **Diagnostic Modalities:**
    - **In-office:** Requires 2 readings, 5 minutes apart.
    - **Ambulatory BP Monitoring (ABPM):** The gold standard for evaluating "white-coat" and "masked" hypertension. Provides prognostic data via nocturnal dipping (an absence of the normal 10-20% nocturnal BP dip indicates a higher cardiovascular risk).
- **Masked Hypertension:** Normal office BP but elevated out-of-office BP. It does *not* have a good prognosis; its cardiovascular risk is similar to that of sustained hypertension.
- **Hypertensive Crises:**
    - **Hypertensive Emergency:** Severe BP elevation (often >180/120) **with** acute target organ damage (e.g., papilledema, acute kidney injury, encephalopathy). Requires immediate IV therapy (e.g., Nitroprusside).
    - **Hypertensive Urgency:** Severe BP elevation **without** acute target organ damage.

Investigations

- **Screening for Secondary Hypertension (Case-based Triggers):**
    - **Primary Hyperaldosteronism (Conn's):** Suspect in young patients with HTN, unexplained hypokalemia (e.g., K+ 3.0), and metabolic alkalosis. **Next best step:** Measure plasma aldosterone-to-renin ratio (ARR).
    - **Liddle Syndrome:** Presents identically to hyperaldosteronism (severe HTN, hypokalemia, metabolic alkalosis) but with **low** plasma renin activity (PRA) and **low** aldosterone.
    - **Autosomal Dominant Polycystic Kidney Disease (ADPKD):** Suspect in patients with HTN, CKD, enlarged cystic kidneys, and a family history of fatal intracranial hemorrhage (ruptured berry aneurysms).
    - **Von Hippel-Lindau (VHL) Disease:** Suspect in patients with HTN, microscopic hematuria, renal cysts/solid lesions (Clear Cell RCC), and a family history of early brain tumors (hemangioblastomas) or unilateral deafness (endolymphatic sac tumors).
    - **Scleroderma Renal Crisis:** Presents as malignant hypertension in a patient with Raynaud's phenomenon and skin thickening. Labs will uniquely show microangiopathic hemolytic anemia (schistocytes, thrombocytopenia) and severe AKI.
    - **Multiple Myeloma (Cast Nephropathy):** Can present with HTN, bone aches, severe fatigue, new-onset frothy urine, hypercalcemia, and AKI. **Key finding:** Urinalysis shows trace/1+ protein on dipstick (which only detects albumin), but 24-hour urine collection shows massive proteinuria (Bence Jones light chains).

Management

- **Non-Pharmacologic:**
    - Weight loss (highly effective).
    - **DASH Diet:** Rich in fruits, vegetables, and low-fat dairy; restricts sodium to < 2.4 g/day.

- Aerobic exercise, moderate alcohol intake, and smoking cessation.

- **Pharmacologic Therapy:**
  - Most hypertensive patients require combination therapy. If BP is confirmed at Stage 2 (e.g., 165/105 mmHg), the best initial step is starting two agents (e.g., Amlodipine + ARB/ACEi).
  - **Resistant Hypertension:** If a patient is uncontrolled on a Thiazide, Beta-blocker, and ACEi/ARB, the next best step is to add a **Mineralocorticoid Receptor Antagonist (MRA)** like Spironolactone. Do *not* stop current effective therapies (like Amlodipine) just because BP is still high.
- **Managing HTN with Hyperkalemia (Exam Scenarios):**
  - *Well-controlled BP (e.g., 134/84) + K+ 5.2 on ACEi/Diuretic/BB:* **No change in medications is required.** Mild hyperkalemia is acceptable if asymptomatic and stable.
  - *Uncontrolled BP (e.g., 145/90) + K+ 5.2 to 5.5 on ACEi/CCB/BB:* **Start a thiazide diuretic (e.g., Hydrochlorothiazide).** This synergistically lowers BP while promoting potassium excretion.
  - *Liddle Syndrome Treatment:* Because the defect is an overactive ENaC channel in the collecting duct, the definitive treatment is **Amiloride**.

Complications / Prognosis

- **Target Organ Damage:**
  - Heart: Left ventricular hypertrophy, heart failure (lowering BP reduces HF incidence by 50%).
  - Brain: Cerebrovascular disease (lowering BP reduces stroke incidence by 35-40%).
  - Kidneys: Hypertensive nephrosclerosis, progressive CKD.
  - Eyes: Retinal damage, papilledema (hallmark of emergency).

Past-Paper High Yield

- **The "High BP + K+ Trap":** You do *not* need to screen for hyperaldosteronism in a patient with uncontrolled HTN who has a high-normal K+ (e.g., 5.2). Aldosterone excess causes *hypo*kalemia.
- **Calcineurin Inhibitors (Tacrolimus/Cyclosporine):** Know their specific renal side effects. They cause **Hypertension**, **Hyperkalemia**, and **Hypomagnesemia**. (They do *not* cause hyperphosphatemia).
- **Diabetic Nephropathy & HTN Timeline:** In Type 1 DM, the onset of hypertension typically coincides with the onset of microalbuminuria (which must be confirmed with a second reading). In Type 2 DM, hypertension is frequently present at the time of diagnosis.
- **Nephritic Syndrome as Secondary HTN:** A young patient with sudden onset edema, HTN, and AKI (e.g., Cr 2.6) without dysuria is classic for glomerulonephritis. The diagnostic urinalysis will show **dysmorphic RBCs and RBC casts**.
- **Causes of CKD with Enlarged Kidneys:** CKD typically causes small, shrunken kidneys. If a question describes a patient with CKD and *enlarged* kidneys, think of **Amyloidosis**, **Polycystic Kidney Disease**, early Diabetic Nephropathy, or HIV-associated nephropathy.
- **Non-compliance:** In a patient on an extensive polypharmacy regimen (e.g., 9 different drugs) presenting with significantly uncontrolled BP and a relatively normal BMI, **non-compliance with the drug regimen** is overwhelmingly the most likely cause.

Memory Pearls

- **Double Trouble:** CV mortality risk *doubles* with every **20/10 mmHg** increase above 115/75.
- **Resistant HTN Step 4:** Always think **Spironolactone** (or Amiloride if Liddle's).
- **Secondary HTN Rapid Associations:**
  - *Young + Hypokalemia* ➔ Hyperaldosteronism (Conn's)
  - *SAH / Berry Aneurysm Family History* ➔ ADPKD
  - *Schistocytes + Raynaud's* ➔ Scleroderma Renal Crisis
  - *Brain tumor + Unilateral Deafness* ➔ VHL Disease
  - *Bone pain + Frothy urine + High Calcium* ➔ Multiple Myeloma

Acid-Base Disorders

Core Concepts

- **Normal Values**: Neutral plasma pH is 7.40 (range 7.36–7.44). A pH of 7.0 is functionally neutral for water but fatal in humans.
- **Intracellular pH**: Tightly maintained at ~6.8 (neutrality at 37°C) to keep metabolite intermediates charged and trapped inside the cell.
- **Hydrogen Ion Concentration [H+]**: pH 7.40 = 40 nM. An increase in [H+] by a factor of 2 causes a decrease in pH of 0.3 (e.g., pH 7.10 = 80 nM).
- **Modified Henderson Equation**: $[H^+] = 24 \times (PaCO_2 / HCO_3^-)$
- **Buffer Systems**:
  - *Extracellular*: Carbonic acid/bicarbonate (primary), Haemoglobin (main buffer for CO2).
  - *Intracellular*: Proteins, Phosphates.
  - *Bone*: Exchanges Ca^{2+}, Na^+, and K^+ for H^+ (chronic buffering).
- **Renal Regulation**:
  - *Proximal Tubule*: Reabsorbs filtered $HCO3^-$ (facilitated by carbonic anhydrase) and produces $NH4^+$ (from glutamine metabolism), which generates *new* $HCO3^-$.
  - *Distal Tubule*: Intercalated cells secrete H^+ via H^+/Cl^- cotransport. Accounts for only 5% of secreted H^+ but creates a massive gradient (up to 900x), dropping urine pH to 4.5.

Diagnosis / Clinical Features

- **Respiratory Acidosis** (Primary ↑ PaCO2 > 40 mmHg):
  - *Causes*: CNS depression (opiates, tumors), neuromuscular (Guillain-Barré, Myasthenia Gravis, organophosphates), airway/lung disease (severe asthma, COPD, pulmonary edema), increased CO2 production (malignant hyperthermia, sepsis).
- **Respiratory Alkalosis** (Primary ↓ PaCO2 < 35 mmHg):
  - *Causes*: Central respiratory stimulation (tumors, salicylates), hypoxia (high altitude, pneumonia), sepsis, liver cirrhosis.
- **Metabolic Acidosis** (Primary ↓ $HCO3^-$):

- *High Anion Gap (HAGMA)*: Due to addition of fixed acids.
- *Normal Anion Gap (NAGMA)*: Due to GI $HCO3^-$ loss (diarrhea, fistulas) or renal $HCO3^-$ loss (Type I, II, or IV Renal Tubular Acidosis).

- **Metabolic Alkalosis** (Primary ↑ $HCO3^-$):
  - *Volume-Depleted*: Gastric acid loss (vomiting, NGT suction), renal chloride loss (diuretics), post-hypercapnia.
  - *Volume-Replete*: Hyperaldosteronism, Cushing's syndrome, Bartter's syndrome, Liddle syndrome, licorice excess, profound potassium depletion.

Investigations

To reliably diagnose simple and mixed disorders, apply this stepwise approach to ABGs:

1. **Identify the Primary Disorder**: Look at pH to determine acidemia (< 7.36) vs. alkalemia (> 7.44). Match it with the directional change of PaCO2 and $HCO3^-$.
2. **Calculate the Anion Gap (AG)**: AG = $Na^+ - (Cl^- + HCO_3^-)$. Normal is ~12.
   - *Albumin correction*: The normal AG expected for a patient drops by 2.5 mEq/L for every 1 g/dL decrease in serum albumin.
3. **Check Respiratory Compensation** (for Metabolic Acidosis):
   - *Winters Formula*: Expected PaCO2 = $(1.5 \times HCO_3^-) + 8$ (±2).
   - If measured PaCO2 > expected = Concomitant **Respiratory Acidosis**.
   - If measured PaCO2 < expected = Concomitant **Respiratory Alkalosis**.
4. **Calculate the Delta Gap** (if HAGMA is present):
   - Delta Gap = Patient's AG – 12
   - Corrected HCO_3^- = Measured HCO_3^- + Delta Gap
   - If Corrected $HCO3^-$ > 26 mEq/L ➔ Concomitant **Metabolic Alkalosis**.
   - If Corrected $HCO3^-$ < 22 mEq/L ➔ Concomitant **NAGMA**.

Complications / Prognosis

- **Effects of Acidosis**:
  - *Cardiovascular*: Impaired cardiac contractility, venoconstriction (centralization of blood volume), arteriolar dilation, decreased BP, increased risk of arrhythmias, reduced response to catecholamines.
  - *Metabolic*: Insulin resistance, hyperkalemia, inhibition of anaerobic glycolysis.
  - *Oxygen Delivery*: Shift of the oxyhemoglobin dissociation curve to the right (facilitates O2 unloading), but simultaneously decreases RBC 2,3-DPG (shifting the curve back left).
- **Effects of Alkalosis**:
  - *Cardiovascular*: Arteriolar constriction, reduced coronary blood flow (decreased anginal threshold).
  - *Metabolic/Electrolytes*: Hypokalemia, hypomagnesemia, hypophosphatemia, and **decreased ionized calcium** (can cause tetany/seizures).

- *Oxygen Delivery*: Left shift of the oxyhemoglobin dissociation curve (impairs O2 unloading to tissues).

Past-Paper High Yield

- **Severe Vomiting + Shock/Dehydration**: A massive exam favorite. Severe vomiting (loss of HCl) causes a primary Metabolic Alkalosis, but concurrent prolonged starvation/hypoperfusion causes a lactic/ketoacidosis (HAGMA).
  - *Trap*: Do not just pick NAGMA or simple Metabolic Alkalosis.
  - *Action*: Calculate the AG (it will be wide) and the Delta Gap (Corrected $HCO3^-$ will be elevated). Diagnosis = **HAGMA + Metabolic Alkalosis**.
- **Aspirin (Salicylate) Toxicity**: Directly stimulates the respiratory center and uncouples oxidative phosphorylation.
  - *Diagnosis*: **HAGMA + Primary Respiratory Alkalosis**.
  - *Clue*: The PaCO2 will be significantly *lower* than the expected Winters formula calculation.
- **DKA with Respiratory Fatigue**: A patient with DKA typically has HAGMA and compensatory Kussmaul respirations. If the patient is obtunded or fatigued, the PaCO2 will rise above the expected low level.
  - *Diagnosis*: **HAGMA + Respiratory Acidosis**. ALWAYS manually calculate the expected PaCO2—do not rely solely on the clinical description of "hyperventilation."
- **The "Triple Disorder" (DKA + Vomiting + Sepsis/Pain)**:
  - You will see an extreme gap (e.g., AG = 24 ➔ HAGMA).
  - Delta gap correction will reveal a hidden elevated $HCO3^-$ (e.g., >30 ➔ Metabolic Alkalosis).
  - PaCO2 will be profoundly low (e.g., 10 mmHg), far below the expected Winters compensation ➔ Primary Respiratory Alkalosis.
  - *Diagnosis*: **HAGMA + Metabolic Alkalosis + Respiratory Alkalosis**.
- **Post-Hypercapnic Metabolic Alkalosis**: A classic presentation involves a patient with severe COPD (chronic respiratory acidosis with renal retention of $HCO3^-$) who is intubated and mechanically ventilated. The ventilator rapidly blows off the CO2, normalizing the PaCO2, but the kidneys take 3-4 days to excrete the retained $HCO3^-$, leaving the patient temporarily highly alkalemic.
- **Liddle Syndrome**: Differentiate from primary hyperaldosteronism. A patient presents with hypertension, hypokalemia, and metabolic alkalosis, but lab tests reveal **low aldosterone levels** (due to a constitutively active ENaC channel mimicking aldosterone).

Memory Pearls

- **Bicarbonate System Limitations**: The bicarbonate buffer system *cannot* buffer a respiratory acid-base disorder (it cannot buffer itself). Acute respiratory acidosis is buffered 99% intracellularly (hemoglobin and phosphates).
- **Delta Gap Rule of Thumb**: For every 1 unit rise in the Anion Gap, the $HCO3^-$ should fall by exactly 1 unit. If the $HCO3^-$ hasn't fallen as much as expected, a metabolic alkalosis is holding it up.

Sodium and Water Disorders

Core Concepts

- **Two Separate Regulatory Systems:**
  - **Tonicity (Water) Disorders:** Regulated by osmoreceptors controlling ADH release and thirst. Affects serum sodium concentration.
  - **Volume (Sodium) Disorders:** Regulated by low- and high-pressure baroreceptors controlling the Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic tone.
- **Osmolality Calculations:**
  - **Calculated Serum Osmolality** = 2(Na) + Urea + Glucose (Normally 280–290 mOsm/kg).
  - **Osmolar Gap** = Measured Osmolality – Calculated Osmolality. Normal is -14 to +10.
- **Sodium Classification:**
  - Hypernatremia & Hyponatremia: Normal limits 135–145 mEq/L.
  - Acute vs. Chronic: The critical cutoff is **48 hours**. This dictates the risk of cerebral edema (acute) vs. osmotic demyelination syndrome (chronic).
- **Fluid Compartment Shifts:**
  - **Isotonic changes:** Only extracellular fluid (ECF) changes (e.g., hemorrhage, diarrhea, isotonic fluid replacement). No intracellular fluid (ICF) shifts.
  - **Hypertonic changes:** Water leaves cells (ECF & ICF disorder).
  - **Hypotonic changes:** Water enters cells causing swelling (increased intracranial pressure).

Diagnosis / Clinical Features

- **Hyponatremia:**
  - Symptoms largely CNS-driven due to cerebral edema.
  - *Acute/Severe:* Lethargy, headache, confusion, stupor, grand mal seizures, coma, respiratory arrest.
  - *Chronic:* Often asymptomatic due to brain adaptation (loss of CNS osmolytes), but can present with unsteadiness, falls, or subtle cognitive deficits.
- **Hypernatremia:**
  - Reflects a state of pure water loss or unreplaced water deficit.
  - *Symptoms:* Intense thirst, lethargy, irritability, spasticity, confusion, fever, labored respiration.

Investigations

- **Diagnostic Algorithm for Hyponatremia:**
  1. **Check Serum Osmolality:**
     - *Normal (Isotonic):* Pseudohyponatremia (hyperlipidemia, hyperproteinemia).
     - *High (Hypertonic):* Translocational hyponatremia (hyperglycemia, mannitol).
     - *Low (Hypotonic):* True hyponatremia. Proceed to step 2.

2. **Check Urine Osmolality (U-Osm):**
    - *U-Osm < 100 mOsm/kg:* Primary (psychogenic) polydipsia or beer potomania. ADH is appropriately suppressed.
    - *U-Osm > 100 mOsm/kg:* ADH is active. Proceed to step 3.
3. **Check Volume Status & Urine Na (U-Na):**
    - *Hypovolemic:* U-Na < 20 (extrarenal loss like GI/sweat) or U-Na > 20 (renal loss like diuretics).
    - *Hypervolemic:* U-Na < 20 (CHF, cirrhosis, nephrotic) or U-Na > 20 (renal failure).
    - *Euvolemic:* U-Na > 20 (SIADH, hypothyroidism, adrenal insufficiency).

- **Criteria for SIADH Diagnosis:**
    - Hyposmolar hyponatremia with euvolemia.
    - Urine osmolality > 100 mOsm/kg (urine is *not* maximally diluted).
    - Urine sodium > 20 mEq/L (often > 40 mEq/L).
    - Low serum uric acid.
    - **Exclusion criteria:** Must have normal renal, cardiac, hepatic, thyroid, and adrenal function. Must lack recent diuretic use or severe physiological stress.
- **Water Deprivation Test (for Polyuria/Hypernatremia):**

DIAGNOSIS	BASELINE U-OSM	POST-DEPRIVATION PLASMA ADH	U-OSM AFTER EXOGENOUS ADH
Normal	> 800	> 2 pg/mL	Little or no change
Central DI (Complete)	< 300	Undetectable	**Great increase (>50%)**
Central DI (Partial)	300–800	< 1.5 pg/mL	> 10% increase
Nephrogenic DI	< 300–800	> 5 pg/mL (High)	**Little or no change**
Primary Polydipsia	> 500	< 5 pg/mL (Low)	Little or no change

Management

- **Severe / Symptomatic Hyponatremia (e.g., seizures, severe confusion, Na <120):**
    - **Treatment of choice:** Hypertonic (3%) Saline. (Typically infused at 30-40 mL/hr or via bolus protocols to stop seizures).
- **Euvolemic / Hypervolemic Hyponatremia (e.g., SIADH):**
    - Fluid restriction is first-line for asymptomatic cases.
    - **Vaprisol (Conivaptan):** Vasopressin (V1A/V2) receptor antagonist. Indicated for euvolemic and hypervolemic hyponatremia in hospitalized patients to induce *aquaresis* (solute-free water excretion).
- **Hypernatremia:**
    - Goal is slow correction over 48 hours to prevent cerebral edema.
    - Calculate water deficit: H_2O Deficit = 0.6 × Weight(kg) × (Plasma Na/140 – 1).

- Replace continuous losses and treat the underlying cause.

Complications / Prognosis

- **Osmotic Demyelination Syndrome (ODS):** Overly rapid correction of chronic hyponatremia leads to massive fluid shifts out of brain cells, causing demyelination (historically Central Pontine Myelinolysis).
- **Cerebral Edema:** Overly rapid correction of hypernatremia (or uncorrected acute hyponatremia).

Past-Paper High Yield

- **SSRI-Induced SIADH:** A highly tested clinical vignette features an older adult or psychiatric patient started on an SSRI (e.g., sertraline, fluoxetine) ~1 month ago presenting with falls/confusion.
  - *Expected Labs:* Hyponatremia, low plasma osmolality (< 275), high urine osmolality (> 100, often 300–400+), and high urine Na (> 20).
- **Primary (Psychogenic) Polydipsia Trap:** A patient with psychiatric history (e.g., bipolar, anxiety) presents with hyponatremia. Look at the urine osmolality. If U-Osm is appropriately suppressed (e.g., **60 mOsm/L** with U-Na of 8), the diagnosis is psychogenic polydipsia. If U-Osm is inappropriately high (>100), it's SIADH.
- **Surreptitious Vomiting:** Suspect in a young female with weakness, hypotension, hypokalemia (e.g., K 2.1), and metabolic alkalosis (HCO3 46). **Key differentiator:** Urine Chloride is **< 10 mEq/L** (unlike diuretic abuse or Gitelman/Bartter syndromes where urine Cl is high).
- **Seizures in Hyponatremia:** Any patient presenting with profound hyponatremia (e.g., Na 110–118) and grand mal seizures or profound neurologic compromise requires immediate **3% saline**; do not restrict fluids or use demeclocycline/conivaptan as first-line in an emergency.
- **Appropriate ADH Response in Hypovolemia:** In a volume-depleted patient (e.g., returning from a marathon), ADH is strongly stimulated to retain water. Therefore, finding a dilute urine (U-Osm < 300) is highly **unlikely** and indicates a renal concentrating defect.
- **Positive Pressure Ventilation (Intubation):** Mechanical ventilation increases intrathoracic pressure, decreases venous return, and can falsely trigger baroreceptors to release ADH, leading to SIADH in euvolemic, intubated patients.
- **Diuretics & Sodium:**
  - **Thiazides** are the *most common* diuretic cause of hyponatremia (they block NaCl reabsorption in the DCT but leave the medullary concentrating gradient intact, allowing ADH to inappropriately retain pure water).
  - **Loop diuretics** (furosemide) wash out the medullary gradient, impairing ADH action, and are *less likely* to cause severe hyponatremia.
- **Lithium:** Causes Nephrogenic Diabetes Insipidus leading to *hypernatremia*, **not** hyponatremia.
- **Bartter Syndrome:** Presents with dehydration, hyponatremia, hypokalemia, metabolic alkalosis, and uniquely **elevated urine calcium**.

Memory Pearls

- **Urine Osmolality dictates the ADH state:** < 100 = ADH is off (Polydipsia). > 100 = ADH is on (SIADH, hypovolemia).
- **Urine Chloride in Alkalosis:** Low (<10) = Vomiting. High (>20) = Diuretics / Bartter / Gitelman.
- **Drugs & Sodium:** **S**SRIs = **S**IADH (HypoNa). **L**ithium = **L**oss of water (HyperNa via NDI).
- **Pseudohyponatremia:** Think "excess solids" (hyperlipidemia, hyperproteinemia) causing an artifactual drop in measured sodium despite normal measured serum osmolality.

Potassium Disorders

Core Concepts

- **Total Body Potassium (K+) Distribution:**
  - Predominantly intracellular (ICF): Muscle (~2500 mEq), Bone (~500 mEq), Liver (~250 mEq), RBCs (~250 mEq).
  - Extracellular fluid (ECF) contains only a small fraction (~65 mEq).
- **Transcellular Shifts (ECF/ICF Redistribution):**
  - **Hormones:** Insulin and Beta-adrenergic stimulation drive K+ *into* cells.
  - **Acid-Base Status:**
    - Metabolic Acidosis forces K+ *out* of cells (H+ enters cells to be buffered, K+ exits to maintain electroneutrality).
    - Metabolic Alkalosis drives K+ *into* cells.
  - **Plasma Tonicity:** Hyperosmolality drives K+ *out* of cells (solvent drag).
- **Renal Handling:**
  - **Proximal Tubule:** Reabsorbs 60–70% of filtered K+.
  - **Ascending Loop of Henle:** Reabsorbs 20–30%.
  - **Distal Tubule (Fine-Tuning):** Aldosterone acts on principal cells to reabsorb Na+ in exchange for secreting K+ or H+.
  - **Factors Favoring Renal K+ Secretion:** Increased distal Na+ delivery, increased fluid flow (washout effect from diuretics), elevated aldosterone, and decreased H+ secretion.
- **Cortisol vs. Aldosterone:** Cortisol binds mineralocorticoid receptors with equal avidity to aldosterone but is normally converted to inactive cortisone by 11β-hydroxysteroid dehydrogenase. If this enzyme is impaired (e.g., real licorice ingestion, Syndrome of Apparent Mineralocorticoid Excess) or if cortisol is massively overproduced (Cushing's), severe hypokalemia occurs.

Diagnosis / Clinical Features

Hypokalemia (K+ < 3.5 mmol/L)

- **Neuromuscular:** Skeletal muscle weakness, paralysis, diminished deep tendon reflexes.
- **Gastrointestinal:** Paralytic ileus.

- **Cardiac:** Arrhythmias, conduction defects, enhanced digoxin toxicity. EKG shows U waves, T wave flattening, ST depression.
- **Renal:** Impaired concentrating ability (nephrogenic diabetes insipidus).
- **Familial Periodic Paralysis:** Autosomal dominant (onset < 30 years) or acquired (thyrotoxicosis in Asian men). Sudden K+ shift into cells. Precipitated by rest post-exercise, high-carbohydrate meals, stress, cold, or insulin/epinephrine administration.

Hyperkalemia (K+ > 5.0 mmol/L)

- **Neuromuscular:** Weakness, paresthesia, paralysis.
- **Gastrointestinal:** Nausea, vomiting, abdominal pain, ileus.
- **Cardiac (Medical Emergency):** Conduction defects, arrhythmias, cardiac arrest. Toxicity is enhanced by hypocalcemia, acidemia, and hypomagnesemia.
- **EKG Progression:** Peaked (hyperacute) T waves → PR prolongation → QRS widening → Sine wave.

Investigations

Hypokalemia Diagnostic Algorithm

1. **Assess Urine K+:**
    - **< 15 mEq/L (Spot) or < 25 mEq/day:** GI losses (diarrhea), poor intake, or transcellular shift.
    - **> 25–30 mEq/day:** Renal losses.
2. **Assess Acid-Base Status:**
    - **Metabolic Alkalosis:** Vomiting, Diuretics, Bartter's, Gitelman's, Hyperaldosteronism.
    - **Metabolic Acidosis (Normal Anion Gap):** Renal Tubular Acidosis (Types 1 or 2), severe diarrhea.
3. **Evaluate Blood Pressure (if Renal Loss + Alkalosis):**
    - **Hypertensive:** Check Renin/Aldo.
        - *High Renin/High Aldo:* Renovascular HTN, malignant HTN, reninoma.
        - *Low Renin/High Aldo:* Primary Hyperaldosteronism (Conn's).
        - *Low Renin/Low Aldo:* Cushing's, Liddle's, Licorice, SAME.
    - **Normotensive:** Diuretic abuse, Bartter's, Gitelman's, Vomiting (loss occurs in urine due to volume-depletion-triggered aldosterone release).

Hyperkalemia Diagnostic Algorithm

1. **Rule out Pseudohyperkalemia:** Hemolysis during phlebotomy, prolonged tourniquet use/fist clenching, marked leukocytosis/thrombocytosis.
2. **Determine Underlying Mechanism:**
    - **Shift from ICF to ECF:** Metabolic acidosis (non-organic), tissue catabolism (tumor lysis syndrome, crush injury/trauma), insulin deficiency, beta-blockade, digoxin overdose.
    - **Decreased Excretion:** Renal failure (most common), hypoaldosteronism (Addison's, Type 4 RTA), drugs (K-sparing diuretics, ACEi/ARBs, NSAIDs, Cyclosporine, Heparin).

Management

Hypokalemia

- **Oral Repletion:** Preferred route unless severe complications are present.
- **IV Repletion:** Maximum administration rate is **10 mmol/hr** peripherally to prevent cardiac toxicity/phlebitis.
- **Deficit Estimation:**
  - Drop from 4.0 to 3.0 mmol/L ≈ 300 mmol deficit.
  - Drop from 4.0 to 2.0 mmol/L ≈ 600 mmol deficit.

Acute Hyperkalemia

1. **Stabilize Myocardium (First Step if EKG changes):** IV Calcium Gluconate.
2. **Shift K+ into Cells:** IV Insulin with D50 (glucose), High-dose Albuterol, NaHCO3 (if acidotic).
3. **Remove K+ from Body:** Loop diuretics, GI cation exchangers (Kayexalate).
4. **Dialysis:** Absolute indication if K+ > 7.0 mmol/L with acute renal failure or severe refractory hyperkalemia.

Past-Paper High Yield

- **Vomiting vs. Diarrhea Mechanisms:**
  - *Vomiting:* Presents with alkalosis (high bicarb), low chloride, and hypokalemia. **Trap:** The mechanism of hypokalemia is *not* primarily direct loss in vomitus, but rather **loss of potassium in the urine** (volume depletion activates RAAS, trading K+ and H+ for Na+).
  - *Diarrhea:* Presents with normal-anion-gap metabolic acidosis (low bicarb), low-normal K+ (loss in stool). The compensatory urinalysis will show highly acidic urine (pH 5) and high specific gravity (1.030 due to volume depletion) with no protein.
- **Tumor Lysis Syndrome:** A patient with AML presenting with massive hyperkalemia off treatment is experiencing a **shift from intracellular to extracellular** compartments due to spontaneous tumor lysis.
- **Distal (Type 1) RTA Differentiators:** Characterized by hypokalemia, hyperchloremic non-AG metabolic acidosis, **alkaline urine (pH > 5.5, e.g., 6.5 or 7.0)**, hypercalciuria, and **kidney stones**.
- **Addison's Disease Trap:** Primary adrenal insufficiency causes *hyperkalemia* (due to loss of aldosterone). It is firmly **not** associated with hypokalemia.
- **Eating Disorders / Covert Abuse:** A young, thin female with poor dentition/caries, severe hypokalemia, hypochloremia, and metabolic alkalosis is suffering from **chronic vomiting (bulimia)**.
- **Dialysis Indications:** In acute renal failure, a **Potassium > 7.0 mmol/L** is an absolute indication for emergency dialysis.

Memory Pearls

- **Type 1 RTA = 1 stone:** Distal (Type 1) RTA is uniquely associated with kidney stones (due to hypercalciuria + alkaline urine), distinguishing it from Type 2 and 4.

- **Type 4 RTA = 4 is high:** Type 4 RTA is the only one with *hyperkalemia* (due to hypoaldosteronism, often seen in diabetic nephropathy).
- **Aldosterone's Swap:** Aldosterone keeps Na+ and dumps K+ & H+. Therefore, Excess Aldosterone = Hypokalemia + Alkalosis; Deficient Aldosterone (Addison's, Type 4 RTA) = Hyperkalemia + Acidosis.

Primary Glomerulonephritis

Core Concepts

- **Glomerulonephritis** implies inflammation of the glomeruli; **glomerulopathy** refers to glomerular disease without evidence of inflammation.
- **Nephritic Syndrome**: Glomerular inflammation leading to impaired filtration.
  - *Urine sediment*: Dysmorphic RBCs, **RBC casts**.
  - *Features*: Hematuria, oliguria, hypertension, elevated serum creatinine, mild/moderate proteinuria.
- **Nephrotic Syndrome**: Podocyte, GBM, or endothelial injury causing a loss of selective size/charge filtration.
  - *Urine sediment*: Oval fat bodies, fatty casts.
  - *Features*: Massive proteinuria (>3.5 g/day), hypoalbuminemia (<3.5 g/dL), generalized edema, hypercholesterolemia, and lipiduria.
- **Clinical Overlap**: Several diseases (e.g., Membranoproliferative GN [MPGN], Lupus Nephritis) frequently present with mixed nephrotic-nephritic features.

Diagnosis / Clinical Features

Predominantly Nephritic Diseases

- **IgA Nephropathy (Mesangioproliferative GN)**:
  - *Most common primary GN*, usually affecting teens/20s (males > females).
  - Presents with **synpharyngitic macroscopic hematuria**: cola/red urine occurring *concurrently* (1–2 days) with a mucosal illness (URI, GI).
  - Normal complement levels.
- **Post-Streptococcal/Post-infectious GN (PSGN)**:
  - Presents 1–4 weeks *after* a Group A beta-hemolytic strep infection (pharyngitis or impetigo).
  - Presents with cola-colored urine, edema, oliguria, and hypertension.
- **Membranoproliferative GN (MPGN)**:
  - Can present as nephrotic (60–80%) or nephritic.
  - *Type I*: Associated with Hepatitis B/C, endocarditis, SLE, and cryoglobulinemia.
  - *Type II*: Dense deposit disease (complement activation).
- **Rapidly Progressive GN (RPGN / Crescentic GN)**:

- Characterized by rapid progression to End-Stage Renal Disease (ESRD) over weeks to months.
- Oliguria, acute renal failure, and sometimes pulmonary-renal syndrome (hemoptysis + nephritis in Goodpasture's or systemic vasculitis).

Predominantly Nephrotic Diseases

- **Minimal Change Disease (MCD)**:
  - Most common cause of nephrotic syndrome in children (4–8 years).
  - Adults: Associated with NSAID use or Hodgkin's lymphoma.
  - Sudden onset of massive, highly selective proteinuria (mainly albumin).
- **Membranous Nephropathy (MN)**:
  - Most common cause of nephrotic syndrome in adults.
  - *Primary/Idiopathic*: Associated with **Anti-PLA2R antibodies** (70–80% of cases).
  - *Secondary*: Solid organ tumors (**colon**, lung, breast), Hepatitis B/C, SLE, or drugs (penicillamine, gold).
- **Focal Segmental Glomerulosclerosis (FSGS)**:
  - Most common cause of idiopathic nephrotic syndrome in adults (US).
  - *Secondary*: HIV, IV heroin use, morbid obesity, NSAIDs, lithium, and sickle cell.
  - Collapsing variant seen in HIV/IVDU implies severe, rapid progression.

Investigations

Blood & Urine Testing

- **Complement Levels (C3, C4, CH50)**:
  - **Low Complement**: PSGN, Lupus nephritis (Diffuse Proliferative), MPGN, Cryoglobulinemia.
  - **Normal Complement**: IgA Nephropathy, MCD, MN, FSGS, ANCA-associated vasculitides.
- **Serology**: ASO titer (high in PSGN), ANA/Anti-dsDNA (Lupus), Hepatitis panel, HIV, Anti-PLA2R (Membranous), ANCA (Vasculitis), Anti-GBM.

Renal Biopsy Findings

- **IgA Nephropathy**:
  - *LM*: Mesangial proliferation.
  - *IF*: IgA-based immune complexes around mesangial cells.
  - *EM*: Mesangial deposits.
- **PSGN**:
  - *LM*: Diffuse glomerular proliferation and cellular infiltration.
  - *IF*: Granular GBM IgG, IgM, C3.
  - *EM*: Dome-shaped subepithelial deposits.
- **Membranous Nephropathy**:
  - *LM*: Thickened capillary basement membrane; BM spikes on silver stain.

    - *IF*: Diffuse granular IgG and C3.
    - *EM*: Subepithelial deposits.
- **Minimal Change Disease**:
    - *LM & IF*: Normal / Negative.
    - *EM*: Fusion/effacement of podocyte foot processes.
- **FSGS**:
    - *LM*: Focal and segmental sclerosis (only some parts of some glomeruli).
    - *IF*: IgM and C3 in sclerotic areas.
    - *EM*: Podocyte foot process effacement.
- **RPGN / Crescentic GN**:
    - *LM*: **>50% of glomeruli contain crescents** (epithelium and inflammatory cells like macrophages/fibrin in Bowman's space).
    - *IF Type 1 (Goodpasture)*: Linear IgG.
    - *IF Type 2 (Immune complex)*: Granular IgG.
    - *IF Type 3 (Pauci-immune/Vasculitis)*: No deposits.

Management

- **IgA Nephropathy**:
    - ACE inhibitors/ARBs for BP control and to reduce proteinuria (target < 500 mg/day).
    - Corticosteroids if disease is progressive.
- **Minimal Change Disease**:
    - Corticosteroids are first-line (highly responsive).
- **Membranous Nephropathy**:
    - Treat secondary causes. Use ACEi/ARB for proteinuria.
    - Immunosuppression for high-risk idiopathic cases. Monitor for spontaneous remission (occurs in 25%).
- **RPGN**:
    - Aggressive immunosuppression: Corticosteroids, Cyclophosphamide, Rituximab, Plasma exchange.
- **Managing comorbidities in CKD (e.g., Gout in IgAN)**:
    - Avoid NSAIDs (Diclofenac) and carefully evaluate Colchicine in patients with CKD.
    - **Prednisolone** is the safest and most appropriate acute gout treatment for patients with established renal impairment.
- **General Nephrotic Syndrome Tx**: Sodium restriction, ACEi/ARB, Statins for dyslipidemia, diuretics for fluid overload.

Complications / Prognosis

- **Thrombosis/Hypercoagulability**: Loss of antithrombin III in urine leads to thromboembolism. **Renal vein thrombosis** is particularly common in Membranous Nephropathy (manifests as flank pain/hematuria).
- **Infection**: Due to urinary loss of immunoglobulins and complement.
- **End-Stage Renal Disease (ESRD) risk**: FSGS and RPGN have poor prognoses with rapid progression to ESRD.
- **Post-transplant Recurrence**:
  - FSGS: 25–50% recurrence rate.
  - MPGN Type II: 90% recurrence rate.
  - IgA Nephropathy: 20–60% recurrence rate.

Past-Paper High Yield

- **IgAN vs. PSGN Timeline**: A patient developing red urine and nephritic symptoms *concurrently* (within 1-3 days) with a sore throat or runny nose is classic for **IgA Nephropathy**. If the onset is weeks *after* the infection, it is PSGN.
- **Complements**: Know which diseases consume complement! **IgA Nephropathy has NORMAL complement.** SLE Nephritis (Diffuse proliferative GN), Post-streptococcal GN, and Cryoglobulinemia have **LOW** complements.
- **Hepatitis C Associations**: HCV is classically associated with **Membranoproliferative GN (Type I)** and **Cryoglobulinemia**.
- **Solid Tumors**: Colonic cancer presenting with nephrotic syndrome (proteinuria/edema) heavily points toward **Membranous glomerulonephritis**.
- **IgA Biopsy Appearance**: Exam questions will explicitly describe "IgA based immune complexes around the mesangial cells on IF."
- **Treatment of Acute Gout in Nephritis/CKD**: Do not pick NSAIDs (Diclofenac) for a patient with IgA nephropathy and elevated creatinine. Systemic steroids (**Prednisolone**) are the right answer for an acute flare in this context.
- **Lupus Nephritis Class IV**: A young female with a malar rash/pleurisy, high ANA/dsDNA, very low C3/C4, and a mixed nephrotic/nephritic urine profile has **Diffuse proliferative glomerulonephritis**.

Memory Pearls

- *Solid Tumor* = **M**embranous (think **M**alignancy).
- *Fat kid, Heroin, HIV* = **F**SGS.
- *Kid with recent strep throat (weeks ago)* = **P**SGN.
- *Kid with concurrent sore throat + red urine* = **I**gA.
- *Hep B/C* = **M**embrano**P**roliferative.
- *Linear IF* = Goodpasture / Anti-GBM (drawing a straight **line** on the BM).
- *Crescents* = RPGN (Medical emergency).

- *Spikes & Domes*: Spikes on silver stain = Membranous; Dome-shaped deposits = PSGN.

Secondary Glomerulonephritis: Diabetic Nephropathy and Lupus Nephritis

Core Concepts

- Distinguish between the two major secondary causes of glomerulonephritis: **Diabetic Nephropathy** (metabolic/hemodynamic injury) and **Lupus Nephritis** (autoimmune immune-complex deposition).
- **Diabetic Nephropathy (DN)**: The leading cause of end-stage renal disease (ESRD). Characterized by progressive albuminuria, declining GFR, and systemic hypertension.
- **Lupus Nephritis (LN)**: One of the most serious manifestations of Systemic Lupus Erythematosus (SLE), typically arising within 5 years of SLE diagnosis. Driven by anti-dsDNA autoantibodies that deposit in the glomeruli and aggressively consume complement.

Diagnosis / Clinical Features

Diabetic Nephropathy

- **Clinical Diagnosis**: Persistent macroalbuminuria (>300 mg/day) + presence of diabetic retinopathy + absence of other kidney diseases.
- **Retinopathy Link**: >90% of Type 1 DM patients with nephropathy also have retinopathy. *The absence of retinopathy in a Type 1 DM patient with proteinuria strongly suggests a non-diabetic cause of renal disease.* (In Type 2 DM, only ~60% have retinopathy).
- **Progression Phases**:
  1. **Hyperfiltration**: High GFR, normoalbuminuria. Reversible with intensive insulin therapy.
  2. **Microalbuminuria**: 30–300 mg/day. Strongest predictor of overt DN and cardiovascular mortality. Can revert with strict glycemic control.
  3. **Overt Nephropathy**: >300 mg/day macroalbuminuria, predictably declining GFR (mean 12 mL/min/yr), onset of hypertension and peripheral edema.
  4. **ESRD**.

Lupus Nephritis

- **Symptoms**: May be asymptomatic early on. Can present with peripheral edema (nephrotic), hypertension (nephritic), or active SLE signs (fatigue, rash, arthritis).
- **Urinary Findings**: Proteinuria (100%), microscopic hematuria (80%), granular and red blood cell (RBC) casts.
- **When to suspect alternative diagnoses to DN**: Presence of significant hematuria, cellular casts, nephrotic-range proteinuria *at the exact time of DM diagnosis*, or signs of systemic autoimmune disease.

Investigations

Diabetic Nephropathy

- **Screening**: Check urine albumin-to-creatinine ratio (UACR).
  - **Type 1 DM**: Screen **5 years after diagnosis**, then annually.
  - **Type 2 DM**: Screen **at the time of diagnosis**, then annually (as they may have had subclinical DM for years).
- **Renal Biopsy**: Usually deferred if the presentation is classical. Indicated if atypical features are present (e.g., hematuria, rapid GFR decline, or no retinopathy in Type 1 DM).
- **Pathology Hallmarks**:
  - Thickened Glomerular Basement Membrane (GBM) with a loss of heparan sulfate (loss of the negative charge barrier).
  - Mesangial expansion (diffuse diabetic glomerulosclerosis).
  - **Kimmelstiel-Wilson nodules**: Nodular glomerulosclerosis (large fibrillar mesangial zones compressing capillaries).
  - **Afferent* and *efferent** arteriolar hyalinosis.

Lupus Nephritis

- **Serology**:
  - **High Anti-dsDNA** (cross-reacts with GBM; rising titer strongly predicts renal flares).
  - **Low Complements (C3, C4, CH50)** (consumed by immune complex activation).
  - High ESR, but *normal CRP*.
  - Anti-C1q antibodies (highly specific for LN).
- **Renal Biopsy**: Gold standard for classifying LN (Classes I–VI) and guiding immunosuppression.
  - **Indications**: Unexplained rising creatinine, proteinuria >1.0 g/day, or proteinuria >0.5 g/day + hematuria/cellular casts.
  - **Class IV** (Diffuse Proliferative) is the most common, aggressive, and frequently tested histological type.

Management

Diabetic Nephropathy

- **Glycemic Control**: Essential to prevent progression from hyperfiltration to microalbuminuria.
- **Blood Pressure Control**: Strict target < 130/80 mmHg.
  - **First-line**: **ACE inhibitors or ARBs**. Beyond systemic BP lowering, they directly reduce intraglomerular pressure (by dilating the efferent arteriole) and slow proteinuria progression.
- **Other Agents**: SGLT2 inhibitors.
- **Diuretics**: Used to enhance the antiproteinuric effects of RAAS blockade and treat edema.
  - Use **Thiazides** if GFR > 40 mL/min.
  - Use **Loop diuretics** if GFR < 40 mL/min.

Lupus Nephritis

- **Induction Therapy** (for active/severe disease, e.g., Class IV):

    - **High-dose Corticosteroids** (e.g., pulse methylprednisolone) + **Cyclophosphamide** OR **Mycophenolate Mofetil (MMF)**.
- **Maintenance Therapy**:
    - **Azathioprine** or **MMF** ± low-dose corticosteroids.
- **Pregnancy Considerations**: High flare risk (50–60%) if conceived during active disease. Patients should avoid pregnancy until they have achieved 3–6 months of remission. Pregnant LN patients are highly prone to preeclampsia.

Complications / Prognosis

- **DN Progression Drivers**: Poor glycemic control, persistent proteinuria, and systemic hypertension. *(Note: Hyperkalemia is a complication of advanced CKD, not a driver of primary progression)*.
- **LN Flare Predictors**: Rising anti-dsDNA, dropping C3/C4 levels, and the appearance of active sediment (RBC/WBC casts).
- **Transplantation**: Outcomes are excellent if the patient is transplanted during SLE inactivity; allograft loss due to recurrence is very rare (<2–4%).

Past-Paper High Yield

- **Predictors of DN:** The presence of **proteinuria** (specifically microalbuminuria) is the most critical and robust predictor for the development of overt diabetic nephropathy.
- **Hypertension in DN:** Uncontrolled blood pressure (e.g., 155/95 mmHg) is a severely bad prognostic factor that aggressively drives CKD progression.
- **CKD Progression Factors:** When asked what does *not* contribute to the progression of diabetic CKD, recognize that **hyperkalemia** is a downstream consequence of renal failure and RAAS blockade, but it does not intrinsically drive glomerular scarring.
- **Retinopathy and DN:** In Type 1 DM, if a patient has significant proteinuria but *no* diabetic retinopathy, suspect an alternative diagnosis (e.g., primary glomerulonephritis) and consider a biopsy.
- **Lupus Nephritis Immediate Treatment:** For active Class IV LN (indicated by cellular casts, low C3/C4, high anti-dsDNA), induction requires **pulse methylprednisolone + Cyclophosphamide** (or MMF).
- **Complement levels in Glomerulonephritis:** Remember that Lupus Nephritis characteristically has **LOW complements (C3/C4)**, differentiating it from Membranous Nephropathy or Minimal Change Disease (which have normal complements).
- **Diagnostic Trap:** A patient with heavy "proteinuria" on urinalysis, hypercalcemia, anemia, high creatinine, but *normal* serum albumin and no hematuria points towards **Light Chain Nephropathy (Multiple Myeloma)**, not Lupus Nephritis. Standard dipsticks primarily detect albumin, so massive proteinuria with normal serum albumin suggests the proteins are immunoglobulins/light chains.

Memory Pearls

- **DN Timeline:** Microalbuminuria starts ~5–10 years post-onset. Screen Type 1 diabetics at 5 years; screen Type 2 diabetics *immediately* (as disease duration is often unknown).

- **Kimmelstiel-Wilson Nodules = Diabetic Nephropathy.**
- **Lupus Flare Triad:** Low C3/C4 + High Anti-dsDNA + Active urinary sediment (RBC casts).
- **ACEi/ARB Mechanism:** Protective because they dilate the efferent arteriole, reducing the glomerular capillary hypertension that forces proteins through the damaged charge barrier.

Acute Kidney Injury (AKI)

Core Concepts

- **Definition:** Abrupt decline in renal function occurring over hours to days (subacute: days to weeks; chronic: weeks to months).
- **Classification Systems:**
  - **AKIN Criteria:** Focuses on underlying injury process. Based on serum creatinine (Cr) increase and urine output (UOP).
    - **Stage 1:** Cr >1.5–2x baseline OR UOP <0.5 mL/kg/h for >6h.
    - **Stage 2:** Cr >2–3x baseline OR UOP <0.5 mL/kg/h for >12h.
    - **Stage 3:** Cr >3x baseline OR anuria for >12h OR UOP <0.3 mL/kg/h for >24h OR *any need for renal replacement therapy (RRT)*.
  - **RIFLE Criteria (Historical):** Risk, Injury, Failure, Loss, ESRD. Requires a baseline Cr and lacks criteria for progression timing or RRT initiation rules. (Note: Studies show AKIN does not significantly improve mortality prediction over RIFLE).
- **Epidemiology:** High mortality (50–60%) in the ICU even with RRT. 4–5% of ICU patients require RRT for AKI. Oliguria is defined as <400 mL/day.

Diagnosis / Clinical Features

AKI is categorized anatomically into Prerenal, Renal (Intrinsic), and Postrenal causes.

1. Prerenal AKI (Decreased Renal Blood Flow)

- **Pathophysiology:** Initially, GFR is preserved via autoregulation: Prostaglandins (PGs) dilate the *afferent* arteriole, and Angiotensin II (ATII) constricts the *efferent* arteriole. Prerenal AKI occurs when this system fails or is overwhelmed.
- **Causes:**
  - True volume depletion (hemorrhage, GI losses).
  - Decreased effective arterial blood volume (cardiogenic shock, cirrhosis, sepsis).
  - Renal vasoconstrictors (cyclosporine, tacrolimus, catecholamines, cocaine, hypercalcemia, amphotericin).
- **Impaired Autoregulation (Drugs):** NSAIDs/COX-2 inhibitors block PGs (constricting afferent); ACEi/ARBs block ATII (dilating efferent).

2. Intrinsic Renal AKI (Ordered by frequency)

- **Ischemic Acute Tubular Necrosis (ATN):** Results from unresolved prerenal states (prolonged hypotension, shock).
  - *Pathophysiology:* Medullary thick ascending limb and straight proximal tubule (S3) are highly vulnerable to hypoxia.
  - *Mechanism:* ATP depletion → breakdown of actin/cytoskeleton → loss of brush border and polarity → viable and necrotic cells shed into lumen → casts form (polymerized Tamm-Horsfall protein) → tubular obstruction & back-leak of filtrate.
  - *Tubuloglomerular Feedback:* Impaired tubular Na reabsorption → increased Na delivery to macula densa → afferent arteriole constriction → further drops GFR.
- **Toxic ATN:** Aminoglycosides, radiocontrast, hemoglobin/myoglobin (rhabdomyolysis), ethylene glycol, cisplatin, amphotericin.
- **Acute Interstitial Nephritis (AIN):** Allergic reaction to drugs (Penicillins, NSAIDs, allopurinol, ciprofloxacin, sulfonamides). Presents with fever, rash, and eosinophilia.
- **Rapidly Progressive Glomerulonephritis (RPGN):** Anti-GBM (Goodpasture's), Immune-complex (SLE, post-infectious, IgA), Pauci-immune (ANCA-positive: Granulomatosis with polyangiitis, Microscopic polyangiitis).
- **Thrombotic Microangiopathy (TMA):** HUS, TTP, malignant hypertension, scleroderma renal crisis. Triad: AKI, hemolytic anemia (schistocytes), thrombocytopenia.

3. Postrenal AKI

- Obstruction of the urinary tract (BPH, bladder outlet obstruction, bilateral nephrolithiasis).

Investigations

- **Urinalysis (UA) & Microscopy: The most critical differentiator in intrinsic AKI.**
  - *Bland UA:* Prerenal AKI.
  - *Muddy brown/granular casts or epithelial cell casts:* ATN.
  - *WBC casts, pyuria, eosinophiluria:* AIN.
  - *Dysmorphic RBCs, RBC casts:* Glomerulonephritis / RPGN.
- **Urine Electrolytes:** In the presence of oliguria, Urine Na or Urine Cl < 20 mmol/L strongly suggests Prerenal AKI.
- **Biomarkers in AKI:**

BIOMARKER	CHARACTERISTICS & LIMITATIONS
Creatinine	Delayed elevation; depends on muscle mass, age, and diet. Low sensitivity/specificity (elevated in CKD and prerenal azotemia).
Cystatin C	Produced by all nucleated cells. Not specific to AKI (better for general GFR); elevated in both CKD and prerenal azotemia.
NGAL	Rises within *hours* of insult. False positives from infections/UTIs and CKD. Not specific to ischemic AKI.

BIOMARKER	CHARACTERISTICS & LIMITATIONS
KIM-1	Highly specific to ischemic AKI (proximal tubule injury). Not affected by UTIs/CKD. *Drawback:* Peak rise is delayed 12–24 hours after insult.

Management

- Treat the underlying cause (volume resuscitate in prerenal, stop offending drugs in AIN/toxic ATN).
- ATN does *not* respond to normalization of volume and blood pressure once established.
- **Indications for Dialysis (RRT):**
  - Refractory Hyperkalemia.
  - Volume overload (e.g., pulmonary edema with high O2 requirements).
  - Severe uremia (usually started when Cr reaches 200–400 µmol/L in severe ICU cases).
  - Decision is heavily influenced by the rate of Cr rise, oliguria, and multi-organ failure.

Past-Paper High Yield

- **Ischemic ATN post-MI:** A classic vignette features a patient with an acute myocardial infarction and persistent hypotension requiring vasopressors over several days, who then develops oliguria and rising creatinine. *Microscopy trap:* Look for "tubular epithelial cell casts" or "granular deposits"; the diagnosis is Acute Tubular Necrosis (ATN).
- **Drug-Induced AIN:** Suspect AIN in a hospitalized patient receiving antibiotics (e.g., treated for bronchopneumonia) who develops a new fever, chills, skin rash, and rising creatinine. *Key differentiator:* Urinalysis showing copious WBCs (15–20/hpf) and WBC casts points directly to Acute Interstitial Nephritis, not glomerulonephritis.
- **Methotrexate (MTX) Toxicity:** A rheumatoid arthritis (RA) patient on MTX presenting with sudden AKI. MTX is a known nephrotoxin (causes crystal nephropathy/tubular toxicity).
- **Gold Therapy Complication:** A patient with long-standing RA (e.g., 30 years) treated with Gold salts for years presenting with *nephrotic syndrome* and AKI. *Diagnosis:* Gold-induced membranous nephropathy or secondary renal amyloidosis.

Memory Pearls

- **AIN ALWAYS has pyuria / WBC casts.** If a vignette gives you a rash, fever, and WBCs in the urine of a patient on Penicillin, NSAIDs, or Sulfa drugs, pick AIN.
- **ATN is a double hit:** Tubular obstruction (from casts of dead cells) + backflow of filtrate + tubuloglomerular feedback causing afferent constriction.
- **Autoregulation rules:** PGs dilate the **A**fferent (**A**pproaching) arteriole. ATII constricts the **E**fferent (**E**xiting) arteriole. Blocking either (NSAIDs or ACEi) in a hypotensive patient triggers Prerenal AKI.

Chronic Kidney Disease (CKD)

Core Concepts

- **Definition:** Kidney damage for ≥ 3 months (structural or functional abnormalities, with or without decreased GFR) OR GFR ≤ 60 mL/min/1.73 m² for ≥ 3 months.
- **Staging (based on GFR):**
  - **Stage 1:** ≥ 90 (with structural/urine abnormalities)
  - **Stage 2:** 60–89 (with structural/urine abnormalities)
  - **Stage 3:** 30–59
  - **Stage 4:** 15–29
  - **Stage 5:** < 15 or End-Stage Renal Disease (ESRD)
- **Pathophysiology of Progression:** Initial nephron loss leads to **adaptive hyperfiltration** in remaining nephrons → increased intraglomerular pressure (P_{GC}) → wall stress → proteinuria → progressive sclerosis and renal insufficiency.

Diagnosis / Clinical Features

- **Glomerular Filtration Rate (GFR) Estimation:**
  - **Cockcroft-Gault:** Incorporates age, weight, and gender. Gives uncorrected creatinine clearance. *Limitations:* Underestimates GFR in normal people; less accurate at extremes of ideal body weight; no correction for Black race.
  - **MDRD:** Incorporates age, gender, and race. Gives eGFR in mL/min/1.73 m². *Limitations:* Less accurate in normal/near-normal GFR populations (best for those with established CKD).
  - **Cystatin C (Investigational/Alternative):** Non-glycosylated protein, produced at a constant rate by all nucleated cells. Freely filtered, catabolized in proximal tubule. *Advantage:* Not influenced by diet or muscle mass.
- **Identifying the Underlying Cause (Exam Differentiators):**
  - **Alport Syndrome:** Sensorineural deafness (bilateral high-tone), progressive ESRD in a young patient. Pathognomonic eye finding: **Anterior lenticonus**.
  - **Autosomal Dominant Polycystic Kidney Disease (ADPKD):** Multiple cysts in kidneys and liver. **CVD complications** are the most common cause of mortality, not renal failure.
  - **Polyarteritis Nodosa (PAN):** HTN, renal infarcts/hematuria without proteinuria, abdominal pain (mesenteric ischemia). Angiography shows aneurysms/occlusions in medium vessels. **Negative ANA and ANCA**.
  - **Cholesterol Crystal Embolization:** Acute/subacute eGFR decline post-vascular procedure, eosinophilia, peripheral atherosclerosis. **Positive ANA is NOT a feature**.
  - **Acute Interstitial Nephritis (AIN):** Hematuria, proteinuria, and urinary eosinophils developing shortly after antibiotic therapy (e.g., treating an abscess).

Investigations

- **General Workup:** Urinalysis (active sediment vs. bland), renal ultrasound (kidney size is generally small in advanced CKD), baseline creatinine, hemoglobin, Ca^{2+}, PO_4^{3-}, PTH.
- **Indications for Renal Biopsy:**
  - Early disease rather than late (avoid biopsying small, echogenic/contracted kidneys).
  - Unexplained CKD (i.e., no obvious history of HTN or Diabetes).
  - Heavy proteinuria or active urinary sediment (hematuria, RBC casts).
  - Younger patients (to rule out hereditary conditions like Alport or Fabry disease).

Management

- **Slowing CKD Progression:**
  - **Blood Pressure:** Target < 130/80 mmHg. ACE inhibitors or ARBs are first-line as they reduce efferent arteriolar vasoconstriction, thereby lowering intraglomerular pressure (P_{GC}) and reducing proteinuria.
  - **Proteinuria:** Target excretion < 0.5–1 g/day (PCR < 60). Combine ACEi + ARB if targets are unmet (requires careful K^+ monitoring).
  - **Diet:** Restrict protein intake (0.8–1.0 g/kg/day).
  - **Metabolic Acidosis:** Keep target serum HCO_3^- at **22 mmol/L**. Supplement with oral Sodium Bicarbonate (0.5–1 g PO BID/TID).
  - **Diabetic Management in CKD + Heart Failure:** SGLT2 inhibitors (e.g., **Dapagliflozin**) provide the greatest benefit for slowing CKD progression and managing HFrEF.
- **Managing Complications:**
  - **Anemia (Begins ≥ Stage 3):** Exclude non-renal causes. Give iron supplementation and Erythropoietin (EPO). **Target Hb is ~10–11.5 g/dL**. *Crucial exam point:* Do not target normal hemoglobin levels (>11.5 g/dL) due to an increased risk of severe cardiovascular and cerebrovascular events. Start EPO if Hb drops to 9 g/dL.
  - **Hyperphosphatemia (Begins Stage 3):** Target 0.87–1.49 mmol/L. Use low phosphate diet and phosphate binders (Calcium Carbonate, Sevelamer).
  - **Renal Osteodystrophy:** Vitamin D3 (Calcitriol) synthesis decreases starting at Stage 3, leading to elevated PTH. Supplement with Calcitriol (0.25 µg/day) and manage phosphate. *Target PTH depends on GFR—do not over-suppress PTH to avoid Adynamic Bone Disease.*
- **Procedural Precautions:**
  - **Contrast Studies (e.g., Coronary Catheterization): Stop Metformin** to prevent contrast-induced lactic acidosis.
- **Preparation for Dialysis (Referral at Stage 4 / eGFR ≤ 30):**
  - AV fistula must be placed ~3 months prior to hemodialysis (HD) initiation to allow maturation. PD catheters require ~1 week.
- **Indications to Initiate Dialysis:**
  - Refractory fluid overload (CHF exacerbation).
  - Refractory hyperkalemia ($K^+ > 6$).

- Signs of uremia (encephalopathy, pericarditis, intractable itching).
- Refractory metabolic acidosis.
- *Note:* eGFR < 15 alone in an asymptomatic, stable patient is **not** an absolute indication to start dialysis.

Past-Paper High Yield

- **Dialysis Initiation Trap:** In a Stage V CKD patient evaluated in clinic, an **eGFR < 15 is the least likely standalone reason** to initiate dialysis compared to absolute indications like uremic encephalopathy, pericarditis, hyperkalemia, or severe uremic pruritus (itching).
- **ADPKD Cyst Infection:** A patient with ADPKD presenting with flank pain, fever, and leukocytosis likely has an infected cyst. The most appropriate treatment is a lipophilic antibiotic that penetrates cysts, such as **Ciprofloxacin**.
- **Malignancy-Associated Nephropathy:** A lung cancer patient (solid tumor) presenting with proteinuria most likely has **Membranous Glomerulonephritis**.
- **Anemia Threshold:** If a patient is stable with CKD Stage 4 and a hemoglobin of 9 g/dL, the next best step is to **give erythropoietin**.
- **Proteinuria in Young Diabetics:** A 17-year-old with Type 1 DM for only 4 years who presents with lower limb swelling and nephrotic-range proteinuria most likely has **Minimal Change Disease**, NOT diabetic nephropathy (diabetic nephropathy generally takes >10 years to manifest).
- **Orthostatic Proteinuria:** Young patients with proteinuria that only occurs when upright require **reassurance** as the next step.

Memory Pearls

- **Alport Eye = Anterior lenticonus** (Deafness + visual defects + CKD).
- **Metformin + Contrast = Stop Metformin** (High risk for lactic acidosis).
- **ADPKD Mortality = Cardiovascular disease**, NOT renal failure.
- **Normal sized kidneys + CKD = Biopsy** (Often indicates a systemic infiltrative disease like amyloidosis, early diabetic nephropathy, or acute-on-chronic processes).
- **eGFR < 15 ≠ immediate dialysis** unless accompanied by uremic symptoms, refractory acidosis, volume overload, or hyperkalemia.

Renal Replacement Therapy (RRT)

Core Concepts

- **Modalities:** Kidney Transplantation (the best modality), Hemodialysis (HD), and Peritoneal Dialysis (PD).
- **Primary Goals of Dialysis:** Clearance of uremic toxins, ultrafiltration to reduce excess fluid volume (most HD patients are anuric), and correction of metabolic abnormalities (e.g., hyperkalemia, severe acidosis).
- **Vascular Access Hierarchy (HD):** Arteriovenous Fistula (AVF) > Arteriovenous Graft (AVG) > Hemodialysis Catheter (CVC). AVF is the preferred access with the lowest complication rates.

- **Mortality:** The most common cause of death in patients with End-Stage Renal Disease (ESRD) on hemodialysis is **cardiovascular disease (Acute Myocardial Infarction)**.

Diagnosis / Clinical Features

Indications for Hemodialysis (AEIOU)

- **A**cidosis: Severe metabolic acidosis refractory to medical management.
- **E**lectrolytes: Severe hyperkalemia refractory to medical therapy (e.g., persistent ECG changes despite calcium gluconate/insulin).
- **I**ntoxications: Overdose of specific dialyzable drugs (e.g., severe antiseizure medication toxicity).
- **O**verload: Severe fluid overload unresponsive to medical treatment (IV diuretics).
- **U**remia: Uremic symptoms (encephalopathy, pericarditis, nausea, vomiting, metallic taste, weakness) in the setting of **CKD Stage 5 (eGFR < 15 mL/min)**.

Note: Asymptomatic patients with eGFR < 15 mL/min do not require immediate dialysis initiation; they should be observed closely with monthly follow-ups.

Investigations

Peritoneal Dialysis (PD) Associated Peritonitis Diagnosis requires **two of the following three** criteria:

1. **Organisms** identified on Gram stain or subsequent culture.
2. **Cloudy fluid** with a white cell count **> 100/mm³** (with **> 50% neutrophils**).
3. **Symptoms/signs** of peritoneal inflammation (abdominal pain in 80–95%, tenderness, fever/chills). *Pathogen profile:* Coagulase-negative *Staphylococcus* was historically most common (touch contamination). The advent of flush-before-fill Y-systems has led to a relative increase in *Staphylococcus aureus* infections.

Management

Hemodialysis Catheter Infection

- **Fever + HD Catheter:** Assume it is a catheter-related bloodstream infection until proven otherwise.
- **Next step:** Admit to the hospital and start empiric broad-spectrum IV antibiotics.

Peritoneal Dialysis (PD) Peritonitis

- **Empiric therapy:** Must cover both Gram-positive organisms (Vancomycin or 1st-generation cephalosporin) and Gram-negative organisms (3rd-generation cephalosporin or Aminoglycoside). Usually resolves with outpatient treatment (75% cure rate).
- **Indications for PD Catheter Removal:**
  - Relapsing/refractory peritonitis or refractory catheter infection.
  - Fungal or mycobacterial peritonitis.
  - Peritonitis associated with intra-abdominal pathology.

- *Red flag:* Multiple enteric organisms or mixed Gram-positive/Gram-negative flora heavily suggests bowel ischemia or diverticular perforation.

Kidney Transplantation

- The definitive treatment of choice, improving survival, quality of life, and cost compared to dialysis.
- **Contraindications:** Active infection, **active malignancy** (e.g., untreated colon cancer), active substance abuse, reversible renal failure, uncontrolled psychiatric disease, documented nonadherence, or significantly shortened life expectancy.

Complications / Prognosis

- **PD and Glycemic Control:** Dextrose (most common osmotic agent) is absorbed from the dialysate, causing weight gain and hyperglycemia. Most diabetic patients require insulin (given via IP or SC route) upon starting PD.
- **Icodextrin Trap:** Using icodextrin-containing dialysate solutions can cause **falsely elevated glucose levels** on standard glucometers. Patients must use glucose-specific monitoring methods to prevent inappropriate insulin dosing and hypoglycemia.

Past-Paper High Yield

- **Scleroderma Renal Crisis vs. HD indication:** A patient presenting with extreme hypertension (e.g., 220/115), acute kidney injury (Cr 3.4), and scleroderma signs (thickened skin, telangiectasia) needs an **ACE inhibitor (Enalapril)** urgently, *not* immediate hemodialysis or beta-blockers.
- **The Asymptomatic CKD 5 Trap:** A patient with CKD 5 (eGFR 9) who feels well and has no uremic symptoms, normal potassium, and normal bicarbonate should be managed with **monthly observation/follow-up visits**. Do not start HD just for the number.
- **The Symptomatic CKD 5 Presentation:** A patient with an eGFR of 7 who develops a **metallic taste**, nausea, and vomiting has symptomatic uremia. Even if K+ is normal, the next best step is to **initiate hemodialysis**. (If the patient also has an active malignancy like colon cancer, preemptive transplant is contraindicated).
- **Non-Indications for HD:** Hyperuricemia in an otherwise asymptomatic patient is explicitly **NOT** an indication for hemodialysis.
- **CKD Stage 3 Overload Trap:** A symptomatic patient with CKD Stage 3, pleural effusions, edema, and acidosis is initially managed medically (e.g., **IV furosemide**, salt restriction, sodium bicarbonate) — *not* with hemodialysis.
- **Cause of Mortality:** In an ESRD patient found dead in bed 2 days post-dialysis, the most likely underlying cause of death is an **Acute Myocardial Infarction**.

Memory Pearls

- **K+ emergencies supersede HD logistics:** If a patient presents with K+ of 7.0 and EKG changes (hyperacute T-waves), the *very first* step is **IV Calcium Gluconate** to stabilize the myocardium, *then* arrange HD or other K-lowering agents.
- **Clear PD fluid with a WBC < 100 is NOT peritonitis:** If a PD patient presents with right lower quadrant pain but clear dialysate fluid and a cell count of 30 WBCs, rule out other intra-abdominal

pathologies (e.g., appendicitis) instead of blindly treating for peritonitis.

- **Fever + Central Line = Source Control:** HD patient in the ER with a fever? Always ask about their access. If it's a catheter, suspect a catheter infection immediately.

Nephrology and Creatinine Notes

Core Concepts

Creatinine & Renal Function

- **Origin:** Byproduct of muscle metabolism; serum levels reflect glomerular filtration rate (GFR).
- **Normal Ranges:**
  - Men: 0.74–1.35 mg/dL (65–120 µmol/L)
  - Women: 0.59–1.04 mg/dL (52–91 µmol/L)
  - Children: 0.2–1.0 mg/dL (age-dependent)
- **Factors Influencing Levels:**
  - *Increased:* Kidney dysfunction (AKI/CKD), dehydration, high muscle mass/intense exercise, nephrotoxic drugs, rhabdomyolysis.
  - *Decreased:* Low muscle mass (elderly, malnourished, muscular dystrophy), pregnancy (due to physiological increase in GFR), severe liver disease.
- **Acute Kidney Injury (AKI) Definition:** Sudden decline in kidney function marked by a rapid increase in serum creatinine (≥0.3 mg/dL within 48 hours) or a decrease in urine output.

Classification of AKI

- **Prerenal AKI (Hypoperfusion):** Decreased blood flow to the kidneys leading to ischemia. Kidneys are structurally intact and attempt to conserve salt and water.
  - *Causes:* Hypovolemia (hemorrhage, GI losses, third-spacing), decreased cardiac output (HF, MI, shock), vasodilation (sepsis, anaphylaxis), renal artery stenosis.
  - *Medication causes:* Diuretics, ACE inhibitors/ARBs, NSAIDs (inhibit prostaglandins, reducing afferent arteriole dilation).
- **Postrenal AKI (Obstruction):** Obstruction of urinary outflow causing increased backpressure and subsequent renal damage.
  - *Causes:* BPH, prostate cancer, kidney stones (most common), strictures, neurogenic bladder, pelvic malignancies.
- **Intrinsic (Renal) AKI:** Direct damage to kidney tissues (glomeruli, tubules, interstitium, or vasculature).
  - *Acute Tubular Necrosis (ATN):* Ischemic (prolonged prerenal state) or Nephrotoxic (aminoglycosides, contrast dyes, rhabdomyolysis, hemolysis).
  - *Acute Interstitial Nephritis (AIN):* Drug-induced (penicillins, NSAIDs, diuretics), infections (pyelonephritis), or autoimmune (SLE).
  - *Glomerulonephritis (GN):* IgA nephropathy, lupus nephritis, post-streptococcal GN.

Albert Syndrome

- A rare, genetic, mildly progressive syndrome (noted distinctly in provided material) characterized by:
  - *Vision loss:* Retinal degeneration.
  - *Hearing loss:* Sensorineural impairment.
  - *Neurological decline:* Cognitive decline, coordination, or balance issues.

Diagnosis / Clinical Features

Clinical Presentation of AKI Subtypes

- **Prerenal:** Hypotension, tachycardia, dry mucous membranes, oliguria/anuria.
- **Postrenal:** Distended bladder, lower abdominal discomfort, flank pain, hematuria (if stones/infection), oliguria/anuria.
- **Intrinsic:**
  - *General:* Oliguria/anuria, edema, elevated BP.
  - *Glomerulonephritis:* Proteinuria, hematuria.
  - *AIN:* Rash, fever.

Physical Examination of the Renal System

- **Inspection:**
  - Fluid retention (generalized edema, periorbital edema, ascites).
  - Signs of uremia (pallor, bruising, jaundice).
  - Abdominal distension, visible masses, or surgical scars.
- **Palpation:**
  - *Kidneys:* Normally non-palpable. Palpable/enlarged kidneys suggest polycystic kidney disease (PCKD) or severe hydronephrosis.
  - *CVA Tenderness:* Hallmark of pyelonephritis or obstructing renal stones.
  - *Bladder:* Palpable above pubic symphysis in urinary retention.
- **Percussion & Auscultation:**
  - Abdominal/CVA percussion assists in identifying ascites or localized tenderness.
  - *Renal bruits:* Auscultated over the abdomen (above umbilicus) or flanks; highly suggestive of renal artery stenosis.

Investigations

General Renal Function Tests

- **Serum Creatinine & BUN:** Core components of BMP/CMP. Serial trending is critical.
- **Estimated GFR (eGFR):** Calculated using MDRD, CKD-EPI, or Cockcroft-Gault formulas (factors in age, sex, body size). More accurate than isolated serum creatinine.
- **Creatinine Clearance:** Requires 24-hour urine collection + serum sample.

Differentiating AKI Subtypes (High Yield)

PARAMETER	PRERENAL AKI	INTRINSIC AKI (E.G., ATN)
BUN:Cr Ratio	> 20:1 (urea reabsorbed)	< 15:1
Urine Sodium	< 20 mEq/L (conserving Na+)	> 40 mEq/L (impaired reabsorption)
FeNa (Fractional Excretion of Na)	< 1%	> 2%
Urine Osmolality	> 500 mOsm/kg (concentrated)	< 350 mOsm/kg (isosthenuria)
Urine Microscopy	Hyaline casts (normal/dry)	Muddy brown casts (ATN)

Diagnostic Modalities

- **Urinalysis & Microscopy:**
  - *Muddy brown casts:* Acute Tubular Necrosis (ATN).
  - *RBC casts:* Glomerulonephritis.
- **Renal Ultrasound:** Most useful first-line tool to rule out postrenal AKI; identifies hydronephrosis (swelling of the kidney due to urine retention) and kidney size.
- **Renal Biopsy:** Reserved for cases of unclear intrinsic AKI (e.g., confirming GN or vasculitis).

Management

- **Prerenal AKI:**
  - Volume resuscitation with IV fluids (Normal Saline or Lactated Ringer's) for hypovolemia.
  - Treat underlying cause (optimize heart failure, manage shock, discontinue offending drugs like NSAIDs/diuretics).
- **Postrenal AKI:**
  - Relieve obstruction immediately (Foley catheter for BPH/bladder outlet, stent/nephrostomy for ureteral obstruction, lithotripsy for stones).
- **Intrinsic AKI:**
  - Supportive care: Strict fluid management to avoid overload, correct electrolyte derangements (e.g., hyperkalemia, metabolic acidosis).
  - Discontinue nephrotoxic agents.
  - **Dialysis Indications:** Severe/refractory cases with life-threatening complications (e.g., refractory hyperkalemia, profound volume overload).

Complications / Prognosis

- **Progression to Ischemic ATN:** Failure to rapidly correct prerenal AKI results in irreversible hypoxic damage to renal tubules, converting a reversible prerenal state into intrinsic ATN.
- **Chronic Kidney Disease (CKD):** Unresolved acute insults or chronic untreated obstruction can lead to permanent nephron loss.

- **Uremic Toxicity:** Severe kidney dysfunction can result in multiorgan dysfunction, requiring renal replacement therapy (dialysis).

Past-Paper High Yield

- **BUN/Cr Ratio Differentiation:** A ratio > 20:1 strongly points to a prerenal etiology, whereas a ratio < 15:1 with an elevated FeNa (>2%) points to intrinsic renal damage (ATN).
- **Urine Microscopy Traps:** Always link "muddy brown casts" or "granular casts" to ATN, and "RBC casts" to Glomerulonephritis.
- **Medication-Induced AKI:**
  - *NSAIDs:* Cause afferent arteriole vasoconstriction (prerenal).
  - *Aminoglycosides / Contrast Dye:* Direct tubular toxicity (intrinsic/ATN).
  - *Penicillins / NSAIDs:* Can cause allergic reaction in kidneys (AIN) presenting with fever and rash.
- **Imaging Choice:** Ultrasound is the definitive initial test for any patient suspected of having an obstructive (postrenal) AKI to visualize hydronephrosis.

Memory Pearls

- **AKI Threshold:** Just a **0.3 mg/dL bump in 48 hours** is enough to diagnose AKI.
- **Prerenal is "Pre-damage":** The kidney is still working properly to save water and salt (Urine Na is low, Urine Osmolality is high).
- **Vascular Bruits:** Auscultating an abdominal bruit = Think **Renal Artery Stenosis** (a prerenal cause of AKI and secondary hypertension).
- **CVA Tenderness:** Tap the back; if they jump, think **Stones or Infection** (Pyelonephritis).

Arterial Blood Gas (ABG) Analysis

Core Concepts

Interpreting an ABG requires a systematic, stepwise approach to identify single, double, or triple acid-base disorders.

Normal Reference Values:

- **pH:** 7.40 (Range: 7.35 – 7.45)
- **pCO_2:** 40 mmHg (Range: 35 – 45 mmHg)
- **HCO_3^-:** 24 mEq/L (Range: 22 – 26 mEq/L)
- **Anion Gap (AG):** 10 mEq/L (Range: 8 – 12 mEq/L)
- **Albumin:** 4.0 g/dL

The 7-Step Analysis Method:

1. **Check pH:** Acidosis (< 7.4) or Alkalosis (> 7.4)?
2. **Determine Primary Disorder:** Is the primary driver Respiratory (pCO_2 moves opposite to pH) or Metabolic (HCO_3^- moves in the same direction as pH)?

3. **Check Compensation:** Is the compensatory response appropriate? (Calculated using specific formulas).
4. **Determine Acute vs. Chronic:** (Applicable only to respiratory disorders).
5. **Calculate Anion Gap (AG):** *Always* check the AG, even if the primary disorder is not metabolic acidosis.
6. **Check Delta-Delta Gap:** If AG is elevated (> 12), compare ΔAG to ΔHCO_3^- to find hidden concomitant metabolic disorders.
7. **Formulate Differential Diagnosis:** Match the calculated disorders to the clinical presentation.

Diagnosis / Clinical Features

1. Compensation Formulas If the measured value differs from the calculated expected value, a **mixed acid-base disorder** is present.

- **Metabolic Acidosis:** Winter's Formula → Expected $pCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$
  - *If measured pCO_2 > expected:* Concomitant Respiratory Acidosis
  - *If measured pCO_2 < expected:* Concomitant Respiratory Alkalosis
- **Metabolic Alkalosis:** Expected $pCO_2 = (\Delta HCO_3^- \times 0.7) + 40$
- **Respiratory Acidosis ($pCO_2 > 40$):**
  - *Acute:* For every 10 ↑ in pCO_2, HCO_3^- ↑ by 1
  - *Chronic:* For every 10 ↑ in pCO_2, HCO_3^- ↑ by 3.5
- **Respiratory Alkalosis ($pCO_2 < 40$):**
  - *Acute:* For every 10 ↓ in pCO_2, HCO_3^- ↓ by 2
  - *Chronic:* For every 10 ↓ in pCO_2, HCO_3^- ↓ by 5

2. Anion Gap & Delta-Delta Gap Calculations

- **Anion Gap (AG) = $Na^+ - Cl^- - HCO_3^-$**
  - *Normal AG:* 8–12 mEq/L (NAGMA).
  - *High AG:* > 12 mEq/L (HAGMA).
- **Albumin Correction:** Hypoalbuminemia artificially lowers the AG, masking a HAGMA.
  - **Corrected AG** = Measured AG + [2.5 × (4 – measured albumin)]
- **Delta-Delta Gap (ΔAG vs ΔHCO_3^-):** Used *only* when HAGMA is present.
  - ΔAG = Measured AG - 12
  - ΔHCO_3^- = 24 - Measured HCO_3^-
  - **Interpretation:**
    - If $\Delta AG \approx \Delta HCO_3^-$ (±6): Pure HAGMA
    - If $\Delta AG > \Delta HCO_3^-$: Concomitant Metabolic Alkalosis
    - If $\Delta AG < \Delta HCO_3^-$: Concomitant NAGMA

3. High-Yield Etiologies by Disorder

- **HAGMA:** DKA, Lactic Acidosis, Salicylate toxicity (late), Uremia.
- **NAGMA:** Severe diarrhea (e.g., *C. diff* / pseudomembranous colitis), Renal Tubular Acidosis (RTA).
- **Metabolic Alkalosis:** Severe vomiting (loss of H^+ and Cl^-).
- **Respiratory Alkalosis:** Hypoxia (the most important cause of hyperventilation), Cirrhosis, Anxiety, Salicylate toxicity (early).
- **Respiratory Acidosis:** COPD, acute respiratory failure.

Investigations

- **Urine Anion Gap (UAG):** Differentiates causes of NAGMA.
  - **Formula:** UAG = Urine Na^+ + Urine K^+ - Urine Cl^-
  - **Negative UAG (< 0):** GI loss of bicarbonate (e.g., severe diarrhea). The kidneys are appropriately excreting NH_4^+ (measured alongside Cl^-).
  - **Positive UAG (> 0):** Renal loss or failure to excrete acid (e.g., Distal RTA).
- **Basic Metabolic Panel (BMP):** Required alongside ABG to calculate Anion Gap and Delta Gap.
- **Serum Albumin:** Mandatory to calculate the Corrected Anion Gap.

Management

- **Respiratory Alkalosis & Hypocalcemia:** Alkalosis causes hydrogen ions to dissociate from albumin, freeing up binding sites for ionized calcium. This drops *ionized* calcium levels (while total calcium remains normal), leading to numbness, tingling, and tetany. Treat the underlying cause of hyperventilation.
- **Salicylate Toxicity:** Presents with a mixed **Primary Respiratory Alkalosis** (due to direct medullary stimulation) + **Primary HAGMA** (due to uncoupling of oxidative phosphorylation).
  - *Management:* Alkalinize the urine using **Sodium Bicarbonate** to facilitate salicylate excretion, even if the patient's systemic pH is relatively normal or acidemic.

Past-Paper High Yield

- **Salicylate Toxicity Trap:** A classic board scenario features an ABG with a mildly low pH (e.g., 7.30), profoundly low HCO_3^- (e.g., 16), and a highly depressed pCO_2 (e.g., 18).
  - *Calculation:* Winter's formula predicts pCO_2 should be (1.5 × 16) + 8 = 32. Since the actual pCO_2 is 18, there is a massive concomitant primary Respiratory Alkalosis.
  - *Exam focus:* Do not give acetazolamide. The most appropriate next step is **Sodium Bicarbonate** for urinary alkalinization.
- **NAGMA Differentiation (Diarrhea vs. RTA):**
  - Given a patient with fatigue, NAGMA (normal AG), and hypokalemia.
  - Check the Urine Anion Gap ($Na^+ + K^+ - Cl^-$). If UAG is strongly **positive** (e.g., +38), the kidneys are failing to excrete acid/ammonium.
  - *Diagnosis:* Distal Renal Tubular Acidosis (Type 1 RTA). If UAG were negative, the answer would be severe diarrhea.

- **Hypocalcemia in Alkalosis:** A young patient with hyperventilation (e.g., anxiety) presents with bilateral hand numbness. The exam tests the mechanism: Respiratory Alkalosis → ↓ ionized calcium → neuromuscular irritability.

Memory Pearls

- **The Compensation Rule of "1, 2, 3.5, 5"**: For every 10 mmHg Δ in pCO_2, HCO_3^- changes by:
  - **1** (Acute Resp Acidosis)
  - **2** (Acute Resp Alkalosis)
  - **3.5** (Chronic Resp Acidosis)
  - **5** (Chronic Resp Alkalosis)
- **"Correct the Gap to find the Trap"**: Always calculate the Corrected AG in patients with hypoalbuminemia (cirrhosis, nephrotic syndrome, malnutrition) to reveal a hidden HAGMA.
- **Triple Acid-Base Disorders**: Only possible if one disorder is Respiratory, one is a HAGMA, and the third is either Metabolic Alkalosis or NAGMA (revealed by the Delta-Delta Gap).

Respiratory

Exam Map

RESPIRATORY TOPIC	QUESTION COUNT	REVISION PRIORITY
Asthma	47	**Highest**
Pneumonia	32	**Highest**
Respiratory Failure	15	**High**
COPD	14	**High**
Pulmonary Function Tests (PFT)	10	**High**
Lung Cancer	7	Medium
Pleural Disease	7	Medium
Chest X-Ray (CXR) & Respiratory Imaging	8	Medium
Interstitial Lung Disease (ILD)	6	Medium
Obstructive Sleep Apnea & OHS	5	Low
Pulmonary Embolism & Pulmonary HTN	4	Low

Recurring Exam Patterns and Revision Priorities:

- **The Asthma PaCO2 Trap:** You will routinely be tested on asthma severity using ABGs. A "normal" or elevated PaCO2 in an acutely dyspneic asthma patient is a massive red flag indicating respiratory muscle fatigue and impending respiratory failure.
- **Asthma Pharmacology Limits:** Memorize the biologic cut-offs (Omalizumab is strictly for IgE between 30 and 700; switch to anti-IL-5 for higher values) and acute treatments (Montelukast is *never* the correct answer for an acute ER exacerbation).
- **CURB-65 Calculations:** Pneumonia vignettes will require you to manually calculate a CURB-65 score to determine the site of care (0-1 = outpatient, 2 = ward, 3+ = ICU) and select the corresponding empiric antibiotics.
- **COPD Prognosis vs. Symptom Control:** Examiners frequently test the difference between therapies that improve survival (Smoking Cessation, Long-Term Oxygen Therapy) and those that only improve symptoms/exacerbation rates (Inhalers, Pulmonary Rehab).
- **NIV vs. Intubation in Respiratory Failure:** Know exactly when to use BiPAP (hypercapnic conscious patients with COPD/OHS) versus when to intubate (low GCS, unmanageable secretions, profound acidemia pH < 7.15).
- **PFTs and the DLCO Differentiator:** Use DLCO to crack restrictive and obstructive vignettes. High DLCO = Asthma or pulmonary hemorrhage. Low DLCO = Emphysema or ILD. Normal DLCO =

Neuromuscular disease, Obesity, or Chronic Bronchitis.

- **Lung Cancer Paraneoplastic Syndromes:** Link tumor histology to specific presentations. Small Cell Lung Cancer (SCLC) = SIADH, Cushing, Lambert-Eaton, and SVC Syndrome. Squamous Cell = Hypercalcemia (PTHrP) and Cavitation.
- **Pleural Fluid Biochemistry:** Master Light's criteria and specific fluid markers. Expect to differentiate an RA pleural effusion (glucose < 50) from a parapneumonic effusion, and know that a milky effusion requires testing for Triglycerides (>110 = Chylothorax).
- **Idiopathic Pulmonary Fibrosis (IPF) Management:** If a vignette describes an older patient with Velcro crackles and an HRCT showing subpleural honeycombing and traction bronchiectasis, the diagnosis is IPF. The correct next step is to start antifibrotics (Pirfenidone/Nintedanib)—do *not* select lung biopsy.
- **Radiology Fundamentals:** Distinguish between lung consolidation (volume preserved, air bronchograms present, no tracheal shift) and atelectasis (volume loss, no air bronchograms, trachea shifts *towards* the lesion).

Asthma

Core Concepts

- **Pathophysiology:** A chronic inflammatory airway disease characterized by a classic triad:
  - **Airway inflammation:** Driven by cytokines such as **IL-4, IL-5** (eosinophil recruitment), and **IL-13**.
  - **Intermittent airflow obstruction:** Early phase involves IgE-mediated acute bronchoconstriction; late phase (6–24 hrs) involves airway edema and mucous plugging.
  - **Bronchial hyperresponsiveness:** Triggers cause hyperinflation to compensate, leading to hypoventilation, vasoconstriction, and V/Q mismatch.
- **Airway Remodeling:** Long-standing, chronic inflammation leads to structural changes in the airways, which can result in fixed/incomplete reversibility.
- **Common Triggers:** Viral infections (rhinovirus, RSV), exercise, GERD, chronic sinusitis ("united airways"), obesity, beta-blockers, and environmental allergens.

Diagnosis / Clinical Features

- **Classic Symptoms:** Non-productive cough (often worse at night or early morning), wheezing, dyspnea, and chest tightness.
  - *Note:* Asthma can present **without wheezing** (especially if obstruction predominantly involves small airways).
- **Phenotypes & Specific Presentations:**
  - **Occupational Asthma (10–15% of adult cases):** Suspect in patients whose symptoms reliably improve on weekends/holidays. Diagnosis is supported by peak-flow monitoring at work vs. away from work.
  - **Aspirin-Induced Asthma (Samter's Triad):** Asthma, aspirin/NSAID sensitivity, and nasal polyps. Mediated by increased eosinophils and cysteinyl leukotrienes. Avoidance and

leukotriene antagonists are the mainstays of treatment.
    - **Exercise-Induced Asthma:** Symptoms peak 5–10 minutes *after* stopping exercise or 10 minutes into activity. Triggered by heat and water loss from the airway. Prevent with warm-up and pre-exercise short-acting beta-agonists (SABA).
- **Physical Examination by Severity:**
    - **Mild:** Patient speaks in full sentences, HR < 100 bpm, O2 > 95%, moderate expiratory wheezing.
    - **Moderate:** Patient speaks in phrases, uses accessory muscles, HR 100–120 bpm, loud expiratory wheezing, pulsus paradoxus (10–20 mmHg).
    - **Severe:** Patient speaks in single words, sits in tripod position, RR > 30/min, HR > 120 bpm, loud **biphasic** (inspiratory and expiratory) wheezing, pulsus paradoxus (20–40 mmHg), O2 < 91%.
    - **Impending Respiratory Failure:** Drowsy/confused, **silent chest** (absence of wheezing due to severe airflow limitation), thoracoabdominal paradox, severe hypoxemia, bradypnea, and an **absent** pulsus paradoxus (indicating respiratory muscle fatigue).

Investigations

- **Spirometry (Best Diagnostic Test):**
    - Demonstrates an obstructive pattern: FEV1/FVC < 70% (or < 75% depending on reference ranges/age).
    - **Reversibility:** FEV1 increases by **≥ 12% AND ≥ 200 mL** following administration of a short-acting bronchodilator.
    - *Note:* Pulmonary function tests (PFTs) can be completely normal between attacks.
- **Bronchoprovocation Testing (Most Specific Test):**
    - Used when baseline spirometry is normal but clinical suspicion is high (e.g., exercise-induced or intermittent asthma).
    - **Methacholine Challenge:** A positive test is a **≥ 20% decrease** in FEV1 at a dose up to 4 mg/mL.
    - Contraindicated if baseline FEV1 is < 65–70%.
- **Peak Expiratory Flow (PEF):**
    - **Best test for evaluating the severity** of an acute asthma attack.
    - A diurnal variability of > 25% is strongly supportive of an asthma diagnosis.
- **Arterial Blood Gas (ABG):**
    - Early/Mild Attack: Respiratory alkalosis (hyperventilation causes low PaCO2).
    - Severe Attack: A **"normal" (e.g., PaCO2 40–43 mmHg) or elevated PaCO2** is a dangerous sign indicating respiratory muscle fatigue, pure hypoventilation, and impending respiratory failure.
- **Lung Volumes:** Total Lung Capacity (TLC) and Diffusion Capacity (DLCO) are typically **normal** in severe asthma (unlike emphysema/COPD).
- **Biomarkers:**
    - Blood eosinophilia (>4%) and elevated serum IgE (>100 IU) support the diagnosis and guide biologic therapy.

Management

- **Chronic Maintenance Therapy (Stepwise Approach):**
  - **Step-Up:** If a patient is using their SABA rescue inhaler multiple times a week, step up therapy by adding a long-acting beta-agonist (LABA) to their inhaled corticosteroid (ICS) regimen.
  - **Step-Down:** If symptoms remain well-controlled for 6 months on a combined ICS + LABA, the best next step is to **halve the dose of the ICS** while continuing the LABA.
- **Biologic Therapies (For Severe Persistent Asthma):**
  - **Omalizumab (Anti-IgE):** Subcutaneous injection. Indicated for moderate-to-severe persistent asthma with proven aeroallergen sensitivity. **Crucial restriction:** Serum IgE must be strictly between **30 and 700 IU**, and patient weight < 150 kg.
  - **Benralizumab / Mepolizumab (Anti-IL-5):** Targets eosinophils. The correct choice for patients with severe eosinophilic asthma and significantly elevated IgE (e.g., > 1000 IU) that excludes them from Omalizumab therapy.
- **Acute Exacerbation Management:**
  - **Indicated:** Oxygen, SABA (Albuterol) nebulizers, systemic glucocorticoids, Ipratropium, and Magnesium sulfate (for severe attacks).
  - **Contraindicated / Not Indicated:** Leukotriene receptor antagonists (e.g., Montelukast) have no role in the acute emergency management of an exacerbation.
- **Pregnancy:** Poor control leads to prematurity and low birth weight. The primary goal is to maintain adequate oxygenation to the fetus; standard asthma medications are generally continued.

Complications / Prognosis

- A severe attack presenting with hypoxia and a **normal A-a gradient** indicates pure alveolar hypoventilation (muscle fatigue) and carries a poor prognosis requiring immediate intervention.

Past-Paper High Yield

- **Diagnostic & Severity Superlatives:**
  - *Best diagnostic test:* Spirometry with reversibility.
  - *Most specific test:* Methacholine challenge.
  - *Best test to evaluate attack severity:* Peak Expiratory Flow (PEF).
- **The PaCO2 Trap:** In an acute asthma attack, the patient should be hyperventilating and blowing off CO2. If an ABG shows a PaO2 of 40 and a **PaCO2 of 43**, this is a sign of life-threatening respiratory muscle fatigue.
- **Acute Exacerbation Pharmacology:** Know that **Montelukast is never the right answer** for acute ER management. Stick to O2, Albuterol, Steroids, and Magnesium.
- **Biologics Decision Point:** If a vignette gives you a patient with uncontrolled asthma, high eosinophils, and an exceptionally high IgE (e.g., 1800 IU), do *not* pick Omalizumab. Choose an IL-5 inhibitor like Benralizumab.
- **Flow-Volume Loop Differentiators:**
  - *Asthma:* Obstructive pattern (scooped-out expiratory limb).

    - *Vocal Cord Dysfunction:* Variable extrathoracic obstruction (flattened **inspiratory** limb) — presents with progressive dyspnea and prominent *inspiratory* wheezes/stridor.
- **Wheezing Differentials:** Interstitial Pulmonary Fibrosis (IPF) causes fine inspiratory crackles but does **not** cause wheezing.
- **Cardiac vs. Bronchial Asthma:** An elderly patient with wheezing, bi-basal crackles, severe peripheral edema, and high BNP has heart failure (cardiac asthma). Treat the underlying fluid overload and hypercapnia with Furosemide and CPAP/BiPAP, not just asthma meds.
- **Aspirin Trigger:** A patient with refractory asthma taking daily over-the-counter aspirin for cardiac protection is likely suffering from aspirin-exacerbated respiratory disease.
- **Symptom Pathogenesis:** The intense sensation of dyspnea during an acute attack is primarily driven by the dramatically **increased work of breathing**.

Memory Pearls

- **Normal CO2 = Abnormal Patient:** In an asthma exacerbation, a "normal" PaCO2 means the patient is crashing.
- **Silent but Deadly:** A "silent chest" (no wheezing) is not an improvement; it means airflow is too poor to generate a wheeze.
- **Weekend Cure:** Symptoms that reliably improve on holidays = Occupational Asthma.
- **Omalizumab "Limits":** Think **"Oh-my-IgE"**—it only works if IgE is strictly between 30 and 700. Too high, and you must switch to an IL-5 inhibitor.

Chronic Obstructive Pulmonary Disease (COPD)

Core Concepts

- **Definition:** A heterogeneous, progressive lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum) and persistent airflow obstruction.
- **Pathophysiology:**
    - **Emphysema (Alveolar disease):** Enlargement of airspaces distal to terminal bronchioles due to the destruction of alveolar walls (elastin breakdown). Results in **increased lung compliance** and loss of elastic recoil.
    - **Chronic Bronchitis (Airway disease):** Inflammatory changes leading to ciliary dysfunction and goblet cell hypertrophy/hyperplasia. Results in excessive mucus secretion.
    - *Diagnostic criteria for Chronic Bronchitis:* Cough and sputum production for most days over **3 months** for **2 consecutive years**.
- **Epidemiology:** 3rd leading cause of death worldwide. More common in patients ≥ 65 years. Associated mortality in women has doubled over the past 20 years.

Diagnosis / Clinical Features

- **Early Symptoms:** Exertional dyspnea, recurrent mild cough, and frequent morning throat clearing.
- **Late Symptoms:** Progressive worsening dyspnea, chronic cough (with or without mucus), fatigue, chest tightness, wheezing, weight loss, and recurrent respiratory infections.

- **Physical Examination:**
  - *Early:* Prolonged expiratory time (most consistent early finding).
  - *Severe disease:* Hyperinflation signs (barrel-shaped chest / increased AP diameter, decreased breath sounds, hyper-resonance to percussion, distant heart sounds), tripod positioning, pursed-lip breathing, and signs of right heart failure (cor pulmonale).

Classic Phenotypes (Heavily Tested)

- **"Pink Puffer" (Emphysema Predominant):**
  - Thin/cachectic (muscle wasting, weight loss).
  - Marked hyperventilation, severe dyspnea, pursed-lip breathing.
  - Increased AP diameter (barrel chest).
  - *Minimal* sputum production (large amounts of sputum are *inconsistent* with pure emphysema).
  - Less hypoxemic early in the disease course ("pink").
- **"Blue Bloater" (Chronic Bronchitis Predominant):**
  - Productive cough with excessive sputum.
  - Decreased ventilation and severe ventilation-perfusion (V/Q) mismatch leading to significant hypoxemia and cyanosis ("blue").
  - Fluid retention and right heart failure leading to edema ("bloater").

Differentiating COPD from Asthma

FEATURE	COPD	ASTHMA
Onset	Later in life (>40 yrs)	Childhood or youth
Course & Symptoms	Chronic, progressive, worse on exertion	Intermittent, variable, worse at night/morning
Inflammatory Cells	Neutrophils, Macrophages (Th-1 type)	Eosinophils, Mast cells (Th-2 type)
Bronchodilators	Partially reversible / irreversible	Largely reversible

Investigations

- **Spirometry:** The gold standard for diagnosis. Demonstrates persistent airflow obstruction (Post-bronchodilator FEV1/FVC < 0.70). *Note: Screening asymptomatic individuals with spirometry is not recommended; screen via history of smoking/exposures.*
- **Flow-Volume Loop (FVL):** Classic obstructive pattern with a "scooped-out" or concave expiratory limb is highly characteristic of **severe emphysema**.
- **Pulmonary Function Tests (PFTs):** Emphysema shows increased Total Lung Capacity (TLC) and Residual Volume (RV) due to air trapping, with **decreased DLCO** (due to alveolar capillary bed destruction).
- **Arterial Blood Gas (ABG):** Indicated for evaluation of severe disease or SpO2 ≤ 92%.
- **Chest X-Ray (CXR):** Primarily used to rule out complications (e.g., pneumonia, pneumothorax) during an acute exacerbation.

Management

Improving Prognosis (Mortality Benefits)

1. **Smoking Cessation:** The *single best intervention* to alter the natural history of the disease and improve prognosis.
2. **Long-Term Oxygen Therapy (LTOT):** Proven to improve survival in patients with severe resting hypoxemia ($PaO_2 \leq 55$ mmHg, or < 59 mmHg if right heart failure/erythrocytosis is present). It works by improving hypoxemia and decreasing pulmonary vascular resistance.

Stable COPD Pharmacotherapy

- **Bronchodilators (LAMA / LABA):** Central to symptom management. Tiotropium (a LAMA) improves dyspnea and quality of life.
- **Inhaled Corticosteroids (ICS):** Do *not* use as monotherapy. When added to bronchodilators, they decrease the number and severity of exacerbations.
- **High Exacerbation Risk (Group E / Frequent Exacerbators):** E.g., a patient with mMRC 2, CAT 15, and ≥2 exacerbations per year. The best next step in management is combination therapy with **LAMA + LABA**.
- **Non-Pharmacological:** Pulmonary rehabilitation highly improves dyspnea and quality of life. Vaccinations are essential.

Acute Exacerbations

- *Definition:* Acute worsening of dyspnea, cough, or sputum production over ≤14 days, often accompanied by tachycardia/tachypnea, typically triggered by airway infection or pollution.
- *Hypoxia Mechanism:* Primary driver is **mixed hypoventilation and V/Q mismatch**.
- *Diagnostic Step:* Avoid spirometry during an acute exacerbation. If a patient presents with sudden severe worsening or hypoxia (SpO_2 92%), evaluate for complications (ABG, CXR).

Complications / Prognosis

- **Secondary Spontaneous Pneumothorax:** COPD patients (especially with emphysema/bullae) are at high risk.
  - *Physical Exam findings:* Respiratory distress, **hyper-resonance** on percussion, **decreased** breath sounds, and **decreased** chest wall movement.
  - *Trap:* Tactile vocal fremitus is **decreased**, *not* increased.
- **Cor Pulmonale:** Right heart failure secondary to chronic hypoxic pulmonary vasoconstriction.

Past-Paper High Yield

- **Emphysema vs. Bronchitis presentations:** If a question describes a young, thin patient with an increased AP diameter and pursed lips, they have emphysema. If the option claims "production of large amounts of sputum," it is the **wrong** choice for this phenotype.
- **Flow-Volume Loop:** A concave, "scooped-out" expiratory phase on an FVL is typical for **Severe Emphysema**.

- **Prognosis Modifiers:** Do not be tricked by inhalers—to improve *prognosis/survival* in a smoking COPD patient, you must recommend **full smoking cessation** and/or **long-term O2 therapy (LTOT)**.
- **O2 Therapy:** Understand that LTOT works by correcting hypoxemia which *decreases* pulmonary vascular resistance (reversing hypoxic vasoconstriction).
- **Hypoxia Mechanism:** Select **"Mixed hypoventilation & V/Q mismatch"** or V/Q mismatch as the mechanism of hypoxia in COPD exacerbations.
- **Pneumothorax Trap:** In a COPD patient presenting with a pneumothorax, tactile vocal fremitus is *decreased*, never increased. Increased fremitus indicates consolidation (e.g., pneumonia).
- **Exacerbation Management (Stable vs Acute):** If a patient has multiple exacerbations (e.g., CAT 15, mMRC 2), the appropriate step-up maintenance therapy is **LAMA + LABA**.
- **Steroids in COPD:** ICS decreases the *number and severity* of exacerbations.
- **Disease Prevalence Myth:** COPD does *not* eventually develop in all smokers (only about 20-25% of smokers develop clinically significant COPD, though cessation benefits all).

Memory Pearls

- **Pink Puffer = Emphysema:** Thin, hyperinflated (Barrel chest), pursed lips, quiet chest, *no/minimal sputum*, low DLCO.
- **Blue Bloater = Bronchitis:** Obese, cyanotic, right heart failure (edema), *copious sputum*, normal DLCO.
- **Prognosis vs. Symptoms:** Oxygen and Smoking Cessation save *lives*. Bronchodilators (LAMA/LABA) and Rehab save *lifestyles* (improve quality of life/dyspnea).
- **Pneumothorax Rule of D's:** **D**ecreased breath sounds, **D**ecreased chest movement, **D**ecreased fremitus (but *hyper-resonant* percussion).

Respiratory Failure

Core Concepts

Definition and Classification

- **Respiratory Failure:** Failure of gas exchange leading to hypoxemia ($PaO_2 < 60$ mmHg).
- **Type 1 (Hypoxemic):** $PaO_2 < 60$ mmHg with a normal or low $PaCO_2$.
- **Type 2 (Hypercapnic):** $PaO_2 < 60$ mmHg with $PaCO_2 > 50$ mmHg (decreased CO_2 elimination).
- **Acute vs. Chronic:**
  - **Acute:** Develops over minutes/hours. Life-threatening ABG derangement; **pH is < 7.3**.
  - **Chronic:** Develops over days/longer. Kidneys compensate by retaining bicarbonate, so pH is only slightly decreased. Characterized by long-standing signs (polycythemia, cor pulmonale).

Alveolar Gas Equation & A-a Gradient

- **Normal A-a gradient is < 10 mmHg.** A normal gradient indicates there is *no defect in the diffusion of gases* across the alveolar membrane.

- $PAO_2 = FiO_2 \times (P\_B - P\_H_2O) - (PaCO_2/R)$
- $PaCO_2 = VCO_2 \times K / V_a$ (Inversely proportional to minute ventilation).

Pathophysiology of Hypoxemia (5 Mechanisms)

1. **Hypoventilation:** Decreased respiratory rate or tidal volume. High PaCO2. **Normal A-a gradient.** Corrects with ventilation/O2.
2. **High Altitude (Low inspired FiO2):** Decreased barometric pressure lowers alveolar PO2. **Normal A-a gradient.** Corrects with O2.
   - *Compensation:* Initial hyperventilation (respiratory alkalosis), right-shift of O2 curve (increased 2,3-DPG), and later polycythemia (increased erythropoietin) + renal bicarbonate excretion.
3. **Diffusion Impairment:** Structural problems (decreased surface area in emphysema, thickened membrane in fibrosis). **Increased A-a gradient.** Corrects with O2.
4. **Ventilation-Perfusion (V/Q) Mismatch:**
   - *Decreased V/Q (< 0.8):* Normal perfusion, poor ventilation (e.g., COPD, asthma).
   - *Increased V/Q (> 0.8):* Normal ventilation, poor perfusion (e.g., Pulmonary embolism).
   - **Increased A-a gradient.** Corrects with O2.
5. **Pulmonary Shunt:** Deoxygenated blood bypasses ventilated alveoli (Right-to-Left shunt, atelectasis, ARDS). V/Q = 0. **Increased A-a gradient.**
   - *Key Feature:* **Does NOT correct with 100% supplemental O2** (refractory hypoxemia).

Diagnosis / Clinical Features

Acute Respiratory Distress Syndrome (ARDS)

- A rapidly progressive non-cardiogenic pulmonary edema initially manifesting as dyspnea, tachypnea, and hypoxemia.
- **Berlin Diagnostic Criteria:**
  - **Timing:** Within 1 week of a known clinical insult or new/worsening respiratory symptoms.
  - **Imaging:** Bilateral opacities on chest radiograph not fully explained by effusions, collapse, or nodules (lacks obvious vascular congestion).
  - **Origin of edema:** Respiratory failure not fully explained by cardiac failure or fluid overload.
  - **Oxygenation (PaO2/FiO2 ratio with PEEP ≥ 5 cm H2O):**
    - *Mild:* 200 – 300 mmHg
    - *Moderate:* 100 – 200 mmHg
    - *Severe:* ≤ 100 mmHg

Investigations

- **ABG:** Differentiates Type 1 vs Type 2 and Acute vs Chronic (via pH).
- **A-a Gradient Calculation:** Directs differential diagnosis of hypoxemia.
- **Hemodynamic Monitoring (Swan-Ganz / Pulmonary Artery Catheter):** Used historically or in complex cases to differentiate ARDS from cardiogenic edema.

- *Cardiogenic Edema:* Pulmonary Capillary Wedge Pressure (PCWP) > 18 mmHg; High Left Atrial Pressure.
- *ARDS:* **PCWP < 18 mmHg**; Normal Left Atrial Pressure.

Management

General Approach

- **ABCs first.** Correct hypoxemia/prevent tissue hypoxia.
- **Target SpO2:** > 90% (PaO2 > 60 mmHg) for most patients; **88–92%** for patients with severe COPD and chronic hypercapnia.

Non-Invasive Positive-Pressure Ventilation (NIV / BiPAP)

- **Indications:** Acute exacerbations of COPD with hypercapnia (greatest reduction in mortality rate), Obesity Hypoventilation Syndrome (OHS), cardiogenic pulmonary edema.
- **Contraindications (Requires Intubation):** Low GCS/coma (e.g., GCS < 8), copious unmanageable secretions, profound acidemia (e.g., pH < 7.15), hemodynamic instability.
- *Note:* BiPAP is preferred over CPAP for Type 2 failure (like OHS or COPD) because the dual pressures provide ventilatory support to blow off CO2.

ARDS Specific Management

- **Mechanical Ventilation:**
  - **Low Tidal Volume:** Prevents alveolar overdistension (volutrauma/barotrauma).
  - **High PEEP (Positive End-Expiratory Pressure):** Recruits collapsed alveoli and improves oxygenation.
  - **Permissive Hypercapnia:** Allowing PaCO2 to run high is beneficial/acceptable to maintain low tidal volumes and avoid lung injury.
- **Positioning:** Prone positioning is recommended for moderate/severe cases.
- **Ineffective/False Therapies:** Glucocorticoids have minimal effect on mortality. Routine Swan-Ganz catheterization does NOT improve mortality.

Past-Paper High Yield

- **COPD Exacerbation Management:**
  - If the patient is **conscious/alert** with hypercapnia (pH ~7.28, PaCO2 ~78), **NIV (BiPAP)** is the indicated next step and provides the **greatest reduction in mortality**. Early intubation here is the *least* indicated step.
  - If the patient has a **low GCS (e.g., 7)** or cannot protect their airway (copious unmanageable secretions) with profound acidosis (pH ~7.10), **intubation with mechanical ventilation** is the immediate next step.
  - Target SpO2 for severe COPD on BiPAP is strictly **88–92%**.
- **ARDS Pathophysiology & Differentiation:**

    - The primary mechanism of hypoxemia in ARDS is **intrapulmonary shunting** (blood perfuses unventilated, fluid-filled alveoli).
    - A patient on 100% O2 whose PaO2 remains severely low (e.g., 65 mmHg) is exhibiting **refractory hypoxemia due to a shunt**.
    - *Cardiogenic edema vs. ARDS:* ARDS uniquely has a **normal Left Atrial Pressure / PCWP < 18 mmHg**.
- **NIV Efficacy:** NIV is highly recommended for COPD and OHS. It is generally **NOT recommended** as a standard primary intervention for acute *asthma* exacerbations.
- **ARDS Management Traps:** Permissive hypercapnia is beneficial. Swan-Ganz catheters do *not* improve mortality. Steroids have minimal effect.
- **Kyphoscoliosis:** Hypoxia is caused by a combination of **hypoventilation** (restrictive chest wall) and **V/Q mismatch** (microatelectasis).
- **Hypoxia Compensation:** The physiologic response to systemic hypoxia includes **increased erythropoietin synthesis**.

Memory Pearls

- **Normal A-a Gradient = "Hypo Hypo": Hypo**ventilation and **Hypo**baric (high altitude) hypoxia.
- **Shunt vs. V/Q Mismatch:** If it corrects with 100% O2, it's a V/Q mismatch. If it doesn't budge, it's a Shunt.
- **ARDS PCWP:** < 18 = ARDS (Non-cardiogenic). > 18 = Cardiogenic.

Pneumonia

Core Concepts

- **Community-Acquired Pneumonia (CAP):** Acute pulmonary parenchymal infection acquired outside of the hospital.
- **Hospital-Acquired Pneumonia (HAP):** Diagnosed ≥48 hours after hospital admission.
- **Ventilator-Associated Pneumonia (VAP):** Diagnosed ≥48 hours after endotracheal intubation (Clinical Pulmonary Infection Score ≥ 6 indicates VAP).
- **Mortality:** Scales with severity and setting; Outpatient (<1%), Ward Admission (10–14%), ICU (30–40%).
- **Bronchiectasis:** Abnormal, irreversible bronchial dilatation (cylindrical, saccular, varicose). Driven by a vicious cycle of impaired mucociliary transport, inflammation, and recurrent infection.

Diagnosis / Clinical Features

- **Presentation:** Cough, dyspnea, sputum production, fever, and pleuritic chest pain.
- **Physical Exam:** Decreased air entry, bronchial breathing, dullness to percussion, and coarse crackles.
- **Bronchiectasis specific:** Chronic daily purulent sputum, wheezes/crackles, and digital clubbing.
- **Pathogen-Specific Clinical Clues:**

- *Streptococcus pneumoniae:* Often associated with cold sores (herpes labialis) and is the most common superinfection following H1N1 influenza.
- *Mycoplasma pneumoniae:* Associated with erythema nodosum, autoimmune hemolytic anemia (jaundice, positive Coombs complement, cold agglutinins), and bilateral hazy interstitial infiltrates.
- *Klebsiella pneumoniae:* Classically seen in alcoholics, presenting with right upper lobe (RUL) consolidation and bloody/currant jelly sputum.

- **Secondary Causes / Syndromes:**
  - *Cystic Fibrosis:* Lower lobe bronchiectasis/pneumonias + loose stools + **absent vas deferens**.
  - *Kartagener's Syndrome:* Frequent pneumonias + chronic sinusitis + **dextrocardia**.
  - *Hypersensitivity Pneumonitis:* Bird exposure (e.g., parrot) + upper lobe noncaseating granulomas.

Investigations

- **Imaging:** CXR or HRCT demonstrating interstitial infiltrates, lobar consolidation, or cavitation.
- **Microbiology:**
  - **Sputum & Blood Cultures:** Yield depends on prior antibiotic exposure. *S. pneumoniae* and *H. influenzae* are hard to grow; *S. aureus* and Gram-negative bacilli grow easily.
  - **Urine Antigens:** Pneumococcal antigen (~70% sensitive, unaffected by antibiotics). Legionella antigen (detects *only* Serotype 1).
  - **Viral PCR:** Essential for COVID-19 and Influenza.
- **Procalcitonin (PCT):**
  - Induced by bacterial toxins, IL-1, IL-6, and TNF. Rises in 2-4 hours, peaks at 24-48 hours.
  - Used to guide the **discontinuation** of antibiotics in CAP/ICU patients (levels <0.5 ng/mL indicate low risk).
  - **Exam Trap:** PCT should *not* be used to withhold initial antibiotics; initiation is based on clinical judgment. PCT is elevated in CKD and drops by 30-80% after hemodialysis.
- **Tuberculosis Workup:** If a patient has a highly suspicious cavitary lung lesion and typical symptoms but has 3x negative sputum Acid Fast Bacilli (AFB) smears, the next best step is **bronchoscopy** with lavage.

Management

- **Triage (CURB-65 Score):** Determines the site of care. 1 point for each:
  - **C**onfusion
  - **U**rea > 7 mmol/L (or BUN > 19 mg/dL)
  - **R**espiratory Rate ≥ 30 breaths/min
  - **B**lood Pressure < 90/60 mmHg (Systolic < 90 OR Diastolic ≤ 60)
  - **65:** Age ≥ 65 years
  - *Scoring:* 0–1 = Outpatient; 2 = Ward admission; 3–5 = ICU admission.

- **Empiric Antibiotic Therapy:**
  - **Outpatient (Healthy):** Amoxicillin, Doxycycline, or Macrolide.
  - **Outpatient (Comorbidities):** Amoxicillin/Clavulanate + Macrolide OR Respiratory Fluoroquinolone (Levofloxacin/Moxifloxacin).
  - **Inpatient (Ward):** Beta-lactam (e.g., Ceftriaxone) + Macrolide (e.g., Azithromycin) OR Respiratory Fluoroquinolone monotherapy.
  - **Inpatient (ICU):** Beta-lactam + Macrolide OR Beta-lactam + Respiratory Fluoroquinolone.
- **Risk-Stratified Coverage:**
  - **MRSA:** Add Vancomycin or Linezolid. Risk factors: recent hospitalization, IV antibiotics, hemodialysis.
  - **Pseudomonas:** Use Piperacillin/Tazobactam, Cefepime, or Meropenem. Risk factors: structural lung disease (bronchiectasis), frequent COPD exacerbations requiring antibiotics/steroids, immunocompromise.
- **Bronchiectasis Management:**
  - Airway clearance techniques.
  - **Nebulized Hypertonic Saline:** Inhibits epithelial sodium channels (ENaC), decreases mucus viscosity, and improves mucociliary clearance.
  - **Long-term Macrolides:** Azithromycin for 6 months significantly reduces exacerbations due to combined antibacterial and immunomodulatory effects.
- **Corticosteroids:** Routine use in CAP has no net benefit and increases the risk of hyperglycemia and secondary infections. *Note: Inhaled corticosteroids (e.g., Budesonide) increase the rate of incident pneumonia in COPD patients.*

Complications / Prognosis

- **Parapneumonic Effusion / Empyema:** Exudative effusion (high LDH, high protein). If CXR/US shows **"multiple pocketing" (loculations)** despite antibiotics, the standard management is a **chest tube and intrapleural fibrinolytics (e.g., streptokinase)**.
- **DVT / VTE Prophylaxis:** Pneumonia and sepsis are provoking factors for DVT. Anticoagulation is typically limited to the standard 3-6 month provoked treatment period (unlike unprovoked DVT, which requires consideration for indefinite anticoagulation).

Past-Paper High Yield

- **CURB-65 Calculations:** Be prepared to calculate this manually.
  - *Example 1:* 44yo, Confusion (1), Urea 8.2 (1), BP 95/65 (0), RR 26 (0). Score = 2 → Admit to ward with IV antibiotics.
  - *Example 2:* 66yo, Confusion (1), BP 80/50 (1), RR 30 (1). Score ≥3 → Admit to ICU with IV Ceftriaxone + Azithromycin.
  - *Example 3:* 35yo, stable vitals, CURB-65 = 1 → Discharge on oral Levofloxacin or Azithromycin.
- **Loculated Effusion:** "Multiple pocketing" on CXR a day after starting antibiotics? Do not wait for antibiotics to work → Insert chest tube and give streptokinase.

- **Diagnostic Differentiation:**
  - Sudden pleuritic chest pain + normal CXR + mild hypoxia = **Pulmonary Embolism**. Next step is **CT pulmonary angiogram (CTPA)**.
  - Diffuse bilateral infiltrates + clubbing + basal crackles = **Idiopathic Pulmonary Fibrosis (IPF)**. HRCT shows honeycombing and traction bronchiectasis (NOT mosaicism/nodules).
  - Polyuria + bilateral hilar adenopathy + erythema nodosum = **Sarcoidosis**.
- **Glucocorticoid Trap:** While systemic steroids are standard for COPD exacerbations, they are *not* indicated for CAP alone. Furthermore, regular use of inhaled glucocorticoids in COPD directly *increases* the risk of developing pneumonia.

Memory Pearls

- **Alcoholic + Right Upper Lobe + Currant Jelly Sputum:** *Klebsiella pneumoniae*.
- **Cold Sore + Lobar Pneumonia:** *Streptococcus pneumoniae*.
- **Hemolysis + Cold Agglutinins + Atypical Pneumonia:** *Mycoplasma pneumoniae*.
- **Absent Vas Deferens + Lower Lobe Bronchiectasis:** Cystic Fibrosis.
- **Dextrocardia + Sinusitis + Bronchiectasis:** Kartagener's Syndrome.
- **Parrot / Bird Exposure:** Hypersensitivity Pneumonitis (Psittacosis).

Interstitial Lung Disease (ILD)

Core Concepts

- **Definition:** A heterogeneous group of pulmonary disorders characterized by:
  - *Clinical:* Respiratory symptoms (progressive breathlessness, chronic dry cough).
  - *Radiological:* Diffuse infiltrates.
  - *Histological:* Distortion of the gas-exchanging units.
  - *Physiological:* Restrictive lung volumes and impaired oxygenation.
- **Physical Examination:**
  - Fine, end-inspiratory "Velcro" crackles at the lung bases.
  - Digital clubbing (highly associated with idiopathic pulmonary fibrosis).

Diagnosis / Clinical Features

- **Idiopathic Pulmonary Fibrosis (IPF):**
  - Most common form of ILD.
  - Chronic, progressive fibrosing interstitial pneumonia of unknown etiology, limited to the lungs.
  - Typically affects older adults (6th–7th decade); **not** typically seen in the 5th decade.
  - Has **no** extra-pulmonary manifestations except for digital clubbing.
- **Connective Tissue Disease-Related ILD (CTD-ILD):**

- **Systemic Sclerosis (Scleroderma):** Presents with shortness of breath, tight skin (sclerodactyly), and digital ulcerations. HRCT typically shows bilateral ground-glass opacities (NSIP pattern).
- Other causes: Rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), Dermatomyositis/Polymyositis.

- **Other Major ILD Categories:**
  - *Hypersensitivity Pneumonitis (HP):* Immunologic reaction to inhaled antigens.
  - *Sarcoidosis:* Systemic granulomatous disease.
  - *Occupational/Environmental:* Asbestosis.
  - *Iatrogenic:* Drug-induced or Radiation-induced.
  - *Smoking-related ILD.*

Investigations

- **High-Resolution CT (HRCT) Chest:** The **gold standard** imaging modality for assessing ILD and secondary pulmonary lobules.
  - *Patterns:* Linear, reticular, nodular, reticulonodular, ground-glass (common in CTD-ILD), and interlobular septal thickening.
  - *UIP Pattern (Usual Interstitial Pneumonia):* The histological hallmark of IPF, appearing radiologically as basal/peripheral **honeycombing** and traction bronchiectasis.
- **Pulmonary Function Tests (PFTs):** Demonstrate a **restrictive** intra-pulmonary process (decreased lung volumes, preserved or increased FEV1/FVC ratio, decreased DLCO).
- **Lung Biopsy:** Surgical biopsy is used for definitive diagnosis if HRCT is atypical or uninformative.
- **Multidisciplinary Team (MDT):** Gold standard for final diagnostic consensus (Pulmonologist, Radiologist, Pathologist).

Management

- **Idiopathic Pulmonary Fibrosis (IPF):**
  - **Pharmacologic:** Antifibrotic agents (**Pirfenidone** and **Nintedanib**) slow lung function decline.
  - *Contraindicated:* Triple therapy (Prednisone, Azathioprine, N-acetylcysteine) is historically tested but now known to increase mortality/hospitalization in IPF.
- **Non-Pharmacologic / Supportive Care:**
  - Smoking cessation, pulmonary rehabilitation, supplemental oxygen.
  - Vaccinations (Influenza, pneumococcal, and other age-appropriate vaccines).
  - Identify and screen for lung cancer (high risk in IPF).
  - **Lung Transplantation:** The **only** therapy that may actually improve survival in advanced IPF.
- **Advanced Disease / Pulmonary Hypertension (Group 3):**
  - Progressive ILD can lead to Cor Pulmonale (right ventricular heave, loud P2, lower extremity edema, right axis deviation on ECG).

- Targeted pulmonary vasodilator therapies tested in core modules include: Endothelin receptor antagonists (Ambrisentan), PDE-5 inhibitors (Sildenafil), and Prostacyclin analogues (Epoprostenol, Treprostinil).

Past-Paper High Yield

- **Primary Ciliary Dyskinesia (Kartagener Syndrome) vs. CF:** A young male with recurrent chest/sinus infections since childhood, clubbing, and **infertility**. If the physical exam or CXR shows **dextrocardia/situs inversus**, the diagnosis is Primary Ciliary Dyskinesia, *not* Cystic Fibrosis. (Repeated question).
- **Cystic Fibrosis Diagnosis:** The most significant test for confirming CF is a **sweat chloride test > 60 mmol/L**.
- **Scleroderma-ILD:** A 25-year-old female with SOB, tight skin, finger ulcerations, and bilateral ground-glass opacities on HRCT is classically **Connective tissue-related interstitial lung disease**.
- **IPF "EXCEPT" Question Traps:** Remember that IPF is a disease of older adults. If an option states "It is typically seen in the 5th decade of life" (40s), this is **FALSE**. True statements about IPF include: restrictive PFTs, surgical biopsy can be used for diagnosis, transplant is the only survival-improving therapy, and there are no extrapulmonary manifestations besides clubbing.

Memory Pearls

- **UIP = IPF:** Usual Interstitial Pneumonia is the defining histology of Idiopathic Pulmonary Fibrosis.
- **Honeycombing = End-stage fibrosis:** Highly characteristic of the UIP pattern on HRCT.
- **Velcro crackles + Clubbing =** Clinical hallmark of IPF.
- **Situs Inversus + Bronchiectasis + Infertility =** Primary Ciliary Dyskinesia.

Obstructive Sleep Apnea and Obesity Hypoventilation Syndrome

Core Concepts

- **Obstructive Sleep Apnea (OSA):** Characterized by repetitive collapse of the upper airway during sleep, leading to obstructive apneas, hypopneas, or respiratory effort-related arousals (RERAs).
- **Obesity Hypoventilation Syndrome (OHS):** Defined by the triad of:
  1. **Obesity:** BMI ≥ 30 kg/m²
  2. **Daytime hypercapnia:** $PaCO_2$ ≥ 45 mmHg (on room air ABG)
  3. **Absence of alternative causes:** No obstructive lung disease (like COPD), neuromuscular, or metabolic explanation for hypoventilation.
- **OSA and OHS Overlap:** ~90% of OHS patients have coexisting OSA, and 70% have *severe* OSA (AHI ≥ 30).
- **Sleep Architecture:** Sleep is scored in 30-second epochs. Normal sleep is ~80% efficient (5% N1, 50% N2, 20% N3 [deep/slow-wave], 20-25% REM). Deep sleep is essential for growth hormone release and protein synthesis.

Diagnosis / Clinical Features

- **OSA Clinical Features & Risk Factors:**
  - **Mallampati Score:** Each 1-unit increase raises the odds of having OSA by 2.5.
  - **Questionnaires:**
    - **Epworth Sleepiness Scale:** Measures daytime sleepiness.
    - **STOP-BANG Questionnaire:** Screens for OSA risk.
      - **0–2:** Low risk.
      - **3–4:** Intermediate (further criteria needed, e.g., BMI > 35 pushes to high risk).
      - **5–8:** High risk (Score ≥ 3 is 93% sensitive for moderate/severe OSA).
- **OHS Clinical Features:**
  - Often presents as acute-on-chronic Type 2 respiratory failure.
  - Referrals are frequently for "suspected OSA," unexplained dyspnea, or pulmonary hypertension/cor pulmonale.
  - **Diagnostic Trap:** ~75% of OHS patients are misdiagnosed and treated for COPD despite having normal (non-obstructive) pulmonary function tests.

Investigations

- **Polysomnography (PSG):** The gold standard diagnostic test. Analyzes EEG, respiratory effort, airflow, and oxygen saturation.
- **Scoring Respiratory Events:**
  - **Apnea:** ≥ 90% reduction (or complete cessation) in airflow for **≥ 10 seconds**. *(Note: Oxygen desaturation is NOT required for the definition of an apnea).*
    - **Obstructive Apnea:** Apnea WITH continued respiratory effort (chest movement persists).
    - **Central Apnea:** Apnea WITHOUT respiratory effort (no chest movement).
    - **Mixed Apnea:** Inspiratory effort is absent at the beginning of the event but *resumes* in the second portion.
  - **Hypopnea:** ≥ 30% reduction in airflow for ≥ 10 seconds **AND** either a ≥ 3% O_2 desaturation OR an EEG arousal.
  - **RERA (Respiratory Effort-Related Arousal):** Flattening of the inspiratory flow with increasing effort leading to an arousal, **WITHOUT** associated desaturation.
- **Disease Severity Indices:**
  - **AHI (Apnea-Hypopnea Index):** (Apneas + Hypopneas) / total sleep hours.
  - **RDI (Respiratory Disturbance Index):** (Apneas + Hypopneas + RERAs) / total sleep hours.
  - **Grading:** Normal (< 5), Mild (5–15), Moderate (15–29), Severe (≥ 30).
- **ABG (For OHS):** Shows daytime $PaCO_2$ ≥ 45 mmHg.
  - *Supportive clue:* Elevated serum bicarbonate (HCO_3^- > 27 mmol/L) is often an early marker of compensated chronic hypercapnia before daytime $PaCO_2$ rises definitively.

Management

- **OSA Management:**
  - **First-line:** CPAP (Continuous Positive Airway Pressure) for moderate-to-severe OSA.
  - **Lifestyle:** Weight reduction (crucial), smoking cessation, avoidance of sedatives/alcohol.
  - **Alternative/Adjunctive:** Dental appliances (mild/moderate cases or CPAP intolerant). Uvulopalatopharyngoplasty (UPPP) surgery is only 30-40% effective and benefits often wane over the years.
  - **Important Caveat on CPAP:** While CPAP vastly improves daytime sleepiness, physical function, depression, and anxiety, major trials indicate it **does not** prevent cardiovascular events or death in patients with established cardiovascular disease.
- **OHS Management:**
  - **BiPAP (Bilevel Positive Airway Pressure):** The best initial management for patients presenting with OHS and acute-on-chronic hypercapnic respiratory failure (acidotic ABG).
  - **CPAP:** Can be used in stable OHS patients who have concomitant severe OSA, but BiPAP is preferred for significant hypoventilation/acidosis.

Past-Paper High Yield

- **Choice of Positive Airway Pressure:**
  - *Scenario:* 52F with known OHS presenting with acute respiratory acidosis (pH 7.29, $PaCO_2$ 64, PaO_2 58, HCO_3^- 31). **Next step:** BiPAP (NPPV is indicated for acute-on-chronic Type 2 respiratory failure).
  - *Scenario:* 48M with BMI 40, AHI 33/hr (Severe OSA). **Initial therapy:** CPAP. (Do not jump straight to bariatric surgery or BiPAP for uncomplicated severe OSA).
- **Scoring Tricks on PSG:** Recognize **Mixed Sleep Apnea** when a question describes an event where "inspiratory effort is absent at the beginning of the event but resumes in the second portion."
- **Inappropriate Treatments:** Lung volume reduction surgery (LVRS) is a treatment for emphysema, **NOT** used in the management of OSA.
- **Low AHI with Severe Sleepiness:** If a young patient (e.g., 17F) presents with overwhelming daytime sleepiness, refreshing short naps that don't last, and a borderline/mild RDI (e.g., 6 events/hr), the next best step is a **Multiple Sleep Latency Test (MSLT)** to evaluate for Narcolepsy, rather than jumping straight to CPAP.

Memory Pearls

- **OSA vs. Central Apnea Arousals:**
  - In **OSA**, the arousal occurs at the *termination* of the obstructive event (to restore airway tone).
  - In **Cheyne-Stokes breathing** (central apneas sandwiched by crescendo-decrescendo breathing), the arousal occurs at the *peak* of hyperventilation.
- **The Indices Math:**
  - AHI = Apneas + Hypopneas
  - RDI = Apneas + Hypopneas + RERAs

- **OHS "Trap":** Suspect OHS (not COPD) in an obese patient with unexplained cor pulmonale and daytime hypercapnia, especially if PFTs show no obstruction. Elevated HCO_3^- > 27 is your early warning sign!

Pulmonary Embolism and Pulmonary Hypertension

Core Concepts

Pulmonary Embolism (PE) & Venous Thromboembolism (VTE)

- **Definition:** Partial or complete occlusion of a pulmonary arterial branch by a blood clot. DVT and PE are different presentations of the same underlying event (VTE).
- **Thrombus Origins:**
  - **Lower extremity (80–95%):** Most originate in the deep veins of the calf and propagate proximally to the popliteal and femoral veins.
  - *Note:* Calf-limited (below the knee) thrombi pose a minimal embolic risk.
  - **Atypical sites:** Upper-extremity veins (associated with central venous catheters or intravascular cardiac devices).
- **Gas Exchange Pathophysiology:**
  - Creates **V/Q mismatch** and **increased dead space**.
  - Causes hypoxemia, an increased A–a gradient, and **respiratory alkalosis** (due to compensatory hyperventilation).

Pulmonary Hypertension (PH)

- **Haemodynamic Definition:** Mean pulmonary arterial pressure (**mPAP**) > 20 mmHg at rest.

PH TYPE	MPAP	PAWP (LEFT HEART FILLING)	PVR (VASCULAR RESISTANCE)
Pre-capillary PH	> 20 mmHg	≤ 15 mmHg	> 2 WU
Isolated Post-capillary PH	> 20 mmHg	> 15 mmHg	≤ 2 WU
Combined Pre/Post-capillary	> 20 mmHg	> 15 mmHg	> 2 WU

Diagnosis / Clinical Features

- **Typical Presentation of PE:** Sudden onset severe pleuritic chest pain and dyspnea. Patients may appear pale and in pain.
- **Massive PE (High-Risk):** Defined by hemodynamic instability (hemodynamic collapse/shock). Carries an early mortality rate of ~15%.
- **Right Heart Strain / Cor Pulmonale Signs (Expected in severe PE/PH):**
  - **Left parasternal heave:** Indicates right ventricular (RV) enlargement/overload.
  - **Loud P2:** Due to forceful closure of the pulmonary valve against high pulmonary arterial pressures.

    - **Right-sided S3:** Suggests RV failure.
    - **Tachycardia:** A universal compensatory mechanism.
- **WHO Clinical Classification of PH:**
    - **Group 1:** Pulmonary Arterial Hypertension (PAH) – includes idiopathic, connective tissue disease, HIV, congenital heart disease, portal HTN, and schistosomiasis. (Rare, progressive, arterial narrowing via smooth muscle proliferation).
    - **Group 2:** PH due to Left Heart Disease (HFpEF, HFrEF, Valvular disease). *Most common overall.*
    - **Group 3:** PH due to Lung Diseases / Hypoxia (COPD, restrictive lung disease, OSA, high altitude).
    - **Group 4:** Chronic Thromboembolic PH (CTEPH) – due to pulmonary artery obstructions.
    - **Group 5:** Unclear/Multifactorial (Hematologic, systemic, metabolic, chronic renal failure).

Investigations

- **D-Dimer:**
    - A nonspecific measure of fibrinolysis with **high sensitivity and high negative predictive value (NPV)**.
    - **Clinical use:** Used strictly in the outpatient/ER setting to *rule out* PE in patients with **low or intermediate clinical probability**.
    - *Age-adjusted cut-off:* For patients > 50 years, cut-off = Age × 10.
- **CT Pulmonary Angiography (CTPA):** Diagnostic standard for PE. Uses a large, rapid dose of contrast.
- **V/Q Scan:** Reserved for patients who cannot undergo CTPA (renal impairment, IV contrast allergy, pregnancy).
- **Electrocardiogram (ECG):**
    - **Sinus tachycardia** is the most common finding.
    - **Right heart strain signs:** Incomplete RBBB, inverted precordial T waves, and the classic (but minority) **S1Q3T3** pattern.
- **Echocardiography:** Useful for suspected *massive* PE in patients too unstable for transport or with contrast contraindications. Evaluates for RV dilation/dysfunction.
- **Cardiac Biomarkers:** Troponin elevation indicates RV myocardial injury and helps classify non-high-risk patients into "Intermediate Risk."
- **Chest X-Ray:** Often abnormal but nonspecific. Crucial for ruling out other causes of chest pain (like pneumothorax).

Management

- **Risk Stratification (determines therapy):**
    - *High Risk:* Hemodynamically unstable.
    - *Intermediate/Low Risk:* Hemodynamically stable; differentiated by the presence of RV dysfunction (echo/CT) and myocardial injury (troponins).
- **Anticoagulation Treatment Phases:**

1. **Initiation phase:** 5–21 days.
2. **Treatment phase:** 3 months.
3. **Extended phase:** 3 months to indefinite (secondary prevention).

- **Medication Choice:**
  - **NOACs (Novel Oral Anticoagulants):** Now the recommended first-line oral treatment. Doses are typically reduced after the initial 3–6 months.
  - **Vitamin K Antagonists (Warfarin):** Less ideal due to narrow therapeutic window, slow onset/offset, dietary interactions, and ICH risk.
  - **LMWH (Low Molecular Weight Heparin):** Standard of care for **pregnancy** and **cancer-associated PE**.
- **NOAC Contraindications:**
  - Severe CKD (CrCl < 30 mL/min, though Apixaban/Edoxaban can be used cautiously at reduced doses if CrCl is 15-30).
  - Moderate-to-severe hepatic impairment.
  - Pregnancy/Lactation (Warfarin is safe in lactation; LMWH is safe in pregnancy).
  - Antiphospholipid syndrome (efficacy not proven).

Past-Paper High Yield

- **The Pulmonary Edema Trap:** PE is **least likely** to cause pulmonary edema. Massive PE decreases LV preload (causing clear lungs on auscultation), unlike heart failure, volume overload, bicuspid regurgitation, or malignant HTN which flood the alveoli.
- **Normal Heart Exam in Sudden Chest Pain:** If a patient presents with sudden severe chest pain and a strictly *normal* heart exam except for tachycardia, papillary muscle dysfunction is highly unlikely (it causes a loud murmur and acute pulmonary edema). Consider PE, MI, aortic dissection, or pneumothorax instead.
- **The D-Dimer Trap:** D-Dimer is **not** diagnostically useful for high-risk patients. High-risk patients need immediate imaging (CTPA) or bedside echocardiography; D-Dimer is only useful to rule out PE in low/intermediate-risk patients.
- **Auscultation / Cardiac Exam in Massive PE:**
  - *Expected findings:* Tachycardia, right-sided S3, loud P2, and a **left parasternal heave** (which represents RV heave, NOT LV).
  - *Unexpected finding:* **Reversed splitting of S2** is historically an *unexpected* finding in PE. PE causes *wide* splitting of S2 due to delayed RV emptying. Reversed splitting occurs with delayed LV emptying (e.g., LBBB, severe aortic stenosis).

Memory Pearls

- **Calf vs. Thigh:** DVT below the knee = minimal embolic risk. DVT in popliteal/femoral = high embolic risk.
- **Pregnancy / Cancer:** Default to LMWH.
- **PE Blood Gas:** Hypoxemia + Respiratory Alkalosis (patient is hyperventilating and blowing off CO2).

- **RV Strain Triad on Exam:** Left parasternal heave, Loud P2, Elevated JVP.

Pleural Disease

Core Concepts

- **Pleural Physiology:** Normal fluid volume is ~0.3 cc/kg. Produced by mesothelial cells at the upper part of the pleura and absorbed at the diaphragmatic and mediastinal surfaces.
- **Fluid Dynamics:** A 10% increase in fluid flow rate can increase pleural fluid volume by 15%.
- **Mechanisms of Fluid Accumulation:**
  - **Exudates (Protein-rich):** Pleural injury causing increased membrane permeability (e.g., pneumonia, malignancy, Rheumatoid Arthritis, SLE).
  - **Transudates (Protein-poor):** Increased intravascular hydrostatic forces and/or decreased oncotic forces (e.g., CHF, liver failure, nephrotic syndrome).
  - **Extravasation:** Fluid from lymphatic/vascular structures or adjacent body compartments (e.g., ascites traversing via diaphragmatic fenestrations).

Diagnosis / Clinical Features

- **Imaging Detection Thresholds:**
  - **Chest X-Ray (CXR):** Can detect fluid volumes > 250 cc.
  - **Lateral Decubitus CXR:** More sensitive for lower volumes.
  - **Ultrasound (US):** Highly sensitive; can detect very small amounts of fluid.
  - **CT Chest with Contrast:** Useful to evaluate pleural thickening and for surgical planning.

Investigations

- **Thoracentesis (1st Step):** Differentiate transudate vs. exudate using **Light's Criteria**.
- **Light's Criteria:** An effusion is an **exudate** if it meets **ANY** of the following:
  1. Pleural fluid/Serum Protein ratio **> 0.5**
  2. Pleural fluid/Serum LDH ratio **> 0.6**
  3. Pleural fluid LDH **> 2/3 the upper limit of normal serum LDH**
  - *Caveat:* Light's criteria falsely classifies ~25% of transudates as exudates, usually due to concurrent diuretic use.
- **Specific Fluid Analyses:**
  - **Triglycerides (TG): > 110 mg/dL** + positive chylomicrons = Chylothorax.
  - **Glucose:** Very low (< 50 mg/dL) typical in Rheumatoid Arthritis (RA) and empyema.
  - **Amylase:** Markedly elevated (> 1000) in pancreatic-pleural fistula or esophageal perforation (salivary amylase).
  - **pH:** < 7.20 in RA, complicated parapneumonic effusions/empyema; < 7.00 in esophageal perforation (Boerhaave).

- **Adenosine Deaminase (ADA):** High sensitivity (92%) and specificity (90%) for TB (lymphocyte-predominant fluid).
- **Hematocrit (Hct):** Pleural Hct > 50% of blood Hct = Hemothorax.
- **Creatinine:** Pleural > Serum = Urinothorax.

Management

- **Parapneumonic Effusion / Empyema:**
  - *Uncomplicated:* Resolves with antibiotics alone.
  - *Complicated / Empyema (Pus/Bacteria):* **Requires immediate drainage** (chest tube) +/- fibrinolytics/DNAase. Delay significantly increases morbidity. Medical failure (1/3 of cases) requires VATS or decortication.
- **Pneumothorax (PTX):**
  - **Primary Spontaneous (PSP):** No underlying disease (tall, male, smoker).
    - *Small (< 3 cm apex-cupola):* Observe in ED for 3-6 hours. Discharge if CXR stable.
    - *Large (≥ 3 cm):* Small-bore catheter (≤ 14F) or chest tube (16-22F).
    - *Prevention:* Reserve thoracoscopy/pleurodesis/bullectomy for the **second** recurrence (unless persistent air leak > 3-5 days).
  - **Secondary Spontaneous (SSP):** Underlying lung disease (e.g., COPD).
    - *All require hospitalization.* Treated with chest tube (cannot manage with simple aspiration or ED observation alone).
- **Hemothorax:**
  - Manage conservatively if stable and minimal (< 400 cc).
  - Requires tube thoracostomy if moderate (400-1000 cc) or massive (> 1000 cc).
- **Chylothorax:** Dietary management includes a **high-protein, low-fat diet with medium-chain triglycerides (MCTs)**.
- **Hepatic Hydrothorax:** Treat with sodium restriction and lowering portal pressures. Spontaneous bacterial pleuritis occurs in 15% (diagnosed via PMN > 250 + positive culture, or PMN > 500 + negative culture).
- **Malignant Effusions:** Treatment is palliative (repeated thoracentesis, tunneled catheters, pleurodesis).

Complications / Prognosis

- **Empyema Mortality:** 10–20% if inadequately drained; Hippocrates noted, "If an empyema does not rupture, death will occur."
- **Retained Hemothorax:** If undrained, can lead to recurrent effusion, infection, and trapped lung/fibrothorax.
- **Spontaneous Pneumothorax Recurrence:** 25–50%, mostly within the first year. Risk factors: female gender, tall stature, low BMI, continuing to smoke.

Past-Paper High Yield

- **Diagnostic Test for Milky Effusion:** If pleural fluid is grossly milky, the absolute best test to confirm chylothorax is **pleural fluid triglycerides** (NOT serum TG or pleural cholesterol).
- **Chylothorax Characteristics:**
  - **Features:** Grossly milky, Pleural TG > 110 mg/dL, Chylomicron-positive.
  - **Trap:** Pleural cholesterol > 220 mg/dL is a feature of *pseudochylothorax*, **NOT** chylothorax.
  - **Treatment:** High-protein, low-fat diet with medium-chain triglycerides.
- **Rheumatoid Arthritis vs. Parapneumonic Effusion in an RA Patient:** Exam questions test your ability to differentiate an RA-flare effusion from a new parapneumonic effusion in immunosuppressed RA patients:

FEATURE	RA-INDUCED EFFUSION	PARAPNEUMONIC EFFUSION (IN RA PT)
Clinical	Gradual dyspnea, RA relapse	Fever, productive cough, acute dyspnea
Glucose	Extremely low (**< 50 mg/dL**, e.g., 30)	Normal to moderate (e.g., **110 mg/dL**)
LDH	Markedly elevated (**> 1000 U/L**)	Mildly/moderately elevated (e.g., 250 U/L)
Cells	Lymphocytes or mixed	Abundant neutrophils

- **When to Tap a Transudate-Prone Patient:** A patient with known Heart Failure or Liver Cirrhosis usually has a transudate, but if they present with a **Fever** (e.g., 39.8°C), **thoracentesis is strictly indicated** to rule out an infectious complication (parapneumonic effusion or spontaneous bacterial pleuritis).
- **Malignant Recurrence:** An older patient with a remote history of radiotherapy for Hodgkin's lymphoma who presents with an exudative, lymphocyte-predominant effusion containing **atypical cells** is most likely suffering from a recurrent/secondary malignancy.

Memory Pearls

- **Right vs. Left Chylothorax:** Thoracic duct crosses to the left at the 5th thoracic vertebra. Injury *below* T5 = **Right**-sided effusion; *above* T5 = **Left**-sided effusion.
- **Meigs Syndrome:** Benign ovarian fibroma + Ascites + Right-sided pleural effusion (elevated CA-125).
- **Boerhaave Syndrome:** Left-sided effusion, extremely low pH (< 7.00), and high salivary amylase.
- **Yellow Nail Syndrome:** Deformed yellow nails, lymphedema, and chylous pleural effusion.
- **Birt-Hogg-Dubé Syndrome:** Multi-focal kidney cancer, benign skin tumors (fibrofolliculomas), and multiple pulmonary cysts leading to recurrent pneumothorax.

Lung Cancer

Core Concepts

- **Epidemiology & Risk Factors:**
  - Average age at diagnosis is 70 years.
  - **Tobacco** causes 80–90% of cases (clear dose-response relationship).
  - **COPD** is an independent risk factor, increasing lung cancer risk by 3–6x compared to smoking alone.
  - Other exposures: Asbestos, radon, arsenic, chromium, nickel. Passive smoking causes up to 25% of cases in non-smokers.
- **Screening (National Lung Screening Trial):**
  - **Modality:** Low-Dose CT (LDCT) of the chest.
  - **Criteria:** Age 55–74 years with a ≥30 pack-year smoking history (must be current smokers or have quit within the last 15 years).
  - **Efficacy:** Reduces lung cancer mortality by 20%.

Diagnosis / Clinical Features

- **General Presentation:** Cough (75%), dyspnea, chest pain, and hemoptysis (15–30%). Only 5–15% are asymptomatic.
- **Histological Subtypes:**

FEATURE	ADENOCARCINOMA (NSCLC)	SQUAMOUS CELL (NSCLC)	SMALL CELL CARCINOMA (SCLC)
Location	Peripheral	Central	Central
Demographics	Most common overall; most common in **never-smokers**	95% are smokers	Almost all are smokers
Key Features	Gland formation, mucin. Minimally invasive (MIA) if ≤3cm with ≤5mm invasion.	Extensive central necrosis causing **cavitation**.	Highly metastatic at presentation. Associated with SVC syndrome.
Markers	TTF-1, Napsin	Keratin, p40, p63, CK5/6, desmoglein	Neuroendocrine markers
Paraneoplastic	Hypertrophic pulmonary osteoarthropathy (HOA)	**Hypercalcemia** (via PTHrP)	SIADH, Cushing, Neurologic syndromes

- **Regional Invasion Syndromes:**
  - **Superior Vena Cava (SVC) Syndrome:** Dilated neck veins, plethoric appearance, facial/upper extremity edema. Most commonly caused by **Small Cell Lung Cancer (SCLC)**. CXR shows a widened mediastinum or right hilar mass.
  - **Pancoast Tumor:** Tumor in the superior sulcus (mostly Squamous Cell).
    - *Shoulder pain:* Most common initial symptom (96%) due to brachial plexus, pleural, or rib invasion.

        - *Horner Syndrome:* Ipsilateral ptosis, miosis, and anhidrosis (sympathetic trunk invasion).
- **Paraneoplastic Syndromes:**
    - *Hypercalcemia:* Due to PTHrP secretion (classic for **Squamous Cell**). Presents with severe constipation, nausea, fatigue, and lethargy.
    - *SIADH:* Hyponatremia (classic for **SCLC**).
    - *Cushing Syndrome:* Ectopic ACTH production (SCLC, neuroendocrine, carcinoid). Portends a worse prognosis.
    - *Neurologic Syndromes:* Immune-mediated (Lambert-Eaton myasthenic syndrome, limbic encephalitis, cerebellar ataxia). Strongly associated with **SCLC**.
    - *Hypertrophic Osteoarthropathy (HOA):* Digital clubbing, periosteal bone proliferation, joint effusions.

Investigations

- **Radiological Staging:**
    - **Contrast CT Chest + Upper Abdomen:** Must include adrenal glands (common site of metastasis).
    - **PET Scan:** Indicated for symptomatic patients, focal findings, or evidence of advanced disease on CT.
    - **MRI Brain:** Indicated for all tumors > 5 cm (high risk of brain metastasis).
- **Invasive Staging:**
    - Endobronchial ultrasound-directed fine needle aspiration (EBUS-TBNA).
    - Mediastinoscopy or VATS.
- **Molecular/Biomarker Testing (for advanced NSCLC):**
    - *Targetable Mutations:* EGFR, ALK, ROS-1.
    - *Immunotherapy Markers:* PD-L1 expression levels.

Management

Non-Small Cell Lung Cancer (NSCLC):

- **Stage I: Surgery** (lobectomy or pneumonectomy + node sampling) is the mainstay. No adjuvant chemotherapy is needed. If pulmonary reserve is poor, consider wedge/segmentectomy (higher local recurrence, equal survival).
- **Stage II:** Surgery followed by **adjuvant chemotherapy**. En-bloc resection if chest wall is invaded.
- **Pancoast Tumor (Usually Stage IIB/IIIA): Neoadjuvant chemoradiotherapy** (cisplatin + etoposide) **followed by surgery**. (Note: The brain is the most common site of recurrence post-surgery).
- **Stage III:** Highly heterogeneous.
    - *IIIA with N1 nodes:* Surgery with curative intent.
    - *IIIA with N2/N3 or IIIB:* **Concurrent chemoradiotherapy** (if good performance status and no weight loss).

- **Stage IV (Incurable):** Palliative intent.
  - *Targeted Therapy:* Erlotinib/Gefitinib (EGFR), Crizotinib (ALK/ROS-1).
  - *Immunotherapy:* Nivolumab or Pembrolizumab (anti-PD-1 antibodies). Pembrolizumab requires >50% PD-L1 expression and negative EGFR/ALK mutations.
  - *Anti-Angiogenesis:* Bevacizumab (anti-VEGF-A) + platinum chemo for *non-squamous* NSCLC. **Contraindicated in Squamous Cell** due to the risk of severe, fatal hemoptysis.

Small Cell Lung Cancer (SCLC):

- *Note: SCLC is highly responsive to chemotherapy but has a very high recurrence rate.*
- **Limited Stage (LS-SCLC):**
  - Isolated peripheral nodule: Lobectomy + adjuvant chemo.
  - Node involvement (hilar/mediastinal): 4-6 cycles of chemo + radiation.
  - *Crucial Step:* If remission is achieved, **prophylactic whole-brain radiation** is indicated to prevent symptomatic brain metastasis and improve overall survival.
- **Extensive Stage (ES-SCLC):** Distant mets, malignant effusions, or contralateral nodes.
  - Treatment: Platinum-based chemotherapy. Offer radiation + prophylactic whole-brain irradiation if remission is achieved. Poor prognosis (median survival 8–13 months).

Complications / Prognosis

- Majority of lung cancers are diagnosed at late stages (28% Stage III, 38% Stage IV).
- Hypercalcemia typically indicates advanced disease and poor overall prognosis.
- *Distractor Note:* In elderly smokers with long-standing intermittent cough and bilateral hyperinflation on X-ray, prioritize COPD/COPD exacerbation as the primary lung pathology, though remember COPD inherently raises lung cancer risk. Similarly, patients with Obstructive Sleep Apnea (OSA) presenting with snoring and daytime sleepiness are at high risk for *systemic hypertension*, an important comorbidity often tested alongside smoking-related respiratory cases.

Past-Paper High Yield

- **SVC Syndrome etiology:** If a patient presents with a swollen face, dilated neck, and chest veins, the most likely cause is **Small Cell Lung Cancer (SCLC)**.
- **SCLC characterization:** It is the most common cause of malignancy-related SIADH and paraneoplastic neurologic syndromes (e.g., Lambert-Eaton). It is very responsive to chemotherapy. It is *NOT* classically associated with Pancoast tumors.
- **Squamous Cell triad:** A smoker with a central/upper lung mass showing **cavitation** + severe constipation/fatigue (due to **hypercalcemia** from PTHrP) = Squamous Cell Carcinoma. Calcium levels can be severely elevated (e.g., >14-18 mg/dL).
- **Pancoast Tumor management:** The definitive sequence for a Pancoast tumor is chemoradiotherapy followed by **surgery**.
- **Differentiating similar presentations:** An elderly patient with a >10-year history of a mild cough and chest hyperinflation is classically demonstrating COPD, not necessarily lung cancer—though new-onset hemoptysis or cavitation should immediately pivot suspicion to malignancy.

Memory Pearls

- **The "S"s of Squamous:** **S**moker, **S**entral, **S**uperior sulcus (Pancoast), **S**ecretes PTHrP (hyper**C**alcemia), **C**avitation.
- **The "S"s of Small Cell:** **S**moker, **S**entral, **S**yndromes (SIADH, Cushing, Lambert-Eaton), **S**VC syndrome, **S**ensitive to chemo.
- **Adeno = Absent smoking** (most common type in non-smokers, though still occurs in smokers) and **Abundant in periphery**.

Chest X-Ray (CXR)

Core Concepts

Chest X-ray interpretation requires evaluating technical quality (patient positioning, penetration) and categorizing lung abnormalities based on tissue density.

Abnormalities with Increased Density (Opacities)

- **Consolidation:** Alveolar spaces fill with fluid, pus, blood, or cells (including tumor cells).
  - *Radiographic features:* Ill-defined homogeneous opacity, **Silhouette sign** (loss of lung/soft tissue interface), **Air-bronchograms**, extends to pleura/fissures but does not cross them.
  - *Key differentiator:* **No volume loss** and no mediastinal shift.
- **Atelectasis:** Collapse of lung tissue due to decreased alveolar air.
  - *Radiographic features:* Sharply defined opacity obscuring vessels, **no air-bronchograms**.
  - *Key differentiator:* **Volume loss** leading to the displacement of the diaphragm, fissures, hila, or mediastinum toward the affected side.
- **Interstitial Disease:** Involvement of the lung parenchyma's supporting tissue, presenting as fine/coarse reticular opacities or small nodules.
- **Nodules or Masses:** Space-occupying lesions (solitary or multiple).

Abnormalities with Decreased Density (Lucencies)

- **Cavity:** Lucency with a *thick* wall.
- **Cyst:** Lucency with a *thin* wall.
- **Emphysema:** Lucency *without* a visible wall.

Diagnosis / Clinical Features

Exam questions frequently pair specific CXR findings with classic clinical vignettes to test diagnostic reasoning.

- **Bilateral Hilar Lymphadenopathy (BHL):**
  - **Sarcoidosis:** Typically presents in young to middle-aged adults (often African American females) with dry cough, fatigue, and systemic symptoms.
    - *Associated features:* Right paratracheal lymphadenopathy, erythema nodosum, non-deforming arthritis, and hypercalcemia. Often resolves spontaneously or with steroids.

    - **Psittacosis (Atypical Pneumonia):** BHL accompanied by patchy infiltrates in a patient with a history of pet bird (e.g., parrot) exposure and cleaning bird cages.
- **Bilateral Diffuse Infiltrates:**
    - **Idiopathic Pulmonary Fibrosis (IPF):** Manifests as progressive dyspnea and chronic dry cough (>6 months) with interstitial infiltrates on CXR.
    - **Transfusion-Associated Circulatory Overload (TACO):** Develops rapidly (e.g., 2 hours post-FFP transfusion). Presents with tachypnea, cyanosis, bilateral crackles, and **raised JVP**.
- **Normal CXR in the context of Respiratory Complaints:**
    - **Obstructive Sleep Apnea (OSA):** Obese patient (BMI >35) with loud snoring, choking at night, daytime somnolence, low libido, and morning headaches. CXR is *not* a diagnostic tool here.

Investigations

- **Sarcoidosis:** While CXR is the typical initial test revealing BHL, **lung biopsy** is the *most diagnostic* test to confirm non-caseating granulomas. If Bronchoalveolar lavage (BAL) is performed, it will show increased **lymphocytes**, *not* neutrophils.
- **Psittacosis / Complex Atypical Infiltrates:** In a patient with parrot exposure, BHL, and patchy infiltrates, **Bronchoalveolar lavage (BAL)** is the next best step for microbiological evaluation over highly invasive (lung biopsy) or inappropriate (PPD, immediate steroids) choices.
- **Obstructive Sleep Apnea:** Diagnosis is strictly confirmed via a **sleep study (polysomnography)**. Do not select CXR or PFTs as the diagnostic step.

Past-Paper High Yield

- **Sarcoidosis Trap:** Increased *neutrophils* on BAL rules **against** sarcoidosis (look for lymphocytic alveolitis instead). Hypercalcemia, non-deforming arthritis, right paratracheal lymphadenopathy, and spontaneous resolution are all highly supportive of the diagnosis.
- **TACO vs. TRALI:** Both present with acute shortness of breath and bilateral infiltrates post-transfusion. The discriminator is volume status: **Raised JVP** strongly points to TACO (hydrostatic pulmonary edema), whereas TRALI is a non-cardiogenic inflammatory pulmonary edema with normal/low JVP.
- **Diagnostic Hierarchy:** Recognize when CXR is merely supportive versus when tissue/specialized testing is required. For sarcoidosis, pick *lung biopsy* for definitive diagnosis; for OSA, pick *sleep study*.
- **Consolidation vs. Atelectasis:** Exam stems often test the physiological difference. Consolidation = Air-bronchograms + Normal volume. Atelectasis = No air-bronchograms + Volume loss (shifted structures).

Memory Pearls

- **Thick cavity, Thin cyst, No-wall emphysema:** The rule of lucency borders.
- **Consolidation fills, Atelectasis shrinks:** Consolidation replaces air with fluid/cells (preserving volume), while atelectasis is the literal deflation of the lung.
- **TACO = Tension in the veins:** High JVP separates it from TRALI.

Chest X-Ray (CXR) with Doctor's Notes

Core Concepts

RIPE Technique for CXR Evaluation Before interpreting a CXR, ensure proper technique using the **RIPE** mnemonic (Rotation, Inspiration, Projection, Exposure) along with verifying the correct patient name and date.

- **R – Rotation**:
  - Check the distance between the medial ends of the clavicles and the spinous processes of the vertebrae.
  - Equal distance = centralized. Unequal distance = patient is rotated.
- **I – Inspiration**:
  - Films must be taken on full inspiration to prevent false abnormalities (e.g., false basal infiltrations).
  - Adequate inspiration: **6 anterior ribs** (oblique) or **8–9 posterior ribs** (horizontal) are visible.
  - *Scapula check*: Scapulae should be *outside* the lung field.
  - *Volume loss*: <8 posterior ribs = hypoinflated; <6 posterior ribs = low lung volume (suggests restrictive disease or poor inspiration).
- **P – Projection**:
  - **Posterior-Anterior (PA) view**: Standard view. X-ray enters posteriorly and exits anteriorly (patient hugs the film). Scapulae are *outside* the lung field.
  - **Anterior-Posterior (AP) view**: Used for bed-bound patients. Film is behind the patient.
    - *Key indicators of AP*: Scapulae are *inside* the field, the heart appears falsely enlarged, the mediastinum appears wider, and false basilar infiltrations may appear. Presence of ECG leads indicates an AP view.
- **E – Exposure (Penetration)**:
  - **Adequate exposure**: The vertebrae should be vaguely visible through the lower one-third of the heart shadow.
  - **Underexposed**: Unclear/white film. Vertebrae cannot be seen behind the heart. You will miss costophrenic angles, pneumonia, and pulmonary nodules.
  - **Overexposed**: Very dark film. Vertebrae are seen perfectly clearly. Normal white lung markings (vessels, lymph nodes, fibroblasts) appear black, falsely suggesting COPD or emphysema.

Radiographic Densities

- **Chest X-Ray**: Solid = White (Radiopaque) | Air = Black (Radiolucent) | Gray = Intermediate.
- **Ultrasound (Contrast)**: Solid = Black | Air = White.

Lung Zones vs. Lung Lobes

- **Frontal View (Zones)**: The lungs are divided into Upper, Middle, and Lower *zones* because anatomical lobes overlap on a 2D frontal image and cannot be consistently demarcated.
- **Lateral View (Lobes)**: Always refer to *lobes* instead of zones. Identify lobes using fissures.

- *Right Lung Fissures*: Oblique and Horizontal. The oblique fissure starts at T4, passes through the hilum, and ends at the anterior third of the hemidiaphragm.
- *Visible Fissures*: Normally seen as fine white lines (pleural soft tissue). If invisible, they are either very thin or parallel to the X-ray beam.

Anatomy of the Hilum

- **Contents**: Pulmonary artery, pulmonary veins, lymph nodes, and bronchus. Normal opacity is driven by blood-filled vessels blocking X-rays.
- **Orientation**: Pulmonary artery travels right to left (downward); pulmonary vein travels upward. The bronchus lies between the artery and the vein.

Diagnosis / Clinical Features

Classification of Lung Abnormalities

- **Increased Density (Opacities/White)**:
  - **Consolidation**: Alveoli filled with fluid, pus, blood, or cells. *Features:* Ill-defined homogeneous opacity, obscures vessels, positive silhouette sign, **air bronchogram present**, extends to pleura/fissure but does not cross it. **No volume loss** and **no mediastinal shift**.
  - **Atelectasis (Collapse)**: Alveoli deflate. *Features:* Sharply defined opacity, obscures vessels, **no air bronchogram**. **Volume loss** causes displacement of the diaphragm, fissures, hilum, or trachea (shifts *towards* the collapse).
  - **Interstitial**: Involvement of lung parenchyma supporting tissue. Appears as fine/coarse reticular (network-like) opacities or small nodules.
  - **Mass**: Space-occupying lesion, typically ≥3 cm and rounded.
  - **Nodule**: Space-occupying lesion, typically <3 cm (e.g., 29 mm).
  - **Patchy Opacity**: Radio-opaque structure with no clear borders.
- **Decreased Density (Lucencies/Black)**:
  - **Cavity**: Lucency with a *thick* wall.
  - **Cyst**: Lucency with a *thin* wall.
  - **Emphysema**: Lucency *without* a visible wall.

Key Diagnostic Signs

- **Silhouette Sign**: Occurs when two structures of the same density lie adjacent to each other, blending their borders and making the margin invisible.
  - *Right middle lobe pathology* obscures the **right heart border**.
  - *Lingula pathology* obscures the **left heart border**.
  - *Lower lobe pathology* ("saluting the hemidiaphragm") obscures the **diaphragm**.
- **Air Bronchogram Sign**: Visible, air-filled airways cleanly outlined by surrounding radiopaque lung consolidation (e.g., pneumonia).
  - *Absence of Air Bronchogram* indicates lung collapse (no air in airway), obstruction (mass blocking airway), or complete consolidation (fluid/pus completely fills the airways).

- **Spine Sign (Lateral CXR)**: Normally, vertebrae appear *more radiolucent (darker)* as you move down the spine. If the spine becomes *whiter/less clear* as you move downward, this is a positive spine sign indicating lower lobe pneumonia/consolidation.

Specific Pathologies

- **Pulmonary Edema**: Left-sided heart failure causes blood backup into pulmonary veins. Fluid preferentially moves to the upper lobes (upper lobe diversion) because upper lobe resting ventilation > perfusion, leaving more space for fluid accumulation compared to lower lobes. Frequently imaged AP (due to patient acuity), showing an enlarged heart, bilateral infiltrates, and patchy opacity.
- **Hilar Enlargement**:
  - *Unilateral*: Consider **lung cancer** until proven otherwise.
  - *Bilateral*: Indicates bilateral lymphadenopathy or bilateral vascular hypertension.

Past-Paper High Yield

- **Differentiating Upper Zone Patchy Opacity**:
  - If the trachea is shifted **towards** the opacity = **Collapse (Atelectasis)**.
  - If the trachea is in the **midline** = **Pneumonia (Consolidation)**.
- **The Upper Lobe Trap**: A lesion appearing in the "upper lobe" on a frontal CXR may actually be located in the **superior segment of the lower lobe**. You must account for the anatomical overlap (upper lobe sits anterior and superior to the lower lobe).
- **Compensatory Expansion**: If an upper lobe completely collapses (e.g., due to an obstructing mass), the lower lobe will undergo compensatory hyperinflation to fill the space. This expansion can mask the volume loss and make the upper lobe collapse less noticeable on the CXR.
- **ECG Leads on CXR**: Instantly identifies the image as an **AP view**, meaning the patient is lying down. You must mentally account for artificial cardiac enlargement and wider mediastinum.

Memory Pearls

- **RIPE**: **R**otation, **I**nspiration, **P**rojection, **E**xposure.
- **Rule of 6 and 8**: Full inspiration requires **6 anterior** ribs or **8 posterior** ribs to be visible.
- **Silhouette Sign Localization**:
  - Right heart border lost = Right Middle Lobe.
  - Left heart border lost = Lingula.
  - Diaphragm lost = Lower Lobes.
- **Unilateral Hilum Enlargement** = Cancer.
- **Consolidation vs. Collapse**: Consolidation maintains volume and shows air bronchograms. Collapse loses volume (tracheal deviation toward the lesion) and lacks air bronchograms.

Respiratory Imaging: CXR and CT

Core Concepts

- **Systematic CXR Evaluation (RIPE & ABCDE):**
  - **RIPE (Technical Quality): R**otation (clavicles equidistant to spinous processes), **I**nspiration (5-7 anterior ribs visible), **P**rojection (AP vs. PA), **E**xposure/Penetration (vertebral bodies just visible behind the heart).
  - **ABCDE (Anatomical Approach): A**irway (trachea midline), **B**reathing (lungs and pleura), **C**ardiac (heart size, hila, mediastinum), **D**iaphragm (costophrenic angles), **E**verything else (bones, soft tissues, tubes/lines).
- **The Silhouette Sign:** Loss of normal anatomical borders (e.g., right heart border obscured by right middle lobe consolidation) indicating a lesion of similar tissue density lying contiguous with that structure.
- **The Secondary Pulmonary Lobule:** The fundamental anatomical unit of the lung used to interpret High-Resolution CT (HRCT) patterns.
- **Windowing in CT:** Images are viewed in specific "windows" to optimize distinct tissues (e.g., **Mediastinal window** for lymph nodes/vessels/masses vs. **Lung window** for parenchyma/interstitium).

Investigations

- **Chest CT Protocols:**
  - **Contrast-enhanced CT:** Ideal for evaluating mediastinal structures, vascular occlusion (e.g., pulmonary embolism), and staging (IASLC lymph node map).
  - **HRCT (High-Resolution CT):** Non-contrast, thin-slice imaging. The gold standard for evaluating interstitial and diffuse lung diseases.
- **Key HRCT Patterns:**
  - **Nodular:** Tree-in-bud pattern (reflects small airway endobronchial spread of infection, e.g., TB), lymphangitis carcinomatosis.
  - **Reticular:** Linear opacities, septal thickening (seen in asbestosis, CHF, pulmonary fibrosis).
  - **Increased Density:** Consolidation (obscures vessels) vs. Ground Glass Opacity (GGO; hazy increase in density that does *not* obscure underlying bronchial/vascular margins).
  - **Decreased Density (Cystic):** True cysts, emphysema, honeycombing.
  - **Mosaic Attenuation:** A patchwork of differing lung attenuation. Requires **expiratory HRCT scans** to differentiate causes:
    - *Obstructive small airways disease:* Due to air-trapping and secondary vasoconstriction (low attenuation areas persist or worsen on expiration).
    - *Occlusive vascular disease:* Due to relative oligemia/hypoperfusion.

Diagnosis / Clinical Features

- **Idiopathic Pulmonary Fibrosis (IPF):** Characterized by a Usual Interstitial Pneumonia (UIP) pattern on HRCT. Hallmarks include **honeycombing** (subpleural, basal cystic spaces) and **traction**

bronchiectasis.

- **Nonspecific Interstitial Pneumonia (NSIP):** Characterized predominantly by **Ground Glass Opacities (GGO)** on HRCT, lacking the classic honeycombing of IPF.
- **Congestive Heart Failure (CHF):** Presents with reticular opacities (septal lines), cardiomegaly, and pleural effusions. *Note on biochemical correlation (BNP):* B-type natriuretic peptide is highly sensitive for CHF and affects prognosis; levels naturally increase with age but are **falsely low in obese patients**.
- **Hypersensitivity Pneumonitis & Drug/Radiation-induced pneumonitis:** Often present with varying degrees of GGO, reticulation, and mosaic attenuation depending on the acute vs. chronic stage.

Management

- **Idiopathic Pulmonary Fibrosis (IPF):** If an older patient (especially with a smoking history) presents with dyspnea and HRCT definitively shows **traction bronchiectasis and honeycombing**, the diagnosis of IPF is clinical-radiological.
  - *Next best step:* **Start antifibrotic therapy** (e.g., pirfenidone, nintedanib).
  - *Avoid:* Lung biopsy is **unnecessary and contraindicated** when classic HRCT features (UIP pattern) are present.
- **Mediastinal Lymphadenopathy:** Utilize the IASLC lymph node map to guide staging. Lymph node tissue sampling is best achieved via **EBUS** (Endobronchial Ultrasound).

Past-Paper High Yield

- **IPF Management based on HRCT:** Recognize the classic HRCT triad of an older smoker + traction bronchiectasis + honeycombing. The definitive management is to **start antifibrotic therapy**. Do *not* choose "Lung biopsy" if the HRCT is classically diagnostic.
- **BNP Characteristics:** In the workup of dyspnea and distinguishing cardiogenic pulmonary edema from primary lung pathology, remember that BNP:
  - Has **higher sensitivity than specificity**.
  - Levels **decrease falsely in obese patients** (a classic exam trap).
  - Levels naturally **increase with aging**.
  - Levels **do** heavily affect and predict clinical prognosis.

Memory Pearls

- **HRCT IPF vs. NSIP: H**oneycombing = **H**ardcore Fibrosis (IPF/UIP). **G**round **G**lass = **G**ood prognosis (NSIP).
- **Tree-in-bud = Seeds in the airway:** Represents endobronchial spread of infection (bronchiolitis/TB).
- **RIPE for CXR Quality: R**otation, **I**nspiration, **P**enetration (Exposure), **E**xposure.

Pulmonary Function Tests (PFT)

Core Concepts

- **Spirometry Requirements:** Requires full inspiration followed by forced maximal expiration. A valid test requires a minimum of **3 technically acceptable attempts** with FEV1 and FVC repeatable within **5%**.
- **Flow-Volume Loop Anatomy:**
  - **X-axis (Volume):** Left extreme is Total Lung Capacity (**TLC**); right extreme is Residual Volume (**RV**). The total horizontal width/interval between these points represents the Forced Vital Capacity (**FVC**).
  - **Y-axis (Flow):** The peak of the upper (expiratory) curve is the Peak Expiratory Flow (**PEF**). The bottom trough is the Peak Inspiratory Flow (**PIF**).
- **DLCO (Transfer Factor for Carbon Monoxide):** Measures gas exchange capacity. Patient inhales a CO and Helium mix to TLC, holds breath for 10 seconds, and exhales. Helium dilution calculates alveolar volume (VA), and CO uptake calculates DLCO.

Diagnosis / Clinical Features

- **Obstructive Pattern:**
  - Defined by **FEV1/FVC < 0.70**.
  - *Causes:* Asthma, COPD (Emphysema, Chronic Bronchitis), Bronchiectasis, Bronchiolitis obliterans.
  - *Note:* Myasthenia gravis and other neuromuscular diseases do *not* cause obstructive patterns.
- **Restrictive Pattern:**
  - Defined by **Normal or High FEV1/FVC ratio (≥ 0.70)** with decreased FVC and decreased TLC.
  - *Causes:* Interstitial Lung Disease (ILD), Idiopathic Pulmonary Fibrosis (IPF), Neuromuscular disease, Obesity.

Specific Disease Patterns

- **Asthma:** Obstructive + Reversible. DLCO is normal or increased.
- **COPD:** Obstructive + Irreversible. Shows hyperinflation (High TLC) and gas trapping (High RV, High RV/TLC).
  - *Emphysema:* Uniquely features **decreased DLCO** alongside high TLC.
- **Interstitial Lung Disease (e.g., IPF):** Restrictive (Low FVC, Low TLC) + **Low DLCO** + Normal FEV1/FVC.
- **Neuromuscular / Motor Neuron Disease:** Restrictive (Low FVC, Low TLC) + **Preserved or High RV** + **Normal DLCO**. FVC characteristically drops further when supine.
- **Obesity:** Restrictive + **Normal FEV1/FVC** + **Severely reduced FRC** + Normal RV. DLCO remains normal (unless obesity is extremely gross).
- **Heart Failure:** Acute presentation = Obstructive; Chronic presentation = Restrictive with low DLCO.

Investigations

- **Bronchodilator Reversibility Testing:**
  - Done off inhalers.
  - **Positive Response:** FEV1 or FVC increases by **≥ 12% AND ≥ 200 mL** post-bronchodilator.
  - *Indicates:* Asthma, COPD with reversibility, or Asthma-COPD Overlap (ACO).
- **Bronchial Challenge Testing (Provocation):**
  - Indicated for suspected asthma with *normal* baseline spirometry.
  - Uses Histamine, Methacholine, Mannitol, or Hypertonic saline.
  - **Positive Test (PD20/PC20):** Reaches the Provocative Dose/Concentration required to cause a **20% drop in FEV1** (e.g., Histamine + if <4 µmol or <8 mg/mL).
  - A negative test *virtually excludes* asthma.
- **COPD Severity Staging (GOLD by Spirometry):**
  - *All stages require FEV1/FVC < 0.70.*
  - **Stage I (Mild):** FEV1 > 80% predicted
  - **Stage II (Moderate):** 50% < FEV1 < 80% predicted
  - **Stage III (Severe):** 30% < FEV1 < 50% predicted
  - **Stage IV (Very Severe):** FEV1 < 30% predicted OR FEV1 < 50% predicted + chronic respiratory failure.

Past-Paper High Yield

- **Flow-Volume Loop Identification:** Exams frequently test the anatomy of the loop. Remember that the **double-headed arrow** spanning the width of the X-axis is the **FVC**, and the highest point on the Y-axis is the **PEF**.
- **DLCO as a Differentiator:**
  - *Decreased DLCO:* Emphysema, IPF/ILD, Chronic Heart Failure. (Rules *in* parenchymal disease).
  - *Increased DLCO:* **Pulmonary hemorrhage** (classic trap!), Asthma.
  - *Normal DLCO:* Neuromuscular disease, Chest wall deformities, Obesity. (Rules *out* parenchymal disease).
- **Neuromuscular Disease Trap:** Motor neuron diseases present with a restrictive pattern (Low TLC, Low FVC) but classically have a **High RV** (due to inability to force expiration) and a **Normal DLCO**.
- **Age and PFTs:** The FEV1/FVC ratio is *not* static; it naturally **declines with age**. TLC generally stays normal or slightly decreases with age.
- **Obesity and PFTs:** Obesity does **not** lower the FEV1/FVC ratio (both FEV1 and FVC decline proportionally).

Memory Pearls

- **"Obesity spares the ratio, drops the FRC."**
- **"Neuromuscular patients can't push air out: High RV, Normal DLCO."**
- **"Blood in the alveoli absorbs CO: Pulmonary hemorrhage = High DLCO."**

Rheumatology

Exam Map

TOPIC	PAST-PAPER WEIGHT	REVISION PRIORITY
Rheumatoid Arthritis	27 Questions (~59%)	**Maximum** - Master diagnostic criteria, early imaging signs, and acute joint emergencies.
SLE & Vasculitis	13 Questions (~28%)	**High** - Focus on lupus nephritis disease markers, drug-induced triggers, and ANCA syndrome pairings.
Myopathies, SpA, Scleroderma	6 Questions (~13%)	**Targeted** - Memorize specific autoantibody clinical syndromes (Anti-Jo-1, Scl-70) and Scleroderma Renal Crisis.

Strongest Repeated Exam Themes & Practical Revision Priorities:

- **RA's Earliest Sign:** The single most tested radiographic finding in early Rheumatoid Arthritis is **juxtaarticular osteopenia** (not joint space loss or erosions).
- **The Single Hot Joint Trap:** An acute monoarthritis flare in a patient already on immunosuppressants (MTX/biologics) requires immediate **joint aspiration** to rule out septic arthritis before adjusting rheumatic therapy.
- **Tracking SLE Activity:** A flare of Lupus Nephritis is classically tested as a presentation of worsening proteinuria/RBC casts combined with **high anti-dsDNA** and **low C3/C4 complements**.
- **Induction for Severe Lupus Nephritis:** For severe Class IV LN, recognize the mandatory need for **Cyclophosphamide or Mycophenolate Mofetil** in addition to pulse steroids.
- **Scleroderma Renal Crisis (SRC):** Suspect SRC in diffuse SSc with new malignant hypertension and MAHA (schistocytes on blood film). The absolute exam answer for management is immediate **Captopril (ACE inhibitor)**—do not withhold it even if creatinine is rising. Corticosteroids are contraindicated.
- **Vasculitis Phenotypes:** Differentiate **GPA / Wegener's** (c-ANCA, upper respiratory + cavitating lung lesions + renal) from **Polyarteritis Nodosa (PAN)** (Hep B associated, microaneurysms, mononeuritis multiplex, and strictly *spares the lungs*).
- **Myositis Lab Traps:** Disease activity in inflammatory myopathies is monitored via **CK and Anti-Jo-1**, *never* ESR or CRP. Furthermore, an isolated high AST/ALT with normal GGT/ALP indicates a primary muscle issue, not liver disease.
- **Anti-Synthetase Syndrome:** Watch for a patient stem featuring Interstitial Lung Disease (ILD), arthritis, proximal weakness, and hyperkeratotic "mechanic's hands." The diagnostic antibody is **Anti-Jo-1**.
- **The Gout "Normal Uric Acid" Trap:** Serum urate is frequently normal or artificially low during an acute gout attack. Never rule out gout based on normal acute labs, and never initiate allopurinol during a flare.

- **Acute Gout in Comorbid Patients:** If a patient has Chronic Kidney Disease (CKD), CHF, or peptic ulcer disease, strictly avoid NSAIDs. Treat acute flares with **corticosteroids** (intra-articular or systemic).
- **Biologic Safety (TNFi):** Before initiating TNF-alpha inhibitors (e.g., for SpA), screen for Hepatitis B and latent TB. Note that **treated** latent TB is safe, but untreated latent TB or chronic Hep B are major contraindications.

Rheumatoid Arthritis

Core Concepts

- **Definition**: A chronic, systemic, inflammatory autoimmune disease primarily affecting the synovial tissue of peripheral joints. Inflammation leads to pannus formation, cartilage destruction, and bone erosions.
- **Epidemiology**: Peak onset in 4th–5th decades. Female to male ratio is 3:1.
- **Genetics**: Highly associated with **HLA-DR4** (and HLA-DR1). These alleles share a 5-amino-acid sequence known as the **Shared Epitope (QKRAA)** on the HLA-DRB1 gene.
- **Risk Factors**:
  - **Smoking** (significantly increases risk and severity, especially in autoantibody-positive patients).
  - **Periodontitis** (infection with *Porphyromonas gingivalis*).
  - Nulliparity and the early postpartum period (OCPs are actually protective).

Diagnosis / Clinical Features

- **Pattern of Joint Involvement**:
  - Symmetrical polyarthritis.
  - Typically involves small joints: **MCPs, PIPs, wrists, and MTPs**.
  - **Spares the DIP joints** (helps distinguish from Osteoarthritis and Psoriatic Arthritis).
  - Spares the axial spine, with the critical exception of the **cervical spine (C1-C2 atlantoaxial subluxation)**.
- **Symptoms**: **Morning stiffness lasting > 1 hour** that improves with activity/movement.
- **Late/Advanced Deformities**:
  - Ulnar deviation at the MCP joints.
  - Swan-neck deformity (PIP hyperextension, DIP flexion).
  - Boutonniere deformity (PIP flexion, DIP hyperextension).
  - Extensor tendon rupture at the dorsum of the hand.
- **Palindromic Rheumatism**: An episodic variant of joint inflammation; presence of Anti-CCP antibodies strongly predicts progression to full-blown RA. Hydroxychloroquine can reduce the risk of progression.

Investigations

- **Autoantibodies**:
  - **Anti-CCP (ACPA - Anti-Citrullinated Protein Antibodies)**: Most accurate marker. ~95% specific. Highly predictive of aggressive, erosive disease.
  - **Rheumatoid Factor (RF)**: Defined as an **IgM antibody directed against the Fc portion of IgG**. Present in 75% of patients (sensitive but not specific). High titers correlate with extra-articular manifestations.
- **Inflammatory Markers**: Elevated ESR and CRP. Reactive thrombocytosis (high platelets) and anemia of chronic disease (normocytic) are common.
- **Synovial Fluid**: Inflammatory profile (elevated WBCs, neutrophil predominance), without crystals or bacteria.
- **Plain Radiography (X-Ray)**:
  - **Earliest finding: Juxtaarticular (periarticular) osteopenia.**
  - *Later findings*: Symmetrical joint space loss, marginal subchondral erosions, and soft tissue swelling.

Management

- **General Strategy**: Start Disease-Modifying Antirheumatic Drugs (DMARDs) early to halt permanent joint damage. *Treat to target*.
- **Symptomatic/Bridging Therapy**: NSAIDs and systemic/intra-articular Glucocorticoids (e.g., Prednisolone) provide rapid symptom relief while waiting for DMARDs to take effect.
- **csDMARDs (Conventional Synthetic)**:
  - **Methotrexate (MTX)**: First-line anchor drug.
  - Others: Sulfasalazine, Hydroxychloroquine, Leflunomide.
- **bDMARDs (Biologics)**: Indicated if inadequate response to csDMARDs after 3-6 months.
  - Anti-TNF (Etanercept, Infliximab, Adalimumab).
  - Anti-CD20 (Rituximab).
  - IL-6 inhibitors (Tocilizumab).
- **Combination Therapy Rules**: Triple therapy (MTX + Sulfasalazine + Hydroxychloroquine) is safe and effective. **Never** combine two biologics, and **avoid** combining MTX with Azathioprine.
- **Acute Flare on Immunosuppression**: If a patient on MTX/Biologics presents with an acutely hot, swollen joint, **always aspirate the joint first** to rule out septic arthritis.

Complications / Prognosis

Extra-articular manifestations occur in ~40% of patients, usually in males with high-titer RF/Anti-CCP and long-standing severe disease.

- **Renal**: RA is a classic cause of secondary **AA Amyloidosis** (suspect if a patient develops proteinuria/nephrotic syndrome).
- **Hematologic (Felty Syndrome)**: A triad of long-standing **RA, splenomegaly, and neutropenia** (recurrent infections).

- **Cardiac**: **Accelerated atherosclerosis** is the leading cause of death in RA (accounts for ~50% of mortality). Asymptomatic pericardial effusions are also common.
- **Pulmonary**: Exudative pleural effusions (characteristically low glucose, high LDH), parenchymal nodules (Caplan syndrome when combined with pneumoconiosis), and interstitial lung disease (ILD).
- **Ocular**: Secondary Sjögren's syndrome (keratoconjunctivitis sicca), episcleritis, and scleromalacia (risk of eyeball perforation).
- **Neurological**: Mononeuritis multiplex (due to vasa nervorum vasculitis), peripheral neuropathy, and cervical myelopathy from C1-C2 subluxation.
- **Prognostic Indicators**: Positivity for RF/Anti-CCP, early erosions, and smoking = poor prognosis. Normal X-ray/MRI = good prognosis.

Past-Paper High Yield

- **The Earliest Radiographic Sign**: Highly tested! The earliest plain film finding of RA is **juxtaarticular osteopenia** (NOT symmetric joint space loss or subchondral erosions, which occur later).
- **Acute Monoarthritis in RA**: A patient on MTX and Etanercept with a sudden red, swollen, painful knee must immediately undergo **joint aspiration** to rule out septic arthritis. Do not just increase steroid/MTX doses.
- **Renal Amyloidosis**: A patient with RA presenting with nephrotic syndrome has **AA amyloidosis**.
- **Rheumatology Differential Diagnosis Traps**:
  - *DIP involvement + bony swellings + negative ESR*: **Osteoarthritis** (treat with paracetamol/NSAIDs).
  - *Acute knee + calcification of cartilage (chondrocalcinosis)*: **Pseudogout** (calcium pyrophosphate crystals).
  - *Acute toe/knee + negative birefringent crystals + CKD*: **Gout** (first-line treatment for an acute flare with CKD stage 3b/peptic ulcer is **intra-articular steroids** or colchicine, *not* NSAIDs).
  - *Sjögren's syndrome (Anti-Ro/SSA, Anti-La/SSB)*: High risk for developing **MALT lymphoma**. Note: Anti-Smith is *not* found in Sjögren's (it is SLE specific).
  - *Difficulty combing hair + heliotrope rash + Anti-Jo1*: **Dermatomyositis** (highly associated with ILD).
  - *Older patient + bilateral shoulder pain/stiffness + high ESR + normal RF*: **Polymyalgia Rheumatica**.
  - *Young male + morning back pain improving with exercise*: **Ankylosing Spondylitis** (HLA-B27 positive, X-ray shows syndesmophytes; next step if NSAIDs fail is an anti-TNF agent like Etanercept).

Memory Pearls

- **RA joints**: "RA spares the DIPs and the spine (except the neck)."
- **Felty's Triad**: **S**anta **C**laus has **R**heumatoid **A**rthritis -> **S**plenomegaly, **C**hronic RA, **N**eutropenia (Leukopenia).

- **RF mechanism**: It's the **M**acroglobulin (**IgM**) attacking the normal **G**lobulin (**IgG**).

Systemic Lupus Erythematosus (SLE)

Core Concepts

- **Pathogenesis:** A chronic, multisystemic autoimmune disease characterized by a global loss of self-tolerance. Dysfunction of T cells, B cells, and dendritic cells leads to the production of antinuclear autoantibodies (ANA).
- **Two-Stage Mechanism:**
  1. Loss of self-tolerance and autoantibody generation (involving self-antigen presentation by dendritic cells).
  2. Immune complex formation leading to widespread tissue inflammation and damage.
- **Epidemiology:**
  - **Sex:** 90% of cases occur in women (10x more susceptible).
  - **Ethnicity:** African American and Asian populations have a 3x–4x higher incidence and 2x–3x higher mortality compared to Caucasians.
- **Genetics:** Associated with HLA-DR2 and HLA-DR3.
  - *Note on biological sex:* Men with SLE generally have more severe disease than women. Men with Klinefelter syndrome (47, XXY) have a higher risk of SLE than 46, XY men, but tend to have less severe disease than other men with SLE.
- **Environmental Triggers:** UV light, drugs (drug-induced SLE), EBV infection, smoking, and silica dust.

Diagnosis / Clinical Features

SLE is highly heterogeneous. Diagnosis relies on clinical reasoning combined with classification criteria (e.g., SLICC or ACR).

- **Constitutional (90-95%):** Fatigue, fever, weight loss, lymphadenopathy.
- **Mucocutaneous (80-90%):**
  - *Acute:* Malar (butterfly) rash, photosensitivity.
  - *Subacute:* Annular polycyclic or psoriasiform rash.
  - *Chronic:* Discoid rash (scarring, localized/generalized), Chilblain LE (pruritic/painful dusky purple patches exacerbated by cold/moisture).
  - *Other:* Painless oral and nasal ulcers, non-scarring alopecia.
- **Musculoskeletal (80-90%):** Symmetric, non-deforming polyarthritis (MCP, PIP, DIP, knees).
  - **Jaccoud's arthropathy:** A non-erosive variant characterized by ligamentous laxity and joint subluxation that is manually reducible.
- **Renal (40-60%):** Lupus nephritis (LN) presenting with edema, hypertension, proteinuria, microscopic hematuria, and red blood cell (RBC) casts.
- **Serositis (50-70%):** Pleuritis (most common pulmonary manifestation), pericarditis.

- **Neuropsychiatric (40-60%):** Seizures, psychosis.
- **Pulmonary:** Acute lupus pneumonitis, shrinking lung syndrome, pulmonary hypertension.
- **Undifferentiated Connective Tissue Disease (UCTD):** Patients presenting with SLE features but not meeting full criteria. 5–30% eventually evolve into definite disease (e.g., SLE, RA, Systemic Sclerosis).

Investigations

- **Basic Labs:**
  - *CBC:* Leukopenia, lymphopenia, mild anemia, thrombocytopenia (autoimmune cytopenias).
  - *Urinalysis:* Proteinuria (quantified by 24-hour urine or protein-to-creatinine ratio), hematuria, and cellular (RBC) casts indicating glomerulonephritis.
- **Immunological Testing (Autoantibodies):**
  - **ANA (Antinuclear Antibody):** Best initial screening test (indirect immunofluorescence on HEp-2 cells). Highly sensitive (~100%). A negative ANA makes SLE highly unlikely.
  - **Anti-dsDNA:** Highly specific for SLE. **Strongly correlates with renal disease activity (Lupus Nephritis) and pathogenesis.**
  - **Anti-Smith (Sm):** Highly specific for SLE. Targets extractable nuclear antigens (ENA). Does not fluctuate with disease activity.
  - **Anti-Ro (SSA) / Anti-La (SSB):** Associated with ANA-negative lupus, profound photosensitivity, subacute cutaneous lupus, Sjogren's overlap, and **congenital heart block (neonatal lupus)**.
  - **Anti-Histone:** Hallmark of drug-induced lupus.
  - **Antiphospholipid Antibodies:** Lupus anticoagulant (LA), anticardiolipin (aCL), anti-beta-2-glycoprotein I.
- **Complement Levels:** Low C3 and C4 (hypocomplementemia) due to immune complex consumption. Highly indicative of active disease/flare.

Management

- **General / Mild Disease (No major organ involvement):**
  - **Hydroxychloroquine (HCQ):** The cornerstone of SLE therapy. Reduces flares, lipids, thrombosis, and organ damage. Improves survival and prevents neonatal heart block.
  - Sunblock/sun avoidance (UV light triggers flares).
  - NSAIDs for joint pain, low-dose corticosteroids.
- **Severe Disease / Major Organ Involvement (e.g., Lupus Nephritis Class IV):**
  - **Induction Therapy:** Pulse IV Methylprednisolone + **IV Cyclophosphamide** OR **Mycophenolate Mofetil (MMF)**.
  - *Note:* HCQ should still be continued as it triples the response to MMF.
- **Refractory/Targeted Biologics:** Belimumab (targets B-cell activating factor), Rituximab (anti-CD20).

- **Vitamin D Supplementation:** Improves disease activity, proteinuria, and blood pressure. *Low Vitamin D in SLE is associated with an increased risk of venous thrombosis.*

Complications / Prognosis

- Survival rate is ~90-95% in the Western world, but mortality remains 2–3x higher than the general population.
- **Leading causes of death:**
  - Cardiovascular disease (heart disease and stroke due to premature atherosclerosis/thrombosis).
  - Infections (due to immunosuppression).
  - Renal failure (from progressive lupus nephritis).
  - Malignancies (hematologic and lung cancer).

Past-Paper High Yield

- **Markers of Active Disease:** A presentation of new-onset or worsening renal disease (proteinuria, hematuria, RBC casts) paired with **low C3/C4 and high anti-dsDNA** is the classic marker of active lupus nephritis.
- **Management of Class IV Lupus Nephritis:** When a patient presents with progressive renal failure and RBC casts requiring immediate intensive therapy alongside pulse methylprednisolone, the correct add-on treatment is **Cyclophosphamide** or **Mycophenolate Mofetil**.
- **Drug-Induced SLE:** Suspect in patients newly developing malar rash, joint pain, and fatigue after starting new medications. **Hydralazine** is a classic high-yield trigger (alongside procainamide and isoniazid).
- **Differentiating SLE from Vasculitis / Other CTDs:**
  - *Negative ANA with mesenteric/renal aneurysms:* Diagnosis is **Polyarteritis Nodosa (PAN)**, not SLE.
  - *Palpable purpura, colicky abdominal pain, hematuria:* Suggestive of small-vessel vasculitis (e.g., IgA Vasculitis/HSP). **Scleroderma** is the *least* likely cause of this specific triad.
  - *Severe proximal myopathy with cardiac involvement (gallop rhythm, S3):* Think necrotizing autoimmune myopathy (associated with **Anti-SRP**), not classic anti-dsDNA/SLE.

Memory Pearls

- **ANA is to "Screen", dsDNA/Sm is to "Confirm".**
- **dsDNA drops Complements:** High anti-dsDNA + Low C3/C4 = **Active Renal Flare**.
- **Jaccoud's vs. RA:** Both can cause ulnar deviation/swan neck deformities, but Jaccoud's in SLE is non-erosive and *reducible* on physical exam.
- **Hydroxychloroquine = Life Insurance:** Give it to almost every SLE patient unless strictly contraindicated (requires baseline and annual ophthalmologic exams for maculopathy).

Spondyloarthropathies

Core Concepts

- **Definition:** A family of highly heritable, polygenic rheumatologic disorders characterized by axial skeletal arthritis, peripheral arthritis, and enthesitis.
- **The SpA Family:** Ankylosing Spondylitis (AS), Non-radiographic axial SpA, Psoriatic Arthritis (PsA), Reactive Arthritis (ReA), Enteropathic (IBD-associated) Arthritis, Undifferentiated SpA, and Juvenile-onset SpA.
- **Common Shared Features:**
  - **Seronegativity:** Negative for Rheumatoid Factor (RF) and Antinuclear Antibodies (ANA).
  - **Genetics:** Strong family history and **HLA-B27** association. (MHC locus; accounts for ~20.1% of AS heritability. *Note: Lecture slides specifically state HLA-B27 is an MHC class II molecule involved in aberrant peptide presentation/misfolding.*)
  - **Peripheral Arthritis:** Typically **asymmetric** oligoarthritis.
  - **Enthesitis:** Inflammation at tendon/ligament insertion sites.
- **Pathogenesis:**
  - **Entheseal stress hypothesis:** Micro-damage or cell stress at the enthesis triggers inflammation.
  - CD8+ T-cells and macrophages invade the junction of bone/cartilage.
  - **TNF-alpha** plays a central role in driving inflammation (making it a prime therapeutic target).
  - Bone remodeling follows three stages: Acute inflammation → bone erosion → new bone formation (syndesmophytosis).

Diagnosis / Clinical Features

1. General SpA Manifestations:

- **Inflammatory Back Pain:** Highest predictive value features are **pain at night** (waking the patient) and **improvement with exercise** (not rest). Associated with prolonged morning stiffness.
- **Enthesitis:** Achilles tendon insertion is most common. Other sites: plantar fascia, iliac crests, lateral epicondyles, costochondral junctions.
- **Dactylitis ("Sausage Digits"):** Swelling of the *entire* digit due to flexor tenosynovitis + soft tissue inflammation. Lacks discrete fusiform joint swelling. *DDx: SpA, TB, syphilis, sarcoidosis, sickle cell, tophaceous gout.*
- **Acute Anterior Uveitis (AAU):** Acute unilateral redness, pain, and photophobia. Present in up to 50% of recurrent AAU cases; 10% risk of permanent vision impairment.

2. Specific Disease Profiles:

- **Ankylosing Spondylitis (AS):**
  - **Demographics:** Males > Females (2-3:1), classic onset age 16–40.
  - **Clinical:** Alternating buttock pain (sacroiliitis), symmetric sacroiliitis, marginal syndesmophytes.
- **Reactive Arthritis (ReA):**

    - **Trigger:** Follows GI (M=F) or GU (M>F, 8:1) infections by 2–4 weeks. Pathogens cannot be cultured from joints.
    - **Clinical:** Acute asymmetric oligoarthritis of large joints.
    - **Dermatologic/Mucosal: Keratoderma blenorrhagica** (vesicles → hyperkeratotic crusts on palms/soles), circinate balanitis (penis), and painless, shallow oral ulcers.
- **Psoriatic Arthritis (PsA):**
    - **Patterns:** 5 types (Distal, Arthritis mutilans, Polyarticular, Oligoarticular, Axial asymmetric sacroiliitis).
    - **Timing:** Psoriasis precedes arthritis in 70% of cases.
    - **Diagnosis:** Requires CASPAR criteria (joint/spine/entheseal inflammation + ≥ 3 specific points).
- **Enteropathic (IBD) Arthritis:**
    - More common in Crohn's colitis than Crohn's ileitis.
    - **Type 1:** Peripheral arthritis that flares *with* GI disease activity (treat the IBD to treat the joints).
    - **Type 2:** Axial spondylitis that runs *independently* of GI disease activity.

Investigations

- **Labs:**
    - HLA-B27 testing.
    - Inflammatory markers (ESR, CRP).
- **Imaging (Sequential approach for Axial Disease):**
    - **1st Line:** AP Pelvis X-ray (look for sacroiliitis).
    - **2nd Line (if X-ray negative):** MRI of the pelvis with STIR sequence (best for detecting early, active inflammation/bone marrow edema in SI joints).
    - **Spine X-ray signs:**
        - *Early:* "Shiny corner sign" / Romanus lesions (small erosions at vertebral body corners with reactive sclerosis).
        - *Late:* "Bamboo spine" (diffuse syndesmophytic ankylosis).
- **Physical Exam:** Schober's test (assesses lumbar spine flexion/mobility).

Management

- **Conservative & First-Line:**
    - **Physical Therapy:** Crucial for maintaining posture, flexibility, and function.
    - **NSAIDs:** First-line pharmacotherapy (e.g., Naproxen, Indomethacin, Meloxicam). May slow radiographic progression.
- **Conventional DMARDs (Sulfasalazine, Methotrexate):**
    - **Only effective for peripheral arthritis.** *Do not use for purely axial disease.*
- **Biologics (For severe/refractory or axial disease):**

- **TNF-alpha inhibitors (TNFi):** Infliximab, Etanercept, Adalimumab, Certolizumab pegol, Golimumab.
- **IL-17 inhibitors:** Secukinumab.

- **Contraindicated:** Glucocorticoids are generally *not* recommended in AS.

Complications / Prognosis

- **Cardiovascular:** Conduction defects, aortitis with aortic valve ring dilatation, resulting in **aortic regurgitation**.
- **Pulmonary: Upper lobe pulmonary fibrosis** and restrictive lung disease (secondary to rigid chest wall / costochondral ankylosis).
- **Skeletal:** Osteoporosis of the spine, leading to a high risk of spinal fractures even with minor trauma.

Past-Paper High Yield

- **Distinguishing ReA from other Arthritides:** Exam questions test your ability to differentiate Reactive Arthritis from Systemic Juvenile Idiopathic Arthritis / Adult-Onset Still's Disease (AOSD).
  - *ReA:* Asymmetric oligoarthritis, preceding infection, keratoderma blenorrhagica, painless oral ulcers.
  - *AOSD (Trap):* Spiking fevers, symmetric polyarthritis, and a **pink macular rash** (often with a history of childhood arthritis).
- **TNFi Contraindications:** When stepping up therapy to TNFi for SpA/IBD, you must screen for specific contraindications:
  - **Chronic Hepatitis B** is a major contraindication (risk of fatal reactivation).
  - *Latent Tuberculosis* is a contraindication *unless* it has been fully treated (e.g., treated with Isoniazid). **Treated latent TB is safe** for TNFi initiation.
  - Other TNFi contraindications include severe heart failure and demyelinating diseases.

Memory Pearls

- **Syndesmophyte Morphology:**
  - AS and IBD = **Marginal** (thin, delicate, symmetric).
  - PsA and ReA = **Non-marginal** (bulky, asymmetric, "jug-handle").
- **HLA-B27 Prevalence by Disease:** AS (85-95%) > ReA (30-70%) > PsA (25-60%) > IBD (7-70%).
- **IBD Arthritis Types:** Type **1** is at **1** with the gut (parallels GI activity). Type **2** acts in **2** separate ways (independent of gut activity).

Gout and Osteoarthritis

Core Concepts

Gout & Hyperuricemia

- **Pathophysiology**: Deposition of monosodium urate monohydrate (MSU) crystals in connective tissues and joints.
- **Hyperuricemia**: Serum urate > 6.8 mg/dL (limit of urate solubility).
  - **Mechanism**: Renal *under-excretion* of urate accounts for 90% of cases; *over-production* accounts for 10%.
- **Inflammatory Cascade**: MSU crystals activate the NALP3 inflammasome → induces IL-1β secretion. TNF-α and IL-8 lead to neutrophil influx, causing acute neutrophilic synovitis. Chronic inflammation leads to metalloproteinase/nitric oxide release, causing cartilage loss and bone erosion.
- **Spectrum of Crystalline Arthropathies**:
  - **MSU**: Acute/chronic gouty arthritis, tophi, renal calculi.
  - **CPPD (Calcium pyrophosphate dihydrate)**: Acute pseudogout, chondrocalcinosis.
  - **Basic calcium phosphate (Hydroxyapatite)**: Calcific periarthritis, destructive arthropathy.
  - **Calcium oxalate**: Acute arthritis in renal dialysis patients.
  - **Cholesterol**: Chronic synovial effusions in RA/OA.
  - **Charcot-Leyden**: Associated with synovial fluid/tissues with eosinophilia.

Osteoarthritis (OA)

- **Definition**: Degenerative joint disease characterized by articular cartilage erosion, marginal bone hypertrophy (osteophytes), and subchondral sclerosis.
- **Epidemiology**: Most common form of arthritis; highly prevalent in >60 years; much more common in women.
- **Classification**:
  - *Primary OA*: Most common; no identifiable predisposing cause.
  - *Secondary OA*: Identifiable cause (metabolic conditions, anatomic factors, trauma); pathologically indistinguishable from primary OA.

Diagnosis / Clinical Features

Acute Gout

- **Demographics**: 8x more common in men; uncommon in women pre-menopause. Peak onset 3rd–6th decade.
- **Presentation**: Sudden onset (often awakens patient from sleep), severe pain, red, hot, swollen joint (mimics infection).
- **Joint Involvement**: 1st MTP joint most common (podagra). Can be polyarticular (~10%), especially in elderly women on thiazide diuretics.
- **Triggers**: Trauma, surgery, starvation, dehydration, fatty foods, drugs altering serum urate (allopurinol, uricosurics, thiazide/loop diuretics, low-dose aspirin).

Chronic / Tophaceous Gout

- **Tophi**: Draining or chalk-like subcutaneous urate deposits under transparent skin.

- *Typical locations*: Ears, olecranon bursa, finger pads, tendons (e.g., Achilles).
- **Chronic Arthropathy**: Erosive, deforming arthritis; may cause dactylitis.

Osteoarthritis

- **Presentation**: Joint pain that worsens with activity/weight-bearing and improves with rest.
- **Gelling Phenomenon**: Morning stiffness lasting **< 30 minutes**. (Night pain only occurs in advanced OA).
- **Joint Involvement**: Asymmetric. Most commonly affects hands, knees, hips, spine, and 1st MTP. (Uncommon in wrists, elbows, ankles, shoulders).
- **Physical Exam**:
  - Heberden nodes (DIP joint enlargement).
  - Bouchard nodes (PIP joint enlargement).
  - Squaring at the base of the thumb (1st carpometacarpal joint).
  - Crepitus during range of motion, limited ROM, bony enlargement, small effusions, abnormal gait.

Investigations

Gout

- **Synovial Fluid (Gold Standard)**: Identification of MSU crystals via polarizing light microscopy. Uses polarizing filters to evaluate birefringent anisotropic materials.
- **Serum Urate**:
  - *Warning*: Can be **falsely low** or normal during an acute attack.
  - *Target for therapy*: < 6 mg/dL.
- **Imaging (X-ray)**: Early disease is typically normal. Late/chronic disease shows "punched-out erosions" with sharp margins and overhanging edges.
- **ACR-EULAR Classification Criteria (2015)**: Diagnosis incorporates clinical patterns, tophi, serum urate levels, synovial fluid microscopy (MSU crystals), and imaging.

Osteoarthritis

- **Clinical Diagnosis**: Primarily diagnosed by history and physical exam.
- **Imaging (X-ray)**: Not sensitive for early disease. Poorly correlated with symptoms. Used in moderate/advanced OA to confirm diagnosis or rule out mimics (bone tumor, avascular necrosis).
- **Labs**: Inflammatory markers (ESR, CRP) are normal. Used only to rule out inflammatory arthritis (e.g., RA).

Management

Acute Gout Treatment

- **Goal**: Rest the joint and halt acute inflammation. **Do not commence allopurinol or uricosuric drugs during an acute attack.**
- **1st Line Options**:

1. **NSAIDs**: Full doses (e.g., indomethacin, naproxen, diclofenac) *if renal function is normal*.
2. **Colchicine**: 0.5 mg twice or three times daily (useful adjunct if NSAIDs fail to settle attack rapidly).
3. **Corticosteroids**: Intra-articular (if 1–2 joints involved and NSAIDs contraindicated) or Systemic (if polyarticular or NSAIDs/colchicine contraindicated due to CKD, PUD, or CHF).

- **Non-Pharmacological**: Avoid diuretic therapy, weight gain, alcohol, and low-dose aspirin.

Complications / Prognosis

Hyperuricemia and Renal Disease

- **Urate Nephropathy**: Deposition of MSU crystals in the renal interstitium causing chronic renal insufficiency. Often exacerbated by concomitant hypertension.
- **Uric Acid Nephropathy**: Acute obstructive uropathy due to rapid formation of uric acid crystals in collecting tubules (e.g., Tumor Lysis Syndrome in dehydrated/ill patients).
- **Uric Acid Nephrolithiasis**: Calculi formation in the renal tract (promoted by high urinary uric acid, low urine pH, and hyperuricemia).

Past-Paper High Yield

- **The "Normal Uric Acid" Trap**: Serum uric acid is frequently normal or falsely low during an acute gout flare due to increased renal excretion driven by inflammatory cytokines. Do not rule out gout based on a normal serum urate level during an attack.
- **Allopurinol Initiation**: Never start allopurinol or other urate-lowering therapies *during* an acute gout flare (it can mobilize stores and worsen the attack).
- **Treatment Contraindications**: Know when to pick steroids over NSAIDs for acute gout. If a patient has Chronic Kidney Disease (CKD), Congestive Heart Failure (CHF), or Peptic Ulcer Disease (PUD), avoid NSAIDs and choose intra-articular or systemic corticosteroids.
- **Joint Involvement (OA vs. RA)**: OA classically involves the DIP joints (Heberden) and PIP joints (Bouchard), while sparing the MCP joints. If MCP joints are swollen/tender, think RA, not OA.
- **Duration of Morning Stiffness**: OA features stiffness lasting < 30 minutes. RA stiffness classically lasts > 1 hour.
- **Radiographic Buzzwords**: Gout = "punched-out erosions with overhanging edges". OA = "subchondral sclerosis, joint space narrowing, marginal osteophytes".

Memory Pearls

- **Heberden's vs Bouchard's**: **H**eberden is **H**igher up (distal/DIP), **B**ouchard is **B**elow (proximal/PIP).
- **Acute Gout Triggers**: Think "The 3 D's" - Diet (purines/alcohol), Diuretics (thiazides/loops), Dehydration.
- **Gout Crystals**: **M**SU crystals = **M**onosodium urate. Think **M**en (more common) and **M**TP (1st joint commonly affected).

Inflammatory Myopathies

Core Concepts

- **Idiopathic Inflammatory Myopathies (IIM):** Rare autoimmune diseases characterized by muscle inflammation. Includes Polymyositis (PM), Dermatomyositis (DM), and Inclusion Body Myositis (IBM).
- **Epidemiology:**
  - More common in females (2:1), except IBM (2-3x more common in males).
  - PM: Peaks at 50–60 years.
  - DM: Bimodal (peaks at 5–15 years and 45–65 years).
  - IBM: Onset strictly > 50 years.
  - 4x more common in Black populations compared to Caucasians.
- **Malignancy Association:** Strongly associated with cancers, especially **DM > PM**.
  - Most common tumors: Ovary, Breast, Melanoma, Colon.
  - Treating the underlying malignancy often improves the myositis.
  - **Cancer screening is mandatory** for all patients > 50 years old (CT chest/abdo/pelvis, scopes, mammogram/gynecology exam, testicular exam).
- **Overlap Syndromes:** 15–20% of cases overlap with other autoimmune connective tissue diseases (SSc, SLE, RA, Sjögren's). Anti-PM/Scl antibody is seen in DM overlapping with systemic sclerosis.

Diagnosis / Clinical Features

- **Muscle Involvement:**
  - **Insidious onset** (over 3–6 months) of **symmetrical, proximal** muscle weakness.
  - Affects shoulders, hips, thighs, trunk, and neck flexors (difficulty standing from a chair, climbing stairs, combing hair, raising head off pillow).
  - **Painless** (differentiates from polymyalgia rheumatica).
  - IBM is unique: Distal weakness is common alongside proximal weakness (quadriceps and arm flexors).
- **Skin Involvement (Dermatomyositis):**
  - *Gottron's papules:* Erythematous scaly plaques over extensor surfaces of PIP/MCP joints.
  - *Heliotrope rash:* Purplish rash over upper eyelids.
  - *V-sign:* Rash over anterior chest and neck.
  - *Shawl-sign:* Rash over upper back and shoulders.
  - *Holster sign:* Erythema on the lateral thighs/hips.
  - *Mechanic's hands:* Fissuring and hyperkeratosis of the fingers.
  - *Nail changes:* Periungual erythema and nail fold capillary telangiectasia/dilatation.
  - *Calcinosis:* Soft tissue calcifications (highly characteristic of **childhood-onset DM**).
  - *Photosensitivity* is common.
  - *Note:* Erythema nodosum is **NOT** a typical feature of DM.

    - *DM vs. SLE:* DM classically involves the nasolabial folds and forehead, whereas SLE classically spares the nasolabial folds.
- **Respiratory & GI:**
    - Interstitial Lung Disease (ILD) and respiratory muscle weakness.
    - Upper dysphagia (swallowing difficulties) → can lead to severe aspiration/chemical pneumonitis.
- **Joints:** Arthralgia and mild rheumatoid-like (but non-erosive) deforming arthropathy.
- **Associated Sjögren's Syndrome:** Lymphocytic infiltration of exocrine glands causing xerophthalmia (dry eyes) and xerostomia (dry mouth). Features parotid enlargement, Anti-Ro/SSA & Anti-La/SSB antibodies, and carries an **increased risk of lymphoma**.

Investigations

- **Muscle Enzymes:**
    - Elevated CK, AST, ALT, LDH, and aldolase.
    - **CK level strongly correlates with disease activity** (as does the Anti-Jo-1 titre).
    - *Trap:* ESR & CRP do **NOT** correlate with disease activity or response to treatment.
- **Autoantibodies (Myositis-Specific):**
    - **Anti-Jo-1 (Antisynthetase):** Targets Histidyl-tRNA synthetase. Diagnostic of Antisynthetase Syndrome.
    - **Anti-Mi-2:** Associated with DM (classic V/Shawl signs) and a **good prognosis**.
    - **Anti-SRP (Signal Recognition Particle):** Associated with PM, profound cardiac involvement, and **resistance to treatment**.
- **Pathology (Muscle Biopsy):**
    - **Polymyositis: Cell-mediated** (CD8+ T-cells and macrophages). Inflammation predominates in the **endomysial** area (around muscle fibers), invading non-necrotic fibers.
    - **Dermatomyositis: Humoral** (CD4+ T-cells and B-cells). Inflammation is primarily **perimysial** and perivascular. Hallmark finding is **perifascicular atrophy**.
    - **Inclusion Body Myositis (IBM):** Shows **red-rimmed vacuoles** (on trichrome stain) and eosinophilic cytoplasmic/nuclear inclusions on electron microscopy.
- **Imaging:** MRI using STIR sequence shows areas of active inflammation as bright signals.

Management

- **First-line:** High-dose Corticosteroids.
- **Immunosuppressants:** Methotrexate (MTX) and Azathioprine are the agents of choice.
    - *Indications:* Failure to respond to high-dose steroids, inability to taper steroids, severe steroid side-effects, or persistent disease activity.
    - Therapy typically lasts 18–24 months.
- *IBM Note:* Patients with Inclusion Body Myositis generally **do not** respond to immunosuppressive treatment.

- *Sjögren's Overlap Management:* Pilocarpine (increases salivary secretion), artificial tears, sugar-free lozenges, meticulous oral hygiene, and Hydroxychloroquine for joint pain. Avoid anticholinergics.

Complications / Prognosis

- **Aspiration Pneumonitis:** A major risk due to severe upper esophageal dysmotility.
- **Cardiac Disease:** Myocarditis, arrhythmias, and pericardial effusions (especially high-risk with Anti-SRP).
- **Interstitial Lung Disease (ILD):** A major driver of morbidity and mortality, prominently seen with Anti-Jo-1 antibodies.

Past-Paper High Yield

- **Anti-Synthetase Syndrome Presentation:** Always suspect this in a patient presenting with proximal muscle weakness, interstitial lung disease (SOB/CT findings), non-erosive joint pain, and **mechanic's hands** (cracked, hyperkeratotic fingers). **Diagnosis:** Anti-synthetase syndrome (driven by **Anti-Jo-1** antibodies).
- **Dermatomyositis Skin Manifestations:** You must recognize what belongs to DM (photosensitivity, mechanic's hands, nail fold telangiectasia, calcinosis) versus distractor findings. Erythema nodosum is *not* a feature of DM.
- **Elevated Transaminases Trap:** A patient with high AST/ALT but normal GGT/ALP and high CK has a primary muscle issue, not liver disease. Do not attribute isolated high AST/ALT to hepatitis without checking GGT/ALP and CK.
- **Monitoring Trap:** Disease activity is tracked using CK and Anti-Jo-1 titres, *never* ESR or CRP.

Memory Pearls

- **PM Pathology: P**olymyositis = **P**enetrates fibers (**Endo**mysial), driven by CD**8** T-cells.
- **DM Pathology: D**ermatomyositis = **D**emarcates the outside (**Peri**mysial / **Perifascicular** atrophy), driven by CD**4** T-cells.
- **The "Anti-Jo" patient:** *Jo works as a mechanic, breathes heavy, and has aching joints.* (Mechanic's hands, ILD, Arthritis).

Vasculitis

Core Concepts

- **Definition & Classification:** A heterogeneous group of disorders characterized by blood vessel wall inflammation. Classified primarily by the size of the predominant vessels involved (Large, Medium, Small).
- **Primary vs. Secondary:** Secondary vasculitis (due to infections, drugs, malignancies, or other autoimmune diseases) is *more common* than primary vasculitis.
- **The "Rule Out" Mandate:** You must explicitly rule out occult infections (e.g., infective endocarditis, Hep B/C, HIV, Syphilis) before initiating immunosuppressive therapy, as mimicking

lesions (like septic emboli causing cavitating lung lesions or splinter hemorrhages) can easily be misattributed to vasculitis.

- **The Most Important Test: Urinalysis**. The presence of an active urinary sediment (hematuria, RBC casts) indicates rapidly progressive glomerulonephritis (RPGN), dictating immediate aggressive treatment and acting as a primary prognostic indicator.

Diagnosis / Clinical Features

Large Vessel Vasculitis

- **Giant Cell Arteritis (GCA):** Most common primary vasculitis. Patients >50 years. Presents with temporal/occipital headache, jaw claudication, scalp tenderness, and amaurosis fugax. High ESR/CRP. Strongly associated with Polymyalgia Rheumatica (PMR).
- **Takayasu's Arteritis:** Usually Asian females <40 years. Features three phases (systemic, vascular, burnt-out). Presents with limb claudication, asymmetric BPs, diminished/absent pulses, bruits, and carotidynia. *No autoantibodies.*

Medium Vessel Vasculitis

- **Polyarteritis Nodosa (PAN):** Necrotizing vasculitis of muscular arteries. Prominently affects renal and mesenteric arteries but **spares the lungs**.
- *Key Features:* Mononeuritis multiplex (e.g., foot drop), livedo reticularis, digital tip infarction, and visceral microaneurysms.
- *Associations:* 10–30% of cases are associated with Hepatitis B. *ANCA negative.*

ANCA-Associated Vasculitis (Small to Medium Vessel)

- **Granulomatosis with Polyangiitis (GPA, formerly Wegener's):**
  - *Triad:* ENT (epistaxis, saddle nose collapse, perforated septum) + Lungs (hemoptysis, *fixed* cavitating pulmonary nodules) + Kidneys (pauci-immune crescentic RPGN).
  - *Other:* Proptosis (retro-orbital mass).
  - *Serology:* **c-ANCA (anti-PR3) positive** (>90%).
- **Microscopic Polyangiitis (MPA):**
  - Presents acutely as a Pulmonary-Renal Syndrome (alveolar hemorrhage + RPGN). *No granulomas.*
  - *Serology:* **p-ANCA (anti-MPO) positive**.
- **Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg-Strauss):**
  - Features a prodromal phase (adult-onset asthma, allergic rhinitis), eosinophilic tissue infiltration, and a vasculitic phase.
  - Unlike GPA, lung infiltrates are *not fixed*.
  - *Serology:* **p-ANCA (anti-MPO) positive**.

Small Vessel Vasculitis (Immune Complex)

- **Henoch-Schönlein Purpura (HSP):** Most common childhood vasculitis (<10 years). IgA-dominant immune deposits. Often follows a URTI. Features a tetrad of palpable purpura (legs/buttocks),

colicky abdominal pain (risk of intussusception), transient arthralgia, and renal disease (hematuria/proteinuria). Complement levels (C3/C4) are normal.

- **Cryoglobulinemia:** Immunoglobulins precipitate at <37°C. Strongly associated with **Hepatitis C**. Features purpura, Raynaud's, peripheral neuropathy, and membranoproliferative GN. Low C4 and high Rheumatoid Factor (RF).
- **Hypersensitivity Vasculitis:** Most common form of vasculitis overall. Primarily cutaneous (palpable purpura) due to drug reactions (e.g., allopurinol, hydralazine, PTU) or infections.

Variable Vessel / Other

- **Behcet's Disease:** Linked to HLA-B51 (Silk Route populations).
- *Diagnostic Triad/Criteria:* Recurrent oral ulcers (heal without scarring) + at least two of:
  - Genital ulcers (leave scars)
  - Eye lesions (anterior uveitis, hypopyon)
  - Skin lesions (acneiform nodules, erythema nodosum, superficial thrombophlebitis)
  - Positive Pathergy test.

Investigations

- **Urinalysis:** Essential for identifying subclinical/active glomerulonephritis (hematuria, proteinuria, RBC casts).
- **Serology & Infection Screen:** ANCA (c-ANCA/PR3, p-ANCA/MPO), ANA, RF, Complement (C3/C4), Cryoglobulins, Hep B, Hep C, HIV, and blood cultures.
- **Imaging:**
  - *GCA:* Temporal artery ultrasound (Doppler halo sign).
  - *Takayasu:* 18F-FDG-PET (shows active vessel wall inflammation), Angiography.
  - *PAN:* Abdominal angiography (reveals microaneurysms and stenoses in mesenteric/renal arteries).
- **Biopsy:** Gold standard.
  - *GCA:* Temporal artery biopsy (skip lesions common).
  - *Skin:* Leukocytoclastic vasculitis (hypersensitivity, HSP, cryoglobulinemia).
  - *GPA:* Granulomatous necrotizing vasculitis.

Management

- **Large Vessel Vasculitis:** High-dose oral steroids (prompt response expected). Steroid-sparing agents (MTX, Azathioprine) for maintenance.
- **ANCA-Associated Vasculitides (AAV):**
  - *Induction:* IV Steroids + IV Cyclophosphamide OR Rituximab.
  - *Maintenance:* Oral steroids + MTX or Azathioprine.
- **Cryoglobulinemia:** Treat underlying Hep C (Interferon alpha + Ribavirin) + Rituximab. Plasma exchange in severe cases.

- **Behcet's Disease:** Colchicine for oral/joint symptoms. Steroids/Immunosuppressants (Azathioprine, anti-TNF) for eye, neurological, and vascular involvement.

Complications / Prognosis

- **GCA:** Untreated inflammation of the ophthalmic and posterior ciliary arteries leads to sudden, irreversible unilateral blindness, quickly followed by the contralateral eye (1-2 weeks).
- **EGPA:** Cardiac involvement is the principal cause of morbidity and accounts for 50% of deaths.
- **GPA / MPA:** The extent of lung and renal involvement are the primary negative prognostic factors.
- **Behcet's:** High risk of lethal aneurysms (pulmonary artery, aorta, carotid) and thrombosis (DVT, cerebral venous sinus thrombosis, Budd-Chiari syndrome).

Past-Paper High Yield

- **Hep B + Microaneurysms + Negative ANCA:** Classic presentation for **Polyarteritis Nodosa (PAN)**. Expect a patient presenting with weight loss, neuropathy, purpura, and fluid-filled cavities (microaneurysms) in the kidneys.
- **c-ANCA + Hemoptysis + RBC Casts:** Diagnosis is **Granulomatosis with Polyangiitis (GPA)**. This combination represents pulmonary-renal syndrome driven by PR3-ANCA.
- **ENT + Lung Cavities + Systemic Symptoms:** Think **GPA**. Classic stems feature a perforated nasal septum or saddle nose deformity, recurrent sinusitis, and cavitating lung lesions.
- **Features of Behcet's Disease: Scleritis is NOT a core feature** of Behcet's (anterior uveitis and hypopyon are the classic eye findings). You must recognize oral ulcers, genital ulcers, acneiform lesions, and erythema nodosum as true features.
- **Differential Diagnosis Trap:** A hospitalized patient developing acute, highly localized joint pain/swelling days post-surgery (e.g., wrist pain on day 5 post-op) is overwhelmingly likely to have **Gouty arthritis** (post-surgical gout flare), *not* acute vasculitis.

Memory Pearls

- **PAN: P**ulmonary **A**rteries **N**ot involved. Spares the lungs, loves the kidneys/gut, associated with Hep B.
- **GPA (Wegener's): c**-ANCA, **C**avitating lung lesions, **C**-shaped (saddle) nose.
- **Complement rules:** HSP has normal complement (IgA-driven alternative pathway). Cryoglobulinemia heavily consumes C4.
- **Lung lesions in AAV:** GPA lung infiltrates are *fixed*; EGPA lung infiltrates are *not fixed*.

Systemic Sclerosis (Scleroderma)

Core Concepts

- **Definition:** A chronic, heterogeneous multisystem disease characterized by widespread vascular dysfunction, immune activation, and progressive fibrosis of the skin and internal organs due to excessive collagen deposition.
- **Epidemiology:**

- Female-to-male ratio is between 3:1 and 8:1.
- **Females:** Tend to have limited disease, younger age of onset, and more vascular involvement (longer interval between Raynaud's onset and SSc diagnosis).
- **Males:** Tend to have diffuse disease and a higher risk of lung, cardiac, and renal involvement.
- **African Americans:** Associated with earlier onset, more severe disease, and increased risk of pulmonary fibrosis and scleroderma renal crisis (SRC).

- **Classification:** Based on the extent of skin involvement, internal organ patterns, and overlap features (Diffuse [dcSSc] vs. Limited [lcSSc]).

Diagnosis / Clinical Features

- **Cutaneous:**
  - Nearly universal; starts in fingers, hands, and face.
  - *Early stages:* Pruritus, edematous swelling, and erythema.
  - *Late stages:* Skin thickening/hardening, flexion contractures, loss of appendicular hair, dry/shiny skin.
  - *Characteristic signs:* Microstomia, peaked nose, "salt and pepper" dyspigmentation, telangiectasia, calcinosis cutis.
- **Vascular (Raynaud Phenomenon - RP):**
  - Virtually always present; can predate limited SSc by years.
  - Abnormal vasoconstriction of digital arteries triggered by cold or emotional stress.
  - Progresses to structural damage causing prolonged ischemia, digital tip ulcers (especially in diffuse disease with anti-Scl-70), pitting, and acro-osteolysis.
- **Renal (Scleroderma Renal Crisis - SRC):**
  - Life-threatening complication occurring in up to 10% of patients, predominantly early in diffuse SSc.
  - *Presentation:* Abrupt onset of malignant hypertension (though some are normotensive), oliguric acute renal failure, microangiopathic hemolytic anemia (MAHA), and thrombocytopenia.
  - *Note:* Glomerulonephritis is uncommon; urinalysis typically shows only mild proteinuria with few cells/casts.
- **Pulmonary (Leading Cause of Death):**
  - **Interstitial Lung Disease (ILD):** Causes restrictive lung disease (decreased FVC and DLCO). Most common in diffuse SSc, positive anti-Scl-70, males, and African Americans.
  - **Pulmonary Arterial Hypertension (PAH):** Mean pulmonary artery pressure > 20 mmHg. Common in long-standing limited SSc or secondary to ILD. Presents as progressive exertional dyspnea leading to cor pulmonale.
- **Gastrointestinal:**
  - Involves the entire GI tract (90% of patients), though half are asymptomatic.
  - *Esophagus:* Dysphagia, GERD, choking.
  - *Stomach:* Early satiety, "watermelon stomach" (Gastric Antral Vascular Ectasia - GAVE).

- *Bowel:* Bacterial overgrowth, malabsorption, pseudo-obstruction, fecal incontinence.

- **Musculoskeletal & Neuromuscular:**
  - Erosive symmetrical polyarthritis of small joints (MCP/wrists), sparing the DIP joints.
  - **Tendon friction rubs:** A critical physical exam marker for highly aggressive disease and increased risk of SRC.
  - Inflammatory myositis and muscle atrophy.

Investigations

Autoantibody Profiling *(Highly specific [>99.5%] but moderately sensitive [20-50%])*

ANTIBODY	ASSOCIATION / RISK PROFILE
Anti-topoisomerase I (Anti-Scl-70)	Diffuse SSc; high risk of severe **Interstitial Lung Disease (ILD)** and digital ulcers.
Anticentromere (ACA)	Limited SSc; high risk of **Pulmonary Arterial Hypertension (PAH)**.
Anti-RNA polymerase III	Diffuse SSc; rapidly progressive skin involvement; extremely high risk of **Scleroderma Renal Crisis (SRC)**.
Anti-Th/To	Limited skin disease; high frequency of ILD; substantially increased risk of PAH.

Key Diagnostic Modalities

- **Lab Tests:** CBC (look for MAHA or anemia of chronic disease/malabsorption), blood film, urinalysis, creatinine, CK (myositis).
- **Pulmonary:** Pulmonary Function Tests (PFTs) to check for restrictive patterns and decreased DLCO. **High-Resolution CT (HRCT)** is the preferred imaging modality for ILD.
- **Cardiac/Vascular:** Doppler Echocardiography is the initial screening test for PAH. Right heart catheterization is required to definitively diagnose PAH.

Management

- **General Principles:** Therapy is organ-based and symptomatic. Systemic immunosuppression is reserved for diffuse skin or active inflammatory organ involvement.
- **Glucocorticoids: AVOID whenever possible.** Even low-dose corticosteroids can trigger Scleroderma Renal Crisis.
- **Renal Scleroderma Renal Crisis (SRC):**
  - **First-line therapy:** ACE inhibitors (e.g., **Captopril**) are strictly indicated and life-saving.
  - Must be initiated immediately even in the setting of rising creatinine or oliguria.
- **Skin & Myositis:** Methotrexate (MTX), Mycophenolate Mofetil (MMF), Rituximab. Cyclophosphamide is reserved for refractory, progressive skin disease.
- **Interstitial Lung Disease (ILD):** MMF, Rituximab (requires systemic immunosuppression).
- **Raynaud Phenomenon:**

- *Non-pharmacologic:* Avoid cold, stop smoking, avoid vasoconstrictors, stress management.
- *Pharmacologic:* **Long-acting dihydropyridine CCBs** (first-line). Alternatives: PDE-5 inhibitors, topical nitrates.

- *Note:* SRC, PAH, and GI dysmotility are generally managed *without* systemic immunosuppression.

Complications / Prognosis

- **Mortality:** Pulmonary complications (ILD, PAH) are the leading causes of death, followed by cardiac and renal causes.
- **Monitoring Protocol:**
  - **Annual:** Echocardiogram, ECG, and PFTs (for at least 5 years post-diagnosis).
  - **Blood Pressure:** Monitor twice weekly in stable patients.
  - **High-Risk BP Monitoring (Daily):** Required in patients with early-stage diffuse disease, rapidly progressive skin changes, tendon friction rubs, or positive Anti-RNA polymerase III.
  - *Red flag:* An increase of ≥15 mmHg systolic or ≥10 mmHg diastolic requires immediate evaluation for SRC.

Past-Paper High Yield

- **Scleroderma Renal Crisis Diagnosis:** A patient with diffuse SSc presenting with malignant hypertension, oliguria, headache, blurred vision, or papilledema has SRC until proven otherwise.
- **SRC Workup:** The most critical immediate investigations are **urinalysis and a blood film**. You are specifically looking for microangiopathic hemolytic anemia (schistocytes on the blood film) and ruling out severe glomerulonephritis (which is uncommon in SRC).
- **SRC Treatment Trap: Captopril** (or another rapid-acting ACE inhibitor) is the undisputed treatment for Scleroderma Renal Crisis. Do not withhold it due to renal failure, and do not select other anti-hypertensives like carvedilol, clonidine, diltiazem, or nitroprusside in exam scenarios.

Memory Pearls

- **Tendon friction rubs** = Red flag for aggressive diffuse disease and impending renal crisis.
- **Anti-centromere** = CREST syndrome (Limited SSc).
- **Scl-70** = Sclerosis of the lungs (Diffuse SSc + ILD).
- **RNA polymerase III** = Renal crisis.
- **Drugs causing secondary Raynaud's:** Bleomycin, Cisplatin, Amphetamines.