RGUHS · MODEL ANSWER BANK

RGUHS MD General Medicine — Paper II

INFECTIOUS DISEASES, CARDIOVASCULAR & GASTROINTESTINAL MEDICINE

2019–2026

125 topics in this volume · from a 411-topic bank · Textbook-grounded model answers

GROUNDED IN:

Harrison's Principles of Internal Medicine 22e — spine text
Braunwald's Heart Disease 13e — cardiology
Williams Textbook of Endocrinology 15e — endocrinology
Murray & Nadel's Respiratory Medicine 7e — respiratory
Sleisenger & Fordtran's GI & Liver 11e — gastroenterology & hepatology
Brenner & Rector's The Kidney — nephrology
DeVita's Cancer 12e — haematology & oncology
Bradley & Daroff's Neurology 8e · Brazis (Localization) · DeJong's Neurologic Examination — neurology
Kaplan & Sadock's Comprehensive Psychiatry 2024 · DSM-5-TR — psychiatry
Rook's Dermatology 10e · Bolognia Dermatology 5e — dermatology
Tintinalli's Emergency Medicine — emergency & toxicology
Textbook of Critical Care 8e — critical care
CMDT 2026 — diagnosis & management

Dr. Harshad Ramineni
@aurapharmlab

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Cardiology

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Aortic regurgitation

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Aortic regurgitation (AR) is the diastolic reflux of blood from the aorta into the left ventricle (LV) due to failure of competent coaptation of the aortic valve leaflets. It arises from **primary disease of the valve leaflets, dilation of the aortic root/ascending aorta, or a combination of both**. It imposes a *combined volume (preload) and pressure (afterload) overload* on the LV, and may present as a slowly tolerated **chronic** lesion or as a catastrophic **acute** lesion causing fulminant pulmonary oedema and cardiogenic shock.

Etiology and pathology

AR is conveniently classified by the structure primarily at fault (Harrison Table 273-1; Braunwald Table 69.1). In contemporary surgical series, **aortic root disease now accounts for >50%** of patients undergoing AVR for isolated AR.

Mechanism	Causes
Valvular (leaflet) disease	Congenital **bicuspid aortic valve (BAV)** — commonest in young; rheumatic heart disease (leaflet thickening, retraction, commissural fusion → mixed AS+AR); **infective endocarditis** (perforation/destruction, vegetation); myxomatous prolapse; calcific degeneration in the elderly; trauma; unicuspid/quadricuspid valves; bioprosthetic degeneration; paravalvular leak after TAVR; radiation; anorectic drugs
Aortic root / ascending aorta disease	Age-related (degenerative) dilation; **systemic hypertension**; **Marfan syndrome** (cystic medial degeneration), annuloaortic ectasia, Ehlers-Danlos, osteogenesis imperfecta; **aortic dissection**; syphilitic aortitis; **ankylosing spondylitis**; Takayasu and giant-cell aortitis; Behçet, reactive/psoriatic arthritis
Combined valve + root	Bicuspid aortic valve with aortopathy; ankylosing spondylitis

- **Acute severe AR** is caused chiefly by **infective endocarditis, aortic dissection (type A), and trauma**.
- Root dilation sets up a *vicious cycle* — dilation separates the cusps → AR → further dilation → more AR.

Pathophysiology

- In contrast to mitral regurgitation (low-pressure run-off into the LA), in AR the **entire LV stroke volume is ejected into the high-pressure aorta**; the regurgitant volume may equal the effective forward stroke volume.
- **Chronic AR — combined preload + afterload overload:** increased end-diastolic volume (preload) is the major compensation. The LV undergoes **eccentric hypertrophy** (sarcomeres replicated *in series*, myocyte elongation) and chamber dilation, normalising wall stress (Laplace law: stress ∝ pressure × radius ÷ wall thickness). This permits a *normal effective forward stroke*

volume and normal EF despite severe regurgitation. Hearts may reach the largest size in all of cardiology — **cor bovinum**, sometimes >1000 g.

- With time, wall thickening fails to keep pace → **afterload mismatch**, rising end-systolic volume, interstitial fibrosis, and a *fall in EF*. Crucially, **LV dysfunction often becomes irreversible before symptoms appear** — the central reason for serial surveillance.
- **Myocardial ischaemia** even with normal coronaries: O_2 demand is high (dilation, hypertrophy, raised systolic wall tension) while O_2 supply is reduced — coronary perfusion occurs mainly in diastole, when aortic pressure is low → reduced coronary driving pressure, subendocardial ischaemia, nocturnal angina.
- **Acute severe AR:** the normal-sized, non-compliant LV cannot accommodate the sudden regurgitant load → LV diastolic pressure rises steeply (>40 mmHg), forcing **premature mitral valve closure**, a sharp fall in forward stroke volume, compensatory tachycardia, and rapid pulmonary oedema/cardiogenic shock. The pulse pressure is **not** widened and peripheral signs are absent — masking severity.

Clinical features

Symptoms — Chronic AR has a long latent period; patients stay asymptomatic for 10–15 years. Early: uncomfortable awareness of the heartbeat, palpitations, head pounding (especially lying down). Later: **exertional dyspnoea** (first symptom of failing reserve) → orthopnoea, PND, diaphoresis; **angina** (often nocturnal, poorly responsive to nitrates) even without coronary disease; finally overt heart failure. Once symptomatic, the course is rapidly downhill — historically death ~4 years after angina and ~2 years after onset of heart failure.

Peripheral signs of a wide pulse pressure (chronic severe AR):

Eponym	Sign
Corrigan pulse	Water-hammer pulse — rapid rise, sudden collapse
de Musset sign	Head bob with each systole
Quincke sign	Visible capillary nail-bed pulsations
Müller sign	Systolic pulsation of the uvula
Traube sign	"Pistol-shot" booming systolic + diastolic sounds over femorals
Duroziez sign	To-and-fro murmur on light femoral compression
Hill sign	Popliteal cuff systolic pressure >40 mmHg higher than brachial
Bisferiens pulse	Twin systolic peaks (esp. mixed AS+AR)

Precordium/auscultation: apex diffuse, hyperdynamic, displaced **down and to the left**; widened pulse pressure (high systolic, low diastolic, often <60 mmHg). The hallmark is a **high-pitched, blowing, decrescendo early-diastolic murmur** beginning immediately after A2, best heard in the **3rd–4th left intercostal space at the lower left sternal border**, with the patient *sitting, leaning forward, breath held in expiration*. A right-sternal-border murmur suggests **root/aortic dilation as the cause**. *Severity correlates with murmur duration (holodiastolic), not loudness.* Associated: soft/absent A2, S3 (LV dysfunction), a basal systolic ejection (flow) murmur, and the **Austin Flint murmur** — a low-pitched

mid-to-late diastolic apical rumble from the regurgitant jet impinging on the anterior mitral leaflet (no organic mitral stenosis). Handgrip (↑afterload) intensifies the murmur. In **acute AR**, signs are deceptively subtle: soft S1, short soft diastolic murmur, near-normal pulse pressure, tachycardia, pulmonary oedema.

Investigations

- **ECG** — LV hypertrophy with "strain" (ST depression, T inversion in I, aVL, V5–V6); left axis deviation/QRS prolongation. In acute AR — sinus tachycardia; progressive heart block on serial tracings suggests an **aortic root abscess**.
- **Chest X-ray** — chronic: cardiomegaly with apex displaced down and left, dilated ascending aorta if root disease. Acute: near-normal heart size with florid pulmonary oedema.
- **Transthoracic echocardiography (TTE)** — cornerstone of diagnosis, aetiology, severity and serial follow-up. Defines leaflet/root anatomy; high-frequency **diastolic fluttering of the anterior mitral leaflet**; measures LV dimensions, volumes, EF and mass. Color/spectral Doppler grades severity.
- **Doppler criteria of severe AR:** central **jet width >65% of LVOT**; **vena contracta >0.6 cm**; **regurgitant volume ≥60 mL/beat**; **regurgitant fraction ≥50%**; **effective regurgitant orifice ≥0.30 cm^2**; **holodiastolic flow reversal in the proximal descending/abdominal aorta**; pressure half-time <200 ms. **Global longitudinal strain (GLS)** detects subclinical dysfunction before EF falls.
- **Cardiac MRI** — most accurate for LV volumes, mass and regurgitant fraction; assesses aortic dimensions and **myocardial fibrosis (late gadolinium enhancement, T1 mapping/ECV)**; used when TTE is suboptimal/discordant.
- **TEE / cardiac CT** — detailed valve, root and ascending-aorta anatomy. **Cardiac catheterisation/aortography** when non-invasive data are discordant; **coronary angiography** before surgery in at-risk patients.

Staging (2020 ACC/AHA)

- **Stage A** — at risk (BAV, root disease, history of rheumatic fever); **Stage B** — progressive mild–moderate AR; **Stage C** — asymptomatic severe AR (**C1** normal EF >55% with mild–moderate dilation; **C2** EF ≤55% or LVESD >50 mm / indexed >25 mm/m^2); **Stage D** — symptomatic severe AR.

Management

Acute severe AR — a *surgical emergency*; **AVR within 24–48 h** is life-saving. While stabilising: IV **vasodilator (sodium nitroprusside) ± inotrope (dopamine/dobutamine)**. **Beta-blockers are avoided** (they blunt the compensatory tachycardia and prolong diastolic regurgitation) and **intra-aortic balloon counterpulsation is contraindicated** (augments diastolic regurgitation). With endocarditis, defer 5–7 days for antibiotics only if haemodynamically stable; operate at the first sign of instability or abscess; in dissection, repair the aorta concurrently.

Chronic AR — medical — No drug halts progression; vasodilators do *not* prolong the compensated phase in asymptomatic patients with normal BP. Treat **hypertension (SBP >140 mmHg)** with vasodilators (ACE-I/ARB, dihydropyridine CCB, hydralazine). **Beta-blockers/losartan** retard root

growth in **Marfan syndrome** (atenolol and losartan equivalent in the paediatric trial). Symptomatic patients unfit for surgery receive guideline-directed heart-failure therapy. Avoid isometric/strenuous exercise with significant aortopathy.

Chronic AR — surgical indications (Class I/IIa):

- **Symptomatic severe AR (Stage D) — AVR regardless of LV function.**
- **Asymptomatic severe AR with EF ≤55% (Stage C2)** — AVR indicated.
- Severe AR (Stage C/D) **undergoing other cardiac surgery**.
- Asymptomatic severe AR, normal EF, but **LVESD >50 mm or indexed LVESD >25 mm/m²** — reasonable (newer data favour an even lower index threshold ≥20 mm/m²).
- IIb: progressive EF decline (to 55–60%) on ≥3 serial studies or LVEDD >65 mm at low surgical risk.
- *Delay beyond ~1 year of symptoms/dysfunction risks failure to recover normal LV size and function*, hence 6–12 monthly surveillance.

Surgical options — AVR with mechanical or bioprosthetic valve is standard (operative mortality ~1–2% for isolated pure AR). For root pathology: **valve-sparing aortic root reconstruction (David reimplantation procedure)**; **composite valve-graft conduit (Bentall)** when both valve and aneurysmal aorta need replacement; concomitant ascending-aorta replacement if diameter **>45 mm**. **Ross procedure** (pulmonary autograft) in selected young adults at expert centres. **Aortic valve repair** is feasible in selected younger patients but, unlike mitral regurgitation, the majority of AR patients ultimately need replacement. **TAVI is NOT recommended for surgical candidates** with pure native AR (limited by annular dilation and lack of valvular calcium for anchoring).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow diagram of AR:** boxes/arrows — *Aortic regurgitation → ↑LV diastolic volume (↑preload) + ↑aortic systolic pressure (↑afterload) → eccentric hypertrophy + chamber dilation (cor bovinum) → maintained EF/forward SV → afterload mismatch → ↑LVESV, ↓EF, interstitial fibrosis → LV failure*; side branch — *↓diastolic coronary perfusion + ↑O_2 demand → subendocardial ischaemia*. Labels: LVEDP, effective stroke volume, regurgitant fraction, myocardial O_2 supply/demand.
- **Auscultation/peripheral-sign figure:** chest outline marking the **decrescendo early-diastolic murmur at 3rd–4th left ICS (lower left sternal border)**, **basal systolic flow murmur**, **apical Austin Flint rumble**, displaced apex (down-and-left); annotate peripheral signs — Corrigan, de Musset, Quincke, Müller, Traube, Duroziez, Hill, bisferiens, wide pulse pressure.

Clinical / Diagnostic significance

- AR uniquely loads the LV with **both preload and afterload**; the danger is **silent, irreversible LV dysfunction preceding symptoms** — mandating serial echo (6–12 monthly in severe AR).
- The **decrescendo diastolic murmur intensity reflects severity poorly; duration (holodiastolic) and a wide pulse pressure are better markers.** Murmur loudest at the **right sternal border points to root/aortic disease.**

- A **deceptively normal pulse pressure in an acutely ill, tachycardic patient with pulmonary oedema** should raise suspicion of **acute severe AR (endocarditis/dissection)** — do not be reassured.
- **Austin Flint murmur** mimics mitral stenosis but lacks a loud S1/opening snap and occurs with a normal mitral valve.
- Newer prognostic markers — **indexed LVESV >45 mL/m², GLS, regurgitant fraction, and LGE-fibrosis on CMR** — increasingly refine the timing of intervention.

High-yield exam pointers

- Commonest cause of **chronic** AR now = **aortic root disease (>50%)**; commonest **valvular** cause in young = **bicuspid aortic valve**; commonest **acute** causes = **endocarditis, dissection, trauma**.
- **Eccentric hypertrophy → cor bovinum** (heart may exceed 1000 g) — largest LV in cardiology.
- Severe AR Doppler: **jet width >65% LVOT, vena contracta >0.6 cm, RVol ≥60 mL, RF ≥50%, ERO ≥0.30 cm², holodiastolic aortic flow reversal.**
- **Hill sign** = popliteal SBP >40 mmHg above brachial; **Duroziez** = to-and-fro femoral murmur; **Traube** = pistol-shot femorals.
- **Operate for symptoms regardless of EF; or EF ≤55%; or LVESD >50 mm (>25 mm/m²); or LVEDD >65 mm.**
- **Acute AR = surgical emergency (AVR within 24–48 h); nitroprusside ± inotrope; AVOID beta-blockers and IABP.**
- **David** = valve-sparing reimplantation; **Bentall** = composite valve-graft; replace ascending aorta if **>45 mm**.
- **TAVI is not recommended** for surgical candidates with isolated native AR.
- Beta-blockers/**losartan** slow root dilation in **Marfan syndrome**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Aortic Regurgitation" (etiology, pathophysiology, physical signs, Doppler severity criteria, management and surgical thresholds).
- **Braunwald's Heart Disease, 13e** — "Aortic Regurgitation" (Bonow & Nishimura): chronic vs acute pathophysiology, ACC/AHA Stage A–D table, indications for AVR (Table 69.4), novel LV-overload markers, valve-sparing/Ross/Bentall operative options.
- **CMDT 2026** — Cardiology (valvular disease): bedside signs (Hill, Duroziez, Corrigan, Austin Flint), echo and surgical-timing pearls.

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Bradyarrhythmias

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — A **bradyarrhythmia** is a sustained or intermittent heart rate **<60 beats/min** arising from disordered impulse *formation* in the sinoatrial (SA) node (**sinus node dysfunction, SND**) or disordered impulse *conduction* through the atrioventricular (AV) node and His–Purkinje system (**AV block / heart block**). It may be **physiologic** (high vagal tone, athletes, sleep) or **pathologic**, and clinically ranges from asymptomatic sinus bradycardia to syncope and asystolic sudden death. **Permanent pacing is the only reliable long-term therapy** for irreversible, symptomatic, or high-risk bradycardia.

Anatomy & physiology of the conduction axis

- **SA node:** crescent of fusiform pacemaker myocytes in the *sulcus terminalis* at the right atrial–SVC junction; supplied by the SA nodal artery (from **RCA in 55–60%**, left circumflex in 40–45%). Slow **phase-4 diastolic depolarization** driven by the **funny current (If)** plus **T- and L-type Ca^{2+} currents**; phase 0 upstroke is Ca^{2+}-mediated (no fast Na^{+} channel). Normal automaticity **60–100/min**.
- **Intrinsic heart rate** (after autonomic blockade with atropine + propranolol) ≈ **100–110/min**, calculated as **118.1 − (0.57 × age)**; it declines **5–6/min per decade**.
- **AV node:** **~1 × 3 × 5 mm** at the apex of the **triangle of Koch** (boundaries: coronary sinus ostium, septal tricuspid annulus, tendon of Todaro); supplied by the AV nodal artery (**RCA 80–90%**, LCx 10%). Provides physiologic conduction delay and **decremental conduction**; subsidiary automaticity **20–60/min**.
- **His–Purkinje system:** fastest conduction (1–3 m/s); His bundle and bundle branches are **insulated and NOT influenced by autonomic tone**; ventricular (idioventricular) escape is slow (**<40/min**) and unreliable.

Sinus node dysfunction (sick sinus syndrome) — subtypes

- **Sinus bradycardia / sinus arrest:** failure of impulse formation.
- **Sinoatrial exit block:** failure of the sinus impulse to propagate to the atrium — Type I (SA Wenckebach: progressive P-P shortening then a pause <2× the cycle) and Type II (sudden pause exactly twice the P-P interval).
- **Tachycardia–bradycardia (tachy-brady) syndrome:** alternating atrial tachyarrhythmia (usually AF/flutter) with symptomatic bradycardia or a long **offset pause** after tachycardia termination; rate-control drugs worsen the bradycardia — a common trigger for pacing.
- **Chronotropic incompetence:** failure to reach **~85% of age-predicted maximum [(220 − age) × 0.85]** on exertion; a major cause of exercise intolerance.
- **Causes:** age-related **sinus node fibrosis** and pacemaker-cell loss (commonest), inferior/posterior MI (SA nodal ischaemia, *Bezold–Jarisch reflex*), carotid sinus hypersensitivity / neurally-mediated (cardioinhibitory vasovagal) syncope, post-cardiac surgery / transplant, AF-ablation injury.

AV (heart) block — ECG classification

Grade	ECG hallmark	Usual site	Escape / risk
First-degree	Fixed **PR >200 ms**, every P conducts	AV node (AH delay)	Benign
2°, Mobitz I (Wenckebach)	**Progressive PR lengthening** → dropped QRS; grouped beating, RR shortens	AV node	Stable, often vagal/benign
2°, Mobitz II	**Fixed PR** then sudden dropped QRS; usually wide QRS	Infranodal (His–Purkinje)	Unreliable escape; risk of sudden CHB
2:1 block	Cannot classify I vs II from a single strip	PR <160 ms + wide QRS → infranodal	Localise by QRS/PR
Third-degree (complete)	**AV dissociation**, atrial rate > ventricular rate, regular slow QRS	Nodal or infranodal	Junctional (narrow, 40–60) vs ventricular (wide, <40) escape

- **Localising rule:** a **narrow QRS** escape implies block in the AV node/proximal His with a faster, more stable junctional escape; a **wide QRS** escape implies distal His/bundle-branch block with a slow, unreliable rhythm.
- **High-grade (advanced) block** = ≥2 consecutive non-conducted P waves with some conduction preserved.

Aetiology of AV conduction disease

- **Degenerative/idiopathic fibrosis (~50%):** *Lev's disease* (proximal bundle-branch fibrosis/calcification, elderly) and *Lenègre's disease* (distal sclerodegeneration, younger patients); accelerated by hypertension, diabetes, atherosclerosis; familial forms with **SCN5A** mutation.
- **Ischaemic:** transient block in **10–25%** of acute MI. *Inferior MI* — block usually **proximal (intranodal)** in ~90%, narrow stable escape >40/min, often reversible (vagal/AV-nodal artery). *Anterior MI* — **infranodal**, wide unstable escape, extensive infarction, high mortality → temporary pacing.
- **Infective: Lyme carditis** (*Borrelia burgdorferi*; reversible with antibiotics), infective endocarditis with **peri-valvular abscess** (surgical emergency), viral myocarditis, **Chagas' disease**, toxoplasmosis.
- **Infiltrative/inflammatory: cardiac sarcoidosis** (suspect AV block age ≤60 → MRI/FDG-PET), amyloidosis, haemochromatosis, SLE, RA, scleroderma.
- **Iatrogenic/drug:** valve surgery, **TAVR**, alcohol septal ablation, catheter ablation; **β-blockers, verapamil, diltiazem, digoxin**; toxins.
- **Congenital:** maternal **anti-Ro/SLE** (neonatal lupus), structural CHD (TGA, ostium primum ASD, endocardial-cushion defects).
- **Neuromuscular: myotonic dystrophy**, **Kearns-Sayre syndrome**, Erb's dystrophy, **Lamin A/C** cardiomyopathy (low threshold to pace even mild block).

Clinical features & diagnostic evaluation

- **Symptoms:** fatigue, exertional intolerance, dyspnoea, dizziness, presyncope/syncope (**Stokes–Adams / Adams-Stokes attacks**), worsening heart failure or angina; asystole → sudden death.
- **Signs:** first-degree — soft S1, prolonged a–c interval in JVP; complete block — cannon 'a' waves, variable S1 intensity, AV dissociation.
- **Investigations:**
  - **12-lead ECG** (initial test) — characterise rhythm, PR, QRS width, escape.
  - **Ambulatory monitoring** — Holter, mobile cardiac telemetry, event/wearable ECG, implantable loop recorder to achieve **symptom–rhythm correlation** (the cornerstone of pacing decisions).
  - **Treadmill exercise testing** — chronotropic incompetence, exercise-related block.
  - **Echocardiography ± advanced imaging** — MRI / FDG-PET / Tc-PYP scan for infiltrative disease, especially block at age ≤60.
  - **Bedside manoeuvres:** carotid massage/vagal manoeuvres *worsen* nodal but *improve* infranodal block; atropine/isoproterenol/exercise *improve* nodal but may *worsen* infranodal block — helps localise.
  - **Electrophysiology study (His-bundle electrogram): AH interval** (AV-nodal conduction) normally <130 ms; **HV interval** (His–Purkinje) normally ≤55 ms; **HV >100 ms** carries an annual incidence of complete block approaching **10%** → indication for pacing. SNRT/SACT for sinus node (rarely needed).

Management

- **Acute / reversible-cause first:** stop offending drugs (β-blockers, CCBs, digoxin), correct **electrolytes, hypoxia, hypothyroidism, ischaemia**; treat sleep apnoea, Lyme, sarcoid.
- **Emergency (symptomatic / unstable bradycardia):**
  - **Atropine 0.5 mg IV** (repeat to 3 mg) — effective for **AV-nodal** block; little effect on infranodal block.
  - **β-adrenergic infusion** — isoproterenol, dopamine, or epinephrine.
  - **Transcutaneous pacing** — pads anterior over apex (cathode) and posterior between spine and scapula (anode); fast but uncomfortable.
  - **Temporary transvenous pacing** — for unstable infranodal/anterior-MI block; more reliable bridge to recovery or PPM.
- **Permanent pacemaker (PPM) — key indications:**
  - **SND:** symptoms documented to correlate with bradycardia; symptomatic bradycardia from *essential* drug therapy; tachy-brady syndrome; symptomatic chronotropic incompetence. *(Asymptomatic sinus bradycardia / sleep pauses are NOT an indication.)*
  - **AV block:** acquired **Mobitz II, high-grade, or third-degree block — pace regardless of symptoms**; symptomatic block of any degree; neuromuscular disease/Lamin A/C with even first-degree or Mobitz I block; asymptomatic infra-His or wide-QRS second-degree block.
- **Pacing nomenclature (NBG code):** I — chamber paced; II — chamber sensed; III — response (I/T/D); IV — Rate response (R). *DDDR* = dual-chamber pace/sense with rate response.

- **Mode/lead selection: atrial-based (single or dual chamber) pacing is superior to ventricular-only pacing in SND**; minimise unnecessary RV pacing. **Physiologic / conduction-system pacing — His-bundle** or **left-bundle-branch-area pacing**, or **CRT** (LV ejection fraction <50% with expected ventricular pacing >40%) — to prevent pacing-induced heart failure. **Leadless pacemakers** for vascular-access limitation or permanent AF.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Conduction system schematic:** label SA node (RA–SVC junction), AV node (triangle of Koch — coronary sinus ostium, tendon of Todaro, septal tricuspid annulus), His bundle, right & left bundle branches (with left anterior & posterior fascicles), Purkinje network; annotate intrinsic rates (SA 60–100, AV junction 40–60, ventricle <40).
- **ECG ladder/rhythm strips of AV block:** label (a) first-degree (fixed long PR), (b) Mobitz I — progressive PR lengthening then dropped QRS, (c) Mobitz II — fixed PR then dropped QRS, (d) complete heart block — independent P waves and QRS (AV dissociation, atrial rate > ventricular rate).

Clinical / Diagnostic significance

- **Symptom–rhythm correlation** decides pacing in SND; in AV block the **site/level of block** (nodal vs infranodal) decides prognosis and pacing — infranodal block is paced even when asymptomatic.
- **Mobitz I + narrow QRS = benign, nodal, vagal**, rarely progresses; **Mobitz II / wide QRS = infranodal**, heralds Stokes–Adams syncope and complete block.
- **2:1 block:** narrow QRS / PR >200 ms → nodal (Type I); wide QRS / short PR → infranodal (Type II).
- **Acute MI:** inferior = reversible nodal block (atropine-responsive); anterior = ominous infranodal block (needs pacing).
- New AV block at **age ≤60** mandates imaging for **sarcoid/infiltrative** disease.

High-yield exam pointers

- Bradyarrhythmia = HR **<60/min**; two mechanisms — **impulse formation (SND)** and **impulse conduction (AV block)**.
- **If (funny current)** drives SA node phase-4 automaticity; **ivabradine** is a selective If blocker (and a cause of drug bradycardia).
- **Intrinsic heart rate = 118.1 − (0.57 × age)**.
- **First-degree PR >200 ms; HV ≤55 ms / AH <130 ms** normal; **HV >100 ms** → ~10%/yr risk of complete block.
- **Mobitz II and complete heart block → permanent pacing regardless of symptoms.**
- **Atropine helps nodal block, not infranodal block**; vagal manoeuvres do the opposite to nodal vs infranodal conduction.
- **Lev's** (proximal, elderly) vs **Lenègre's** (distal, younger) degenerative conduction disease; **SCN5A**/Lamin A/C genetic forms.

- **Atrial-based / physiologic (His or LBB-area) pacing** preferred over RV-only pacing to avoid pacemaker-induced heart failure; **DDDR** is the standard dual-chamber rate-responsive mode.
- Causes of **reversible** bradycardia mnemonic: drugs, hypothyroidism, hypoxia/sleep apnoea, ischaemia, electrolytes, Lyme, raised ICP, hypothermia.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "The Bradyarrhythmias: Disorders of the Sinoatrial Node" and "The Bradyarrhythmias: Disorders of the Atrioventricular Node."
- **Braunwald's Heart Disease, 13e** — "Bradyarrhythmias and Atrioventricular Block" (escape rhythms, Wenckebach criteria, His-bundle intervals, Lev/Lenègre, Stokes–Adams).
- **CMDT 2026** — "Disorders of Cardiac Rhythm" (sinus node dysfunction, AV block, atropine dosing, pacing modes, current management).

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Bundle branch blocks

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Bundle branch blocks (BBBs) are *intraventricular conduction disturbances* caused by intrinsic delay or block of the impulse in the right or left bundle branch (or their fascicles). Because one ventricle is then activated late through slow cell-to-cell (myocardial) spread rather than the rapid His–Purkinje system, the QRS complex widens and assumes a characteristic morphology. **Complete block** is defined by a QRS duration **≥120 ms**; **incomplete block** by a QRS of about **110–120 ms** (≈100–120 ms for incomplete RBBB) with the same morphology in lesser degree. The terminal/major QRS vector points toward the myocardial region whose depolarisation is delayed.

Anatomy and physiology of the conduction system

- The His bundle bifurcates into a **right bundle branch (RBB)** — a thin, discrete, relatively *fragile* structure — and a **left bundle branch (LBB)** which fans into two (functionally) main divisions: the **left anterior fascicle (LAF)** and **left posterior fascicle (LPF)**; a variable third *left median/septal fascicle* often arises from the LPF and drives initial left-to-right septal activation.
- Normal ventricular activation: the LBB system activates the left side of the interventricular septum first, giving the normal *left-to-right* septal vector (the small **septal q** in I, V5, V6 and small **r** in V1), followed by near-simultaneous, rapid endocardium-to-epicardium, apex-to-base activation of both free walls — producing a narrow QRS (<110 ms).
- The LPF is thick and dual-supplied (protected near the LV inflow); the LAF and RBB are thin and vulnerable — explaining why LAFB and RBBB are common and LPFB is rare.

Classification of intraventricular conduction disturbances

Category	Lesion	QRS width	Frontal axis
RBBB (complete)	Right bundle	≥120 ms	Usually normal (axis not directly altered)

Category	Lesion	QRS width	Frontal axis
LBBB (complete)	Left bundle / both fascicles	≥120 ms	Normal, left, or rarely right
Incomplete RBBB	Lesser RBB delay	100–120 ms	rSr′ in V1
Incomplete LBBB	Lesser LBB delay	100–119 ms	Slurred upstroke; ~⅓ → full LBBB in 2 yr
LAFB (left anterior hemiblock)	Anterior fascicle	<120 ms	**−45° to −90°** (marked LAD)
LPFB (left posterior hemiblock)	Posterior fascicle	<120 ms	**>+90° (>+110–120°)** (RAD)
Bifascicular block	RBB + one LBB fascicle	≥120 ms	RBBB + LAD (commonest) or + RAD
Trifascicular block	Bifascicular + His delay / alternating BBB	≥120 ms	Variable

Right bundle branch block (RBBB) — criteria and mechanism

- **Diagnostic criteria** (AHA/ACCF/HRS): QRS **≥120 ms**; **rsr′, rsR′ or rSR′** ("M-shaped"/rabbit-ear) pattern in **V1–V2**; **wide slurred S wave (≥40 ms)** in leads **I and V6**; normal time to peak R wave in V5–V6 but **>50 ms in V1**.
- **Mechanism:** right septum is activated only after slow *transseptal* spread from the left; the late, unopposed RV forces (right lateral wall and RV outflow tract) generate the terminal *rightward and anterior* vector → terminal R′ in V1 and wide terminal S in V6.
- **Secondary ST-T changes:** T-wave inversion in right precordial leads (V1–V3), discordant with the terminal R′.
- **Causes:** often seen with a structurally **normal heart** (incidental; commoner than LBBB in normals); RV catheter/moderator-band trauma; congenital (**atrial septal defect** with RV volume overload — iRBBB pattern + RAD), valvular and ischaemic heart disease, cor pulmonale/PE (acute right heart strain), and a **Brugada**-type RBBB-like pattern with right precordial ST elevation.

Left bundle branch block (LBBB) — criteria and mechanism

- **Classic criteria** (AHA/ACCF/HRS): QRS **≥120 ms**; **broad, notched/slurred R waves** in **I, aVL, V5, V6**; **small or absent initial r** in V1–V2 followed by deep S (often **QS** in V1); **absent septal q** in I, V5, V6; prolonged time to peak R wave (**>60 ms**) in V5–V6.
- **Stricter (specific) criteria:** QRS **>140 ms (men) / >130 ms (women)** with **mid-QRS notching/slurring in ≥2 lateral leads** — correlates better with true complete block (only ~⅔ of patients meeting classic criteria have true complete LBB block).
- **Mechanism:** loss of normal left-to-right septal activation → septum depolarises *right-to-left* (hence absent septal q); LV free wall is activated late (delay ~40–80 ms) by slow transseptal/myocardial spread → wide monophasic R in V6 and QS/rS in V1.

- **Secondary ST-T:** ST-T vector *discordant* — opposite in polarity to the terminal QRS (ST elevation/upright T in right precordial leads, T inversion in lateral leads).
- **Clinical associations (Harrison's four high-risk conditions): coronary heart disease** (frequently with impaired LV function), **hypertensive heart disease**, **aortic valve disease** (including after **TAVR**), and **cardiomyopathy**. >70% have preceding LVH; <10% have no demonstrable heart disease; present in >⅓ of heart-failure patients.

RBBB vs LBBB at a glance

Feature	RBBB	LBBB
QRS (complete)	≥120 ms	≥120 ms
V1	rSR′ ("M"), terminal R′	wide QS / rS
V6 / I	wide slurred **S**	broad notched **R**, no q
Septal q (I, V5, V6)	Preserved	**Absent**
Terminal vector	Right + anterior	Left + posterior
Heart disease	Often none/incidental	Usually structural; higher risk
Population prevalence	~1.4% men, 0.5% women	~0.5% (ARIC)

Fascicular, bifascicular and trifascicular blocks

- **LAFB (left anterior hemiblock):** the commonest cause of marked **left axis deviation** in adults — axis **−45° to −90°**, **qR in aVL**, rS in II/III/aVF, time-to-peak R in aVL ≥45 ms, **QRS <120 ms** (fascicular blocks alter the *sequence* but not overall duration of LV activation).
- **LPFB (left posterior hemiblock): right axis deviation** (>+90–120°), rS in I/aVL with qR in III/aVF, QRS <120 ms; *rare in isolation* — requires exclusion of other causes of RAD (RVH, lateral MI, normal variant, vertical heart).
- **Bifascicular block:** RBBB + LAFB (**commonest**, RBBB with marked LAD) or RBBB + LPFB.
- **Trifascicular block:** bifascicular block plus demonstrable His-bundle (HV) delay — historically inferred from added **first-degree AV block**, but true trifascicular disease is best shown by **alternating BBB**, which signals advanced infranodal disease and impending complete heart block.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Cardiac conduction system schematic:** label *SA node, RA, LA, AV node, His bundle, Right bundle branch, Left bundle branch, Left anterior fascicle, Left posterior fascicle, Purkinje network, RV, LV* — mark the level of block for RBBB, LBBB, LAFB, LPFB.
- **Diagram 2 — QRS-T morphology in V1 and V6:** three rows — *Normal* (rS in V1, qR in V6), *RBBB* (rSR′ in V1 with terminal T inversion, wide S in V6), *LBBB* (wide QS in V1, broad notched R in V6 with T inversion) — annotate "secondary T-wave inversion (discordant)" and "absent septal q (LBBB)".

Clinical / Diagnostic significance

- **Masking effect:** LBBB obscures/simulates LVH, the ECG diagnosis of ischaemia/MI, exercise-ECG interpretation and rate-corrected QT computation; RBBB lowers LVH sensitivity and complicates RVH diagnosis.
- **MI in the presence of LBBB — Sgarbossa criteria:** (1) **concordant ST elevation** (in leads with a positive QRS) or **concordant ST depression in V1–V3**, and **excessively discordant ST elevation >5 mm (>0.5 mV)** in leads with QS/rS (least specific; *modified*: ST/S ratio ≤ −0.25 is more accurate); (2) **QR complexes** in I, V5, V6 or II, III, aVF suggest underlying MI. Note: <10% of patients with new/possibly-new LBBB actually have acute MI.
- **Dyssynchrony & CRT:** LBBB produces septal "flash", reduced stroke volume (~10%), raised LV end-diastolic volume (~15%) and progressive remodelling — the rationale for **cardiac resynchronisation therapy** (biventricular pacing), with greatest benefit in **LBBB + QRS >150 ms**.
- **Acute MI:** new RBBB or new bifascicular block in **anterior STEMI** implies a large infarct (proximal LAD/septal perforator) and worse prognosis; new **LBBB** with ischaemic symptoms is managed as an STEMI-equivalent when the clinical picture fits.
- **Pacing / EP evaluation (2018 ACC/AHA/HRS; ESC): alternating BBB → permanent pacing, Class I**; **syncope + BBB + prolonged HV interval (>70 ms) on EP study → Class I pacing**; **unexplained syncope + bifascicular block → consider electrophysiology study (Class IIa)**; consider **genetic testing** in early-onset (<50 yr) progressive conduction-system disease. Asymptomatic bifascicular block alone does **not** mandate pacing.
- **TAVR:** new LBBB and high-degree AV block are the commonest conduction complications, frequently requiring permanent pacemaker implantation and carrying adverse outcomes.

High-yield exam pointers

- Complete BBB = QRS **≥120 ms**; incomplete = ~110–120 ms with same morphology.
- **V1 rule:** terminal **R′ in V1 = RBBB**; **QS/wide negative V1 + tall notched R in V6 = LBBB**.
- **RBBB** is commonly **benign/incidental**; **LBBB** almost always means structural heart disease (Harrison's four: CAD, hypertensive HD, aortic valve disease incl. post-TAVR, cardiomyopathy).
- **LAFB = marked LAD (−45° to −90°)**, the commonest cause of LAD in adults; **LPFB = RAD**, rare and a diagnosis of exclusion.
- **Bifascicular block = RBBB + LAFB** (commonest); add 1°AV block ("trifascicular") or **alternating BBB** = advanced His-Purkinje disease at risk of complete heart block.

- BBB ST-T changes are **secondary and discordant** (T opposite to terminal QRS); concordant/disproportionate changes flag ischaemia (**Sgarbossa**).
- **Rate-related (tachycardia-dependent) BBB** appears above a critical heart rate; ventricular pacing produces an **LBBB-like** QRS preceded by a pacing spike.
- LBBB + QRS >150 ms + EF ≤35% + HF symptoms → **CRT candidate**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Electrocardiography" (BBB and fascicular-block morphology, axis, secondary ST-T changes, LBBB associations).
- **Braunwald's Heart Disease, 13e** — "Electrocardiography" (AHA/ACCF/HRS diagnostic criteria for complete/incomplete RBBB & LBBB and fascicular blocks, mechanisms, prevalence/ARIC & LIFE data, Sgarbossa criteria, bifascicular block) and "Bradyarrhythmias and Atrioventricular Block" (alternating BBB, HV interval, pacing indications); "Transcatheter Aortic Valve Replacement" (post-TAVR LBBB).
- **CMDT 2026** — Bradycardia/conduction-delay management: pacing indications (ACC/AHA/HRS, ESC), EP study and genetic-testing recommendations.

Coverage note: The eponyms **Lev disease** and **Lenègre disease** (idiopathic/age-related progressive fibrosis and degeneration of the conduction system) are standard textbook causes of chronic bundle/fascicular block but are not named in the available corpus, which instead refers to "progressive cardiac conduction system disease"; they are included as universally accepted internal-medicine knowledge.

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Cardiac syncope

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Syncope* is a transient, self-limited loss of consciousness (TLOC) with loss of postural tone, due to acute global cerebral hypoperfusion, characterised by rapid onset, brief duration and prompt spontaneous complete recovery. **Cardiac (cardiovascular) syncope** is that subset caused by **arrhythmias** or **structural heart disease** that abruptly reduce cardiac output. Though it accounts for only ~10–20% of syncopal episodes (second to reflex/orthostatic causes), it is the most dangerous category — it may be the only warning before **sudden cardiac death (SCD)** and carries a markedly increased mortality, making its identification the central goal of any syncope work-up.

Pathophysiology

- Cerebral metabolism is exquisitely perfusion-dependent; cessation of cerebral blood flow produces loss of consciousness within **~6–10 seconds**, and a fall in systolic BP to ~50 mmHg generally causes syncope.
- Blood pressure = cardiac output × systemic vascular resistance. Cardiac syncope results from an **abrupt fall in cardiac output** due to: brady- or tachyarrhythmia (loss of effective ventricular filling/contraction, loss of AV synchrony) or a **fixed/dynamic obstruction** to flow.

- Structural disease and arrhythmia often **coexist** — scarred/hypertrophied myocardium is an arrhythmogenic substrate, so the two mechanisms compound one another.
- In aortic stenosis and hypertrophic cardiomyopathy, an **inappropriate reflex vasodilatation** (provoked by vigorous ventricular contraction/mechanoreceptor activation) may add a neurally mediated component, classically precipitated by exertion.

Classification of cardiac syncope

Category	Specific causes
Bradyarrhythmias	Sinus node dysfunction (sinus arrest, sinoatrial block); **tachycardia–bradycardia syndrome** (post-tachycardia pause); AV block — Mobitz type II, high-grade, complete (third-degree) AV block; drug-induced bradycardia; pacemaker/ICD malfunction
Tachyarrhythmias	**Ventricular tachycardia** (commonest arrhythmic cause); ventricular fibrillation; supraventricular tachycardia (AVNRT, WPW/AVRT), atrial fibrillation with rapid response
Inherited channelopathies / electrical disease	Long-QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT (CPVT), short-QT syndrome, idiopathic VF
Structural / obstructive ("mechanical")	Severe aortic stenosis, hypertrophic obstructive cardiomyopathy, pulmonary stenosis, atrial myxoma/ball-valve thrombus, pericardial tamponade, acute MI/ischaemia, aortic dissection, massive pulmonary embolism, pulmonary hypertension

Arrhythmic causes — key points

- **Bradyarrhythmias**: Syncope from bradycardia or asystole is the classic *Stokes–Adams attack* — sudden collapse, often without prodrome, with rapid recovery and reactive flushing. Sinus node disease frequently coexists with atrial tachyarrhythmia (tachy-brady syndrome); a long pause on termination of the tachycardia is a typical trigger.
- **Ventricular tachycardia** is the most common arrhythmia uncovered (~20% on electrophysiologic study). The likelihood of syncope rises with **faster ventricular rate** (rates <200/min less often cause syncope) and **poorer LV function**; haemodynamic collapse is due to ineffective contraction, short diastolic filling, loss of AV synchrony and concurrent ischaemia.
- **Inherited channelopathies** arise from mutations in ion-channel subunit genes:
  - *Long-QT syndrome* — prolonged repolarisation predisposing to *torsades de pointes* (polymorphic VT that may degenerate into VF); linked to K^+ channel α- and β-subunit genes, the voltage-gated Na^+ channel, and the scaffolding protein **ankyrin-B (ANK2)**.
  - *Brugada syndrome* — syncope, polymorphic VT and idiopathic VF with **coved ST-elevation/RBBB pattern in V1–V3** and a structurally normal heart; most often a Na^+-channel α-subunit (**SCN5A**) mutation.
  - *CPVT* — exercise- or emotion-induced ventricular arrhythmias from abnormal calcium handling.
  - Acquired QT prolongation (drugs, electrolytes) likewise causes torsades and syncope.

Structural / obstructive causes

- **Severe aortic stenosis** and **HOCM** — exertional syncope from a fixed/dynamic outflow obstruction that prevents an adequate rise in stroke volume on demand (± reflex vasodilatation).
- **Atrial myxoma / ball-valve thrombus** — positional mitral inflow obstruction.
- **Pericardial tamponade**, **aortic dissection**, **acute myocardial ischaemia/infarction**, **massive pulmonary embolism** and **pulmonary hypertension** — by acutely impairing right- or left-sided output.
- These typically produce **abrupt, often unheralded** collapse, frequently with injury, and are commonly **exertional or post-exertional**.

Clinical clues — cardiac vs neurally mediated syncope

Feature	Cardiac syncope (arrhythmia/structural)	Neurally mediated (vasovagal)
Prodrome	Absent or very brief (<5 s); may have abrupt palpitations	Longer warning (>5 s): nausea, warmth, diaphoresis, pallor, blurred vision
Trigger/posture	At rest, **supine**, or **on exertion**	Standing, warm room, emotion, pain
Demographics	Older age, male > female, fewer prior episodes; family history of SCD	Younger, female > male, recurrent episodes
Recovery	Prompt, oriented; injury common	Prompt but prolonged fatigue common
Background	Structural heart disease / abnormal ECG	Structurally normal heart, normal ECG

Diagnostic evaluation

- **History, eyewitness account and examination** with **supine and standing (orthostatic) vital signs** are the most valuable step — establish the cause in ~25–50% of cases and stratify risk.
- **High-risk "red-flag" features mandating admission/urgent work-up**: exertional or supine syncope; abrupt palpitations preceding syncope; chest pain; known severe structural/coronary disease or low ejection fraction; family history of SCD; persistent bradycardia <40/min; undiagnosed systolic murmur; SBP <90 mmHg.
- **12-lead ECG** in all patients — look for prolonged QT (>500 ms), short PR + delta wave (WPW), RBBB with ST-elevation V1–V3 (Brugada), T-inversion ± epsilon wave V1–V3 (arrhythmogenic RV cardiomyopathy), bi-/trifascicular block or QRS ≥120 ms, AV block, ischaemia/old MI, non-sustained VT. Initial ECG is diagnostic in ~5% and suggestive in another ~5%.
- **Ambulatory ECG monitoring**, matched to event frequency: in-patient telemetry/Holter for frequent (≈daily) episodes; external loop recorder for episodes ~monthly; **implantable loop recorder** for infrequent, unexplained, high-suspicion syncope (battery up to ~3 years). Symptom –rhythm correlation is the diagnostic goal.
- **Echocardiography** when structural disease is suspected — diagnostic of severe aortic stenosis, HOCM, tamponade, aortic dissection, myxoma; also stratifies SCD risk by LV ejection fraction.
- **Exercise (treadmill) testing** for syncope during/after exertion (exercise-induced AV block, ischaemia, exaggerated vasodilatation); **coronary angiography** if ischaemia-mediated.

- **Electrophysiologic study (EPS)** — reserved for suspected arrhythmic cause with structural heart disease/abnormal ECG (low yield with a normal ECG and normal heart). EPS is **diagnostic** when it shows: a prolonged corrected sinus node recovery time (**CSNRT >525 ms**); bundle-branch block with a baseline **H-V interval ≥100 ms** or pacing-/procainamide-induced infra-Hisian block; **induction of sustained monomorphic VT** in a patient with prior MI; or induction of SVT that **reproduces the spontaneous symptoms**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Classification tree of syncope** (single page): Root *Syncope (TLOC from global cerebral hypoperfusion)* → three branches — *(1) Neurally mediated / reflex* (vasovagal, situational, carotid sinus), *(2) Orthostatic hypotension*, *(3) Cardiac syncope*. **Expand the cardiac branch into** Arrhythmic (**sub-label: *Bradyarrhythmias — SND, AV block; Tachyarrhythmias — VT/VF, SVT; Channelopathies — LQTS, Brugada, CPVT***) **and** Structural/Obstructive* *(sub-label:* aortic stenosis, HOCM, atrial myxoma, tamponade, PE, MI/ischaemia*).
- **Annotated rhythm strips**: label (a) *complete (third-degree) AV block with a long ventricular pause — "Stokes–Adams"*, (b) *monomorphic ventricular tachycardia*, and (c) *torsades de pointes on a long-QT baseline*.

Clinical / Diagnostic significance

- Cardiac syncope independently predicts **increased SCD and all-cause mortality**, in contrast to the benign prognosis of young neurally mediated syncope — risk stratification, not merely diagnosis, drives management.
- **Management is cause-specific**: permanent **pacemaker** for symptomatic sinus node disease and high-grade/Mobitz II/complete AV block (with documented pauses >3 s); **implantable cardioverter-defibrillator (ICD)** for VT/VF and for syncope with ischaemic or non-ischaemic cardiomyopathy and reduced ejection fraction; **catheter ablation** for SVT/WPW and selected VT; **antiarrhythmic drugs** as adjuncts; surgical/transcatheter correction of structural obstruction (e.g. aortic valve replacement, septal reduction in HOCM, myxoma excision); withdrawal of offending drugs and correction of electrolytes for acquired QT prolongation.
- Reversible/temporary causes (heart block in inferior MI, drug effect, electrolyte disturbance) often do **not** need a permanent device once corrected.
- **Driving advice**: temporary/treated causes — restrict ~1 week after recovery; symptomatic VT or aborted SCD (whether drug-, ICD- or ablation-treated) — restrict **3–6 months**, mindful of local law.

High-yield exam pointers

- Cardiac syncope = **arrhythmia + structural disease**; ~10–20% of cases but the **highest-mortality** group and a harbinger of SCD.
- **VT is the commonest arrhythmic cause**; bradycardia/asystole causing syncope = **Stokes–Adams attack**.

- **Exertional or supine syncope, syncope without prodrome, palpitations-then-collapse, family history of SCD, and an abnormal ECG** are the cardinal red flags.
- Channelopathy triad to remember: **LQTS (→ torsades, ANK2/K^+/Na^+ genes), Brugada (SCN5A, coved ST-elevation V1–V3), CPVT (exertion-triggered, calcium-handling)**.
- Exertional syncope with an ejection systolic murmur → think **severe aortic stenosis** or **HOCM**.
- **ECG in everyone**; choose the monitor (telemetry → external loop → implantable loop recorder) by event frequency; **echo** if structural disease suspected.
- EPS "diagnostic" numbers: **CSNRT >525 ms**, **H-V ≥100 ms**, **inducible sustained monomorphic VT** post-MI.
- Treatment is mechanism-driven: **pacemaker** (brady), **ICD** (VT/VF, low-EF cardiomyopathy), **ablation** (SVT/WPW), structural correction; remember **driving restrictions**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Syncope" (Freeman & Raj): definition, classification, cardiac syncope (arrhythmias, channelopathies, structural disease), Stokes–Adams attack, evaluation and high-risk features.
- **Braunwald's Heart Disease, 13e** — "Hypotension and Syncope" (Calkins & Chen): epidemiology/prognosis, proportion due to cardiac causes, VT predominance, high-risk hospitalisation criteria, diagnostic testing and electrophysiologic study criteria, management/driving guidance (per 2017 ACC/AHA/HRS and 2018 ESC syncope guidelines).
- **CMDT 2026** — "Disorders of Cardiac Rhythm" (Syncope): essentials of diagnosis, cardiogenic mechanical vs arrhythmic causes, current evaluation and management, driving restrictions.

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Cardiac tamponade

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Cardiac tamponade is the accumulation of fluid (or blood, pus, gas) within the pericardial space in a quantity sufficient to cause serious obstruction to the inflow of blood into the ventricles, producing a fall in cardiac output that may be rapidly fatal if not recognised and treated. It is the haemodynamic end-point of a pericardial effusion in which intrapericardial pressure rises to equal and then exceed cardiac filling pressures. Tamponade is a **clinical and echocardiographic diagnosis** and a true cardiovascular emergency; relief by pericardiocentesis is potentially life-saving.

Aetiology

- The volume needed to cause tamponade depends on the **rate** of accumulation, not absolute volume — as little as **200 mL** when fluid develops rapidly (acute), but **>2000 mL** in slowly developing effusions where the pericardium has stretched to adapt (the curvilinear, J-shaped pericardial pressure–volume relationship).

- **Most common causes (Harrison):** idiopathic pericarditis, and pericarditis secondary to neoplastic disease or tuberculosis; **bleeding into the pericardial space** after aortic dissection, cardiac surgery, trauma, or anticoagulant therapy.
- **Categorised (Braunwald, Table 78.1):**

Category	Representative causes
Infective	Viral (coxsackie, echovirus, adenovirus, CMV, HIV, SARS-CoV-2); **tuberculous**; pyogenic bacterial (pneumococcus, staphylococcus, streptococcus); fungal
Neoplastic	Secondary — lung & breast carcinoma, lymphoma, Kaposi sarcoma; primary mesothelioma; radiation-induced
Haemorrhagic / mechanical	Type A aortic dissection, free-wall rupture post-MI, chest trauma, post-cardiotomy, device/procedure-related (PCI, pacemaker leads, ablation, valve procedures), oral anticoagulants
Inflammatory / autoimmune	SLE, rheumatoid arthritis, scleroderma; *Dressler syndrome*; drug-induced (procainamide, hydralazine, isoniazid)
Metabolic / miscellaneous	Uraemia / dialysis-associated, hypothyroidism (cholesterol "gold-paint" effusion), chylopericardium

Pathophysiology

- As fluid accumulates, intrapericardial pressure rises; right- and left-sided diastolic pressures rise and, in severe tamponade, **equalise** at a level close to pericardial pressure, typically **20–25 mmHg** (CMDT: intrapericardial pressure >15 mmHg defines haemodynamic significance). Equalisation is closest during inspiration.
- The high pericardial pressure markedly reduces **transmural filling pressure**, so end-diastolic ventricular volume (preload) and hence **stroke volume** fall; compensatory tachycardia and increased contractility (adrenergic drive) initially maintain blood pressure, but eventually cardiac output and arterial pressure decline → shock.
- The primary direct effect is to **impede right-heart filling**, with left-heart effects largely secondary to under-filling. In terminal tamponade a depressor reflex with paradoxical bradycardia may supervene.
- **Total cardiac volume is fixed** within the rigid pericardial envelope, producing two hallmark phenomena:
  - **Exaggerated ventricular interdependence** — inspiratory enlargement of the RV bulges the interventricular septum leftward, encroaching on the LV and reducing LV volume, stroke volume and systolic pressure → *pulsus paradoxus*.
  - **Altered venous waveform** — blood can enter the heart only when blood is simultaneously leaving (during ventricular ejection): the systolic **x descent is preserved/prominent** but the early-diastolic **y descent is lost** (diastolic filling is abolished because the tricuspid opens against a fixed heart volume).
- **Low-pressure tamponade:** in a volume-depleted patient (haemorrhage, over-diuresis, haemodialysis) a modest pericardial pressure can compromise stroke volume while venous pressure is only mildly raised — diagnosis is easily missed.

- **Regional / loculated tamponade:** a localised effusion or clot (commonly post-cardiac surgery) selectively compresses one chamber, producing atypical haemodynamics without classic global signs.

Clinical features

- **Beck's triad** (acute tamponade): (1) **hypotension**, (2) **soft / muffled or absent heart sounds**, (3) **raised jugular venous pressure** with a **prominent x descent and absent y descent**.
- **Pulsus paradoxus** — an inspiratory fall in systolic arterial pressure of **>10 mmHg** (an exaggeration of the normal <10 mmHg fall). Severe forms cause palpable weakening/disappearance of the pulse on inspiration; usually quantified by sphygmomanometry during slow respiration. It is the *rule* in tamponade but is **not pathognomonic** — also seen in constrictive pericarditis (≈⅓), severe asthma/COPD, massive PE, and hypovolaemic shock; it may be *absent* in low-pressure tamponade, with coexisting LV dysfunction, severe aortic regurgitation, or ASD.
- **Sympathetic compensation:** sinus tachycardia, tachypnoea, narrow pulse pressure with relatively preserved systolic pressure, diaphoresis, cool cyanotic extremities, oliguria, and depressed sensorium (cardiogenic shock).
- **Kussmaul's sign is characteristically ABSENT** in pure tamponade (it is a feature of constriction) because the normal inspiratory fall in systemic venous pressure is retained.
- Peripheral oedema and ascites are *uncommon* in acute tamponade and, if present, suggest a more chronic process or constriction.

Investigations

- **Echocardiography (diagnostic test of choice, urgent, bedside):**
  - Pericardial effusion with a **swinging heart**.
  - **Early-diastolic collapse (inversion) of the RV free wall** and **late-diastolic collapse of the right atrium** (RA collapse is more sensitive, RV collapse more specific).
  - **Plethoric (dilated) IVC** with blunted (<50%) respiratory variation — reflects raised right-atrial pressure.
  - **Exaggerated respiratory variation in transvalvular Doppler flow** — inspiratory *increase* in tricuspid/pulmonary inflow with reciprocal *decrease* in mitral/aortic inflow (the echocardiographic equivalent of pulsus paradoxus).
  - TOE / CT / cardiac MRI are reserved for loculated or post-surgical (regional) effusions not seen well transthoracically.
- **ECG:** sinus tachycardia, **low-voltage QRS complexes**, and **electrical alternans** (beat-to-beat alternation of P–QRS–T amplitude from the heart swinging in a large effusion) — *electrical alternans is occasional but virtually pathognomonic* of a large effusion with tamponade.
- **Chest X-ray:** enlarged, globular ("water-bottle") cardiac silhouette with clear lung fields; may be normal in acute, rapidly accumulating effusions.
- **Cardiac catheterisation (when needed):** elevation and **diastolic equalisation** of RA, RV, pulmonary-capillary-wedge and LV diastolic pressures (~20–25 mmHg); RA waveform shows a

preserved x descent with a blunted/absent y descent (contrast with the prominent y/"M–W" pattern of constriction).

- **Pericardial fluid analysis** (after drainage): cell count, Gram stain/culture, cytology for malignant cells; for suspected TB — **adenosine deaminase (ADA)**, unstimulated interferon-γ, lysozyme and **PCR for *M. tuberculosis***. (Light's criteria for pleural fluid do *not* apply — normal pericardial fluid is often "exudative".)

Differential diagnosis — tamponade vs constriction vs restriction vs RV infarction

Feature	Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy	RV infarction
Pulsus paradoxus	+++	+	+	+
Prominent y descent (JVP)	**Absent**	++	+	+
Prominent x descent	+++	++	+++	+
Kussmaul's sign	Absent	+++	+	+++
Pericardial knock	–	++	–	–
Low ECG voltage / electrical alternans	++ / ++	++ / –	+ / –	–
Pericardial effusion (echo)	+++	–	–	–
Thickened/calcified pericardium	–	++ to +++	–	–
Equalisation of diastolic pressures	+++	+++	–	++

Management

- **Tamponade is a medical emergency** — admit, monitor, and proceed to drainage. The **definitive treatment is removal of pericardial fluid**.
- **Temporising / supportive measures** (must NOT delay drainage): intravenous **normal saline** to augment filling, plus inotropes/vasopressors as a bridge. **Avoid vasodilators and diuretics** (they reduce preload and precipitate collapse). **Stop anticoagulants** and reverse if bleeding.
- **Pericardiocentesis:**
  - Preferably **echocardiography-guided** (or fluoroscopy/CT-guided); commonest route is **subxiphoid**, alternatively apical or parasternal. Echo-guided pericardiocentesis has a **>95% success and <2% serious-complication rate**.
  - Measure intrapericardial pressure before withdrawal where possible; drain as completely as possible; leave an indwelling **pigtail (multi-holed) catheter** in situ for **2–3 days** for continued drainage and to reduce reaccumulation.

- Removal of even a *small* volume produces a disproportionately large fall in pericardial pressure (steep portion of the pressure–volume curve) and rapid haemodynamic improvement.

- **Surgical drainage** (subxiphoid window, video-assisted thoracoscopic pericardial window, or limited thoracotomy) is preferred for **loculated/clotted effusions, recurrent (especially malignant) effusions, the need for pericardial tissue/biopsy, and purulent pericarditis**; pericardial windows are more effective than needle drainage at preventing recurrence.
- **Special situations:**
  - **Type A aortic dissection** or **post-MI free-wall rupture / traumatic haemopericardium** → closed pericardiocentesis is generally **avoided/relatively contraindicated** (decompression may worsen bleeding); urgent **surgery** is needed (controlled "cycle" drainage may bridge a peri-arrest patient to theatre).
  - Treat the **underlying cause** (anti-tuberculous therapy, dialysis for uraemia, chemo/radiotherapy or sclerosant for malignant effusion, antibiotics ± drainage for purulent pericarditis).
- **Pericardial decompression syndrome** — a rare, poorly understood, life-threatening complication after drainage, with pulmonary oedema and shock (favoured by very rapid/complete removal of large effusions).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pericardial pressure–volume (compliance) curve:** plot intrapericardial pressure (y-axis) against pericardial volume (x-axis) as a J-shaped curve. Labels: *flat (compliant) initial limb — slow effusion adapts*; *"elbow"/inflection point*; *steep limb — small added volume causes large pressure rise (rapid effusion → tamponade)*; arrow showing *pericardiocentesis of a small volume → large pressure drop*.
- **Jugular venous pulse waveform in tamponade vs constriction:** label *a wave*, *prominent x descent (preserved)*, **absent y descent (tamponade)** versus *prominent rapid y descent / "M or W" pattern (constriction)*.
- **(Optional) Subcostal 2-D echo:** pericardial effusion (echo-free space) with labels — *late-diastolic RA collapse*, *early-diastolic RV free-wall collapse*, *dilated plethoric IVC*, *LV*, *effusion*.

Clinical / Diagnostic significance

- Suspect tamponade in any patient with **unexplained hypotension + raised JVP + tachycardia**, sudden enlargement of the cardiac silhouette, or shock with clear lungs ("**hypotension with raised venous pressure**").
- In the post-cardiac-surgery, post-MI, post-procedure (PCI, pacemaker, ablation) or trauma patient, a falling BP with rising filling pressures should trigger **immediate bedside echo**.
- **Pulseless electrical activity (PEA) arrest** with a narrow QRS — tamponade is one of the reversible "**H's and T's**" and warrants emergency pericardiocentesis/thoracotomy.
- Pericardial effusion in **pulmonary arterial hypertension** is a poor prognostic marker; drainage in this setting can be hazardous (RV may not collapse).

- Distinguishing tamponade from constriction and restriction guides definitive therapy (drainage vs pericardiectomy vs cardiomyopathy management).

High-yield exam pointers

- **Beck's triad** = hypotension + muffled heart sounds + raised JVP (prominent **x**, absent **y** descent).
- **Pulsus paradoxus >10 mmHg** inspiratory systolic fall — the cardinal sign; absent in low-pressure tamponade, ASD, severe AR, LV dysfunction.
- **Kussmaul's sign and the prominent y descent are ABSENT in tamponade** but PRESENT in constriction — a favourite discriminator.
- ECG: **low voltage + electrical alternans** (alternans ≈ pathognomonic of large effusion/tamponade).
- Echo: **RA collapse (sensitive) and RV diastolic collapse (specific), dilated IVC, respiratory Doppler swing**.
- Haemodynamics: **equalisation of diastolic pressures ~20–25 mmHg**; intrapericardial pressure >15 mmHg.
- As little as **200 mL** (acute) vs **>2000 mL** (chronic) can tamponade — *rate matters more than volume*.
- Treatment = **urgent echo-guided pericardiocentesis** (subxiphoid); **avoid diuretics/vasodilators**; give IV fluids as a bridge only.
- **Aortic dissection / haemopericardium → surgery, not needle drainage.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pericardial Disease" (definition, Beck's triad, pulsus paradoxus, Table distinguishing tamponade from constriction/restriction/RV infarction, pericardiocentesis, fluid analysis).
- **Braunwald's Heart Disease, 13e** — "Pericardial Diseases" (aetiology Table 78.1, pathophysiology and haemodynamics, ventricular interdependence, loss of y descent, echocardiographic signs, low-pressure and regional tamponade, pericardiocentesis technique and success/complication rates, pericardial decompression syndrome).
- **CMDT 2026** — "Pericardial Effusion & Tamponade" (essentials of diagnosis, intrapericardial pressure thresholds, current management, when to refer).

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Cardiogenic pulmonary oedema

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Cardiogenic (hydrostatic) pulmonary edema is the rapid accumulation of transudative fluid in the pulmonary interstitium and alveoli caused by an acute rise in pulmonary capillary (and hence left atrial) hydrostatic pressure, almost always from acute left-ventricular failure. It is a life-threatening medical emergency presenting with sudden dyspnoea at rest, severe hypoxaemia and bilateral crackles, and frequently coexists at the severe end of the spectrum with **cardiogenic shock** when left-ventricular dysfunction also produces systemic hypoperfusion. It must be distinguished from **non-cardiogenic (high-permeability) pulmonary edema / ARDS**, where the pulmonary capillary wedge pressure (PCWP) is normal.

Pathophysiology — the Starling balance

- Movement of fluid across the pulmonary capillary is governed by **Starling forces**: net filtration rises when **capillary hydrostatic pressure exceeds plasma oncotic pressure**. Extravascular lung water is determined by the **PCWP, pulmonary vascular permeability and intravascular volume status** (Harrison).
- Acute LV systolic and/or diastolic failure → ↑ LV end-diastolic pressure → ↑ left atrial pressure → ↑ pulmonary venous and capillary pressure → transudation of protein-poor fluid.
- **Stages of fluid accumulation** (standard teaching):
  - **Stage 1 – interstitial edema**: when PCWP exceeds ~18–20 mmHg, fluid floods the peribronchovascular interstitium; pulmonary lymphatics are initially overwhelmed → dyspnoea, Kerley B lines, peribronchial cuffing.
  - **Stage 2 – alveolar flooding**: when PCWP rises further (CMDT: PCWP usually > **25 mmHg**), fluid breaches the alveolar epithelium → alveolar flooding, severe hypoxaemia and **pink, frothy sputum**.
- Alveolar flooding plus airway-wall edema and peribronchial cuffing cause **wheeze ("cardiac asthma")** in addition to crackles. Endogenous **catecholamine release** raises afterload and BP, worsening the congestion in a vicious cycle.

Etiology (Harrison Table 316-1; CMDT)

Category	Examples
Acute MI / ischemia (commonest)	LV failure; ventricular septal rupture; papillary-muscle/chordal rupture → acute severe MR; free-wall rupture
Acute decompensation of chronic HF	The single commonest presentation in developed countries; precipitated by drug non-adherence, dietary salt/fluid excess, ischaemia, **rapid atrial fibrillation**, infection
Valvular	Critical aortic or mitral stenosis; acute severe aortic or mitral regurgitation
Hypertensive / afterload	Hypertensive crisis ("flash" pulmonary edema), acute kidney injury with volume overload
Arrhythmia	Refractory tachy- or brady-arrhythmias

Category	Examples
Myocardial	Fulminant myocarditis; end-stage cardiomyopathy; **Takotsubo** (apical-ballooning) syndrome; HOCM with severe LVOT obstruction; myocardial contusion
Other	Aortic dissection with acute AR/tamponade; β-blocker or calcium-channel-blocker overdose; post–cardiac-arrest stunning; septic myocardial depression

- *Contrast — non-cardiogenic edema* (normal PCWP): IV opioids, raised intracranial pressure (neurogenic), high-altitude, sepsis/ARDS, inhaled toxins, transfusion-related (TRALI), DIC, re-expansion edema.

Clinical features

- **Symptoms**: abrupt or subacute severe **dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea**, cough with **pink frothy sputum**, marked anxiety and diaphoresis.
- **Signs**: tachypnoea, tachycardia, **cyanosis**, cold clammy skin; bilateral **fine crepitations in all lung fields with wheeze/rhonchi**; raised JVP, **S3 gallop**, and the murmur of the underlying lesion (e.g., acute MR, VSR). Hypertension is common from catecholamine surge; **hypotension signals coexistent cardiogenic shock** (poor prognosis).
- **Hemodynamic profiles** are clinically useful:
  - **Nohria–Stevenson bedside profile** (Braunwald): assess *congestion* ("wet" vs "dry") and *perfusion* ("warm" vs "cold"). Most pulmonary-edema patients are **"warm and wet"**; the **"cold and wet"** profile (hypoperfused + congested) overlaps with cardiogenic shock and carries the worst outcome.
  - **Forrester haemodynamic subsets** (acute MI):

Subset	PCWP	Cardiac index	State
I	< 18	> 2.2	Normal — no congestion/hypoperfusion
II	**> 18**	> 2.2	**Pulmonary congestion / edema**
III	< 18	< 2.2	Hypoperfusion / hypovolaemia
IV	**> 18**	**< 2.2**	Congestion + hypoperfusion = **cardiogenic shock**

Investigations

- **Chest radiograph**: cardiomegaly (may be normal in acute MI/first event); **upper-lobe vascular redistribution (cephalization)**, blurring of vascular margins, **Kerley B lines**, peribronchial cuffing, **perihilar "bat-wing"/butterfly alveolar opacities**, and pleural effusions.
- **ECG**: identifies the trigger — ST-elevation/evolving Q waves (acute MI mandate immediate reperfusion), arrhythmia, LVH; may be non-specific.
- **Echocardiography**: pivotal — defines LV systolic/diastolic dysfunction, valvular lesions, mechanical complications (VSR, acute MR), tamponade, and RV involvement; helps separate cardiogenic from non-cardiogenic causes.

- **Natriuretic peptides**: a substantially elevated **BNP/NT-proBNP** supports a cardiac cause of acute dyspnoea (low values argue against it).
- **ABG / lactate**: hypoxaemia; respiratory alkalosis early, metabolic (lactic) acidosis with anion gap when hypoperfusion supervenes.
- **Cardiac troponin**, renal function and electrolytes; **pulmonary artery catheter (PAC)** is reserved for diagnostic uncertainty, refractory edema or accompanying refractory hypotension — it distinguishes **high-pressure (PCWP high, cardiogenic)** from **normal-pressure (non-cardiogenic)** edema, though it confers no mortality benefit.

Management (Harrison; Braunwald; CMDT 2026)

Immediate supportive measures (treat as an emergency, concurrently with work-up):

- **Sit the patient upright with legs dangling** — reduces venous return (preload).
- **Oxygenation**: high-flow O2 to target SpO2 ≥ 92% (PaO2 > 60 mmHg); avoid hyperoxia (>98%) and routine high-FiO2 in normoxic patients (risk of hyperoxia-induced vasoconstriction).
- **Non-invasive ventilation (CPAP/NIPPV)**: improves oxygenation and symptoms and **reduces the need for intubation and mortality** in cardiogenic pulmonary edema; positive end-expiratory pressure decreases preload and afterload, redistributes alveolar lung water and recruits collapsed alveoli. Endotracheal intubation and mechanical ventilation if respiratory distress/hypoxaemia is refractory (~4–5%).

Preload reduction (the therapeutic core):

- **IV loop diuretics** — first-line: **furosemide** (initial ≤ 0.5 mg/kg, or **40 mg IV**; 1 mg/kg or ~2–2.5× the usual oral dose in those on chronic diuretics or with renal impairment) or bumetanide 1 mg. Furosemide is also a **venodilator** that lowers preload before diuresis begins. The **DOSE trial** showed bolus and continuous infusion are equally effective.
- **Nitrates** — venodilators that rapidly lower LV filling pressure: **sublingual nitroglycerin 0.4 mg every 5 min**, then **IV nitroglycerin starting 5–10 µg/min**; especially valuable with concomitant **hypertension/ischaemia**. **IV sodium nitroprusside (0.1–5 µg/kg/min)** for severe hypertensive edema (avoid in active ischaemia; needs arterial-line monitoring).
- **Morphine 2–4 mg IV** — venodilates, relieves anxiety and dyspnoea, but use cautiously: some registry data link it to increased mortality and need for ventilation; avoid in opioid-induced and neurogenic edema.
- **ACE inhibitors** reduce afterload and preload and improve survival in acute MI with HF (favoured in hypertensive patients). **Nesiritide** (recombinant BNP) is reserved for refractory cases (not in ischaemia/MI).

Inotropes / vasopressors — only when hypoperfused (overlap with shock):

- **Dobutamine** or **milrinone** (PDE-3 inodilator, 50 µg/kg then 0.25–0.75 µg/kg/min) for low-output states; milrinone showed **no benefit** in unselected decompensated HF (OPTIME-CHF) and increased hypotension/AF.
- **Norepinephrine** is the preferred first-line vasopressor if shock supervenes; **dopamine** is avoided first-line (arrhythmogenic).

- **Mechanical circulatory support** (IABP no longer routine; Impella/VA-ECMO in selected refractory shock) and **renal replacement therapy / ultrafiltration** for refractory volume overload.

Treat the cause/trigger: emergency **primary PCI** for STEMI-associated edema (in-hospital mortality 20–40%); rate/rhythm control or cardioversion for rapid AF; surgery for acute mechanical complications and critical valve lesions; control of severe hypertension.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 – Starling balance at the alveolar-capillary unit (with stages).** Labels: *pulmonary capillary*, *alveolus*, *type I & type II pneumocytes*, *basement membrane / interstitial space*, *↑ capillary hydrostatic pressure (PCWP)*, *plasma oncotic pressure*, *lymphatic drainage (overwhelmed)*, *Stage 1 interstitial edema*, *Stage 2 alveolar flooding (transudate / pink frothy fluid)*.
- **Diagram 2 – Chest radiograph of cardiogenic pulmonary edema.** Labels: *cardiomegaly*, *upper-lobe vascular redistribution (cephalization)*, *Kerley B lines*, *peribronchial cuffing*, *perihilar bat-wing / butterfly alveolar opacities*, *blunted costophrenic angle (pleural effusion)*.

Clinical / Diagnostic significance

- **Echocardiography + BNP + ECG** rapidly separate cardiogenic from non-cardiogenic edema and identify a treatable mechanical or ischaemic cause — directing emergency reperfusion or surgery.
- **PCWP** is the pivotal discriminator: **high (> 18–25 mmHg) = cardiogenic**; normal/low = ARDS/high-permeability edema, which does not respond to diuresis.
- **Blood pressure dictates therapy**: hypertensive "flash" edema responds dramatically to vasodilators + NIV + diuretics; hypotensive edema (cardiogenic shock) needs inotropes/pressors and revascularisation, and **over-aggressive vasodilatation/diuresis can precipitate iatrogenic shock**.
- A first **inferior MI presenting with shock/edema** should prompt a search for **RV infarction or a mechanical complication**.

High-yield exam pointers

- Cardiogenic pulmonary edema = **hydrostatic edema from ↑ PCWP**; commonest cause is **acute LV failure due to MI / decompensated chronic HF**.
- **Pink frothy sputum + bilateral crackles + S3 + orthopnoea/PND** is the classic bedside picture; wheeze = "cardiac asthma".
- CXR: **cephalization, Kerley B lines, peribronchial cuffing, bat-wing alveolar shadowing, pleural effusion**.
- **PCWP > 18 mmHg → interstitial; > 25 mmHg → alveolar flooding**; normal PCWP = non-cardiogenic.
- First-line emergency bundle (mnemonic **LMNOP**): **L**asix (loop diuretic), **M**orphine, **N**itrates, **O**xygen/NIV, **P**osition (upright, legs dependent).

- **NIV/CPAP reduces intubation and mortality**; sit up, target SpO2 ≥ 92%, avoid routine hyperoxia.
- **Nohria "warm-and-wet"** is the typical profile; **"cold-and-wet"** overlaps with shock and has the worst prognosis.
- **Forrester subset II = pulmonary edema; subset IV = cardiogenic shock**; STEMI with edema → **emergency primary PCI** (mortality 20–40%).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cardiogenic Shock and Pulmonary Edema" (etiologies, pathophysiology, oxygen/ventilation, preload reduction, drug doses, Forrester hemodynamics).
- **Braunwald's Heart Disease, 13e** — "Diagnosis and Management of Decompensated Heart Failure" (NIV/CPAP evidence, loop-diuretic dosing, Nohria warm/cold–wet/dry profiles) and "Chest Radiography in Cardiovascular Disease" (cephalization, Kerley B lines).
- **CMDT 2026** — "Heart Failure & Cardiomyopathy: Acute Heart Failure & Pulmonary Edema" (precipitants, clinical picture, CXR butterfly pattern, PCWP > 25 mmHg, morphine/diuretic/nitrate/nesiritide regimens, DOSE trial).
- *Coverage note:* The PCWP staging thresholds (interstitial ~18–20 mmHg) and the **LMNOP** mnemonic are universally accepted standard internal medicine used to organise corpus-sourced facts; CMDT explicitly supports the > 25 mmHg alveolar-edema threshold.

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Cardiomyopathies

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Cardiomyopathy* denotes primary disease of the heart muscle itself, traditionally excluding myocardial dysfunction arising from coronary, valvular, hypertensive or congenital heart disease (though common usage admits ischaemic, valvular and hypertensive "cardiomyopathy"). It is best understood as a heterogeneous group of myocardial diseases with mechanical and/or electrical dysfunction, frequently genetic, that may be confined to the heart or part of a systemic disorder. Classification rests on a **phenotype-first** morphologic approach — **hypertrophic (HCM)**, **dilated (DCM)** and **restrictive (RCM)** — now complemented by **arrhythmogenic cardiomyopathy (ACM/ARVC)** and increasingly informed by genotype.

Classification

Three classic morphologic phenotypes plus the arrhythmogenic phenotype, defined by left-ventricular (LV) wall thickness, ejection fraction (LVEF) and diastolic physiology:

Phenotype	Defining criteria	Key features	Common challenges
HCM	Septal/wall thickness ≥15 mm (men), ≥13 mm (women); LVEF ≥ normal, usually >0.60; LV cavity ≤ normal	Asymmetric septal, concentric, mid-ventricular or apical patterns; sarcomere disease; outflow obstruction in ~30%	Distinguish from athlete's heart, hypertensive heart, amyloid, storage disease (Fabry, Danon, PRKAG2)
DCM	LVEF ≤0.50 (most ≤0.40) and/or LV dilation (LVEDD >95% predicted / LVEDV >112%)	Global hypokinesis, mitral regurgitation; ~30% spontaneously recover ("reverse remodelling")	Exclude coronary, valvular and primary structural disease
RCM	Moderate–severe diastolic dysfunction / raised filling pressures; LVEF usually mildly reduced (~30–50%)	Marked **biatrial enlargement**, right-sided congestion dominates; wall thickness normal or increased	Differentiate from **constrictive pericarditis**; identify amyloid/storage
ARVC / ACM	Ventricular arrhythmias dominate before/without reduced LVEF; *2010 modified Task Force Criteria*	Fibrofatty replacement; desmosomal genes; RV-dominant (ARVC), LV-dominant (ACM-LV) or biventricular	Distinguish PVC-related CM from genetic ACM

- The **AHA (Maron)** scheme divides cardiomyopathies into *primary* (genetic, mixed, acquired) and *secondary* (systemic infiltrative/storage/inflammatory), and uniquely includes electrical disorders (channelopathies).
- The **ESC 2023** scheme keeps the phenotypic approach but adds a *non-dilated left ventricular cardiomyopathy* category (LV systolic dysfunction without dilation). *Left-ventricular non-compaction (LVNC)* is regarded as a trait rather than a distinct disease.
- Phenotypes **overlap and evolve**: DCM may reverse-remodel to higher LVEF, and ~5% of HCM progresses to "burned-out" HCM with reduced EF (HCM-rEF).

Hypertrophic Cardiomyopathy (HCM)

- **Genetics/pathology:** Commonest inherited cardiac disease, prevalence ~**1:500**; autosomal dominant with age-dependent, incomplete penetrance. A sarcomere variant is found in ~40–50%; ~80% involve **MYH7 (β-myosin heavy chain)** or **MYBPC3 (myosin-binding protein C)**. Histology shows **myocyte disarray**, interstitial and replacement fibrosis (late gadolinium enhancement on MRI), and small-vessel disease causing microvascular ischaemia.
- **Pathophysiology of obstruction:** Dynamic LV outflow tract (LVOT) obstruction in ~30% at rest and a further ~30% on provocation, initiated by drag forces drawing an enlarged anterior mitral leaflet onto the hypertrophied septum — **systolic anterior motion (SAM)** with posteriorly-directed mitral regurgitation. The murmur is harsh, late-peaking, and *augmented* by Valsalva or standing (reduced preload).
- **Treatment:** β-blockers and non-dihydropyridine calcium-channel blockers (**verapamil**) are first line; **disopyramide** (negative inotrope) for refractory obstruction. **Cardiac myosin inhibitors — mavacamten (FDA-approved), aficamten (investigational)** — relieve symptomatic obstruction (monitor LVEF). Refractory severe symptoms (~5%): **septal myectomy** or **alcohol septal**

ablation (chief complication: complete heart block needing pacing). Avoid digoxin/vasodilators/excess diuresis.

- **Sudden cardiac death (SCD):** Baseline risk ~0.5%/year. **Major risk factors:** prior cardiac arrest/sustained VT, unexplained syncope, family history of SCD, LV wall ≥30 mm, LV apical aneurysm, LVEF <50%, plus modifiers (extensive LGE, non-sustained VT). The **ESC HCM Risk-SCD calculator** guides ICD: ≥6% 5-yr risk → ICD advised, 4–6% → consider, <4% → not advised.

Dilated Cardiomyopathy (DCM) and acquired causes

- Familial in 30–40%, monogenic cause identifiable in ~25%; the commonest gene is **truncating variant of titin (TTN, ~25% of familial DCM)**; **LMNA (lamin A/C)** and **FLNC (filamin C)** carry high arrhythmic risk and warrant early ICD (before LVEF falls to 0.35).
- **Major acquired causes:** prior **myocarditis** (viral — coxsackie, adenovirus, COVID-19, HIV; *Trypanosoma cruzi* — Chagas); **toxic** — alcohol (≥60–80 g ethanol/day for ≥5 yr; *"holiday heart"* AF; reversible with abstinence), **anthracyclines** (doxorubicin — dose-related, dexrazoxane chelation), **trastuzumab** (anti-HER2, often reversible), checkpoint inhibitors; **endocrine/metabolic** — thyroid disease, phaeochromocytoma, haemochromatosis, thiamine deficiency (beri-beri), selenium deficiency (Keshan); **tachycardia-mediated** CM.
- **Peripartum cardiomyopathy (PPCM):** LVEF ≤0.45 in the last trimester to 5–6 months postpartum (commonly first 2 weeks) without other cause; ~1:1000–1:4000 deliveries; associated with antiangiogenic signalling (sFLT1), an abnormal prolactin fragment, and **TTN** variants (~15%). Higher risk and poorer recovery in Black women. Avoid ACE-inhibitors/ARBs antenatally (use hydralazine-nitrate); anticoagulate if LVEF <0.35; LVEF recovers to ≥0.50 in 50–80%.
- **Takotsubo (stress / "broken-heart") syndrome:** apical ballooning with basal sparing in older women after intense stress; catecholamine-mediated; mimics infarction but coronaries patent; usually recovers in days–weeks (recurrence ~2%/yr).
- **Therapy:** guideline-directed medical therapy as for HFrEF — the **four pillars**: ARNI/ACE-inhibitor/ARB, β-blocker, mineralocorticoid-receptor antagonist, **SGLT2 inhibitor**, plus diuretics, device therapy (CRT for LBBB, primary-prevention ICD for persistent LVEF ≤0.30–0.35) and anticoagulation for AF/LV thrombus.

Restrictive Cardiomyopathy and Cardiac Amyloidosis

- **RCM physiology:** stiff, non-compliant ventricles with preserved cavity size; biatrial enlargement; raised biventricular filling pressures; right-sided congestion (oedema, ascites), **prominent Y descent**, positive **Kussmaul sign**, S4 > S3; haemodynamics show a **"square-root" (dip-and-plateau)** sign.
- **Causes:** *infiltrative* (amyloid — commonest), *storage* (haemochromatosis, Fabry, glycogen storage), *fibrotic* (radiation, scleroderma, **endomyocardial fibrosis**, **Löffler endocarditis** from hypereosinophilia), carcinoid, and genetic (DES desminopathy, sarcomeric overlap with HCM).
- **Cardiac amyloidosis:** extracellular fibrillar deposition staining with **Congo red → apple-green birefringence**; nonbranching fibrils ~10 nm. Two dominant precursors:

Feature	AL (light-chain)	ATTR (transthyretin)
Source	Clonal plasma cells (λ > κ free light chains)	Liver TTR — wild-type (ATTRwt) or variant (ATTRv)
Demographics	Younger; plasma-cell dyscrasia/myeloma	Elderly men (ATTRwt, M:F ~20:1); ATTRv **Val122Ile** in ~3.5% African-Americans
Extra-cardiac clues	**Periorbital purpura**, macroglossia, nephrotic proteinuria, autonomic neuropathy	Bilateral **carpal tunnel syndrome**, spinal stenosis, ruptured biceps tendon
Diagnosis	Tissue biopsy mandatory (fat-pad/cardiac); mass spectrometry typing	**Tc-PYP/DPD bone scintigraphy** positive (grade ≥2) *after excluding plasma-cell dyscrasia*
Untreated survival from HF onset	~6 months (worst prognosis)	ATTRwt ~4–5 yr; Val122Ile ~2–3 yr
Specific therapy	**Dara-CyBorD** (daratumumab, bortezomib, cyclophosphamide, dexamethasone); ± autologous SCT	**Stabilisers** tafamidis, acoramidis; **TTR silencers** patisiran/eplontersen/vutrisiran

- **Imaging clues:** thick walls with **low ECG voltage**, biatrial enlargement, and **apical-sparing "bull's-eye" longitudinal-strain** pattern; CMR shows expanded extracellular volume, diffuse subendocardial LGE and abnormal myocardial nulling. NT-proBNP and troponin are disproportionately elevated. Avoid ACE-inhibitors/β-blockers (poorly tolerated); anticoagulate AF; ICD rarely useful.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Morphologic phenotypes (4-panel cross-section):** *Normal* heart; *DCM* — globally dilated thin-walled LV with enlarged LA; *HCM* — asymmetric septal hypertrophy, small LV cavity, anterior mitral leaflet showing **SAM** and **LVOT gradient**; *RCM* — normal-size cavity, mildly thickened walls with **massive biatrial enlargement**. Labels: *LV cavity, interventricular septum, LV free wall, RV, left atrium (LA), mitral valve, SAM, LVOT obstruction*.
- **Cardiac-amyloid strain "bull's-eye":** concentric polar map with **preserved apical strain (red)** and **impaired basal strain (blue)** — label *apical sparing, impaired base*.

Clinical / Diagnostic significance

- **Presentation:** exertional dyspnoea/fatigue, congestion, arrhythmias (AF), embolic events (LV/apical thrombus) or SCD; *"congestive heart failure" is a syndrome, not an aetiology* — always seek the cause.
- **Work-up (Harrison Table 266-2):** detailed family history (SCD, pacemaker/AF by middle age, muscular dystrophy), ECG, chest radiograph, 2-D/Doppler **echocardiography** (initial modality), **cardiac MRI** (tissue characterisation, LGE, T1/T2 mapping), bloods (TSH, iron studies/transferrin saturation >45–60%, troponin, eosinophils, serum/urine immunofixation + free light chains), genetic counselling/multigene panel, and **endomyocardial biopsy** when a specific therapy-altering diagnosis (giant-cell, eosinophilic, sarcoid, amyloid, Fabry) is suspected.

- **RCM vs constrictive pericarditis** is the pivotal differential — both cause right-sided congestion and Kussmaul sign; pericardial thickening/calcification, respiratory septal shift and discordant ventricular pressures favour constriction (surgically curable), whereas biatrial enlargement, low voltage and positive bone scan/LGE favour restrictive amyloid.
- **Therapeutic leverage:** many cardiomyopathies are *treatable* — abstinence in alcoholic CM, phlebotomy/chelation in haemochromatosis, enzyme replacement/migalastat in Fabry, tafamidis in ATTR, Dara-CyBorD in AL, and reverse remodelling on GDMT.

High-yield exam pointers

- Three classic phenotypes = **HCM, DCM, RCM**; fourth = **arrhythmogenic (ARVC/ACM)**; LVNC is a trait.
- HCM commonest gene pair **MYH7 + MYBPC3** (~80%); hallmark = SAM + dynamic LVOT obstruction; murmur ↑ with **Valsalva/standing**.
- HCM is the **leading cause of SCD in the young athlete**; ICD by ESC Risk-SCD score (≥6% → implant). Newest drug class = **myosin inhibitors (mavacamten)**.
- DCM commonest genetic cause = **titin (TTN) truncation**; **LMNA/FLNC** = arrhythmic, early ICD.
- Cardiac amyloid: **Congo red apple-green birefringence**; **apical-sparing bull's-eye strain**; ATTR diagnosed *non-invasively* by **Tc-PYP scan** after excluding light chains.
- **AL** clues = periorbital purpura, macroglossia; **ATTR** clues = bilateral carpal tunnel, ruptured biceps tendon; AL prognosis worst (~6 months untreated).
- **ARVC** = desmosomal disease (PKP2, DSP, DSG2, DSC2, JUP); **epsilon wave**, T-inversion V1–V3, fibrofatty RV replacement; *Naxos* (with woolly hair/palmoplantar keratoderma) and *Carvajal* syndromes.
- **Peripartum CM** = LVEF ≤0.45, last trimester–6 months postpartum; avoid ACE-i antenatally; anticoagulate if LVEF <0.35.
- **Takotsubo** = apical ballooning, post-stress, women, coronaries normal, usually reversible.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Classification of Cardiomyopathy," "Genetic Cardiomyopathies," "Acute and Chronic Myocarditis," "Dilated Cardiomyopathies," and "Amyloidosis and Other Restrictive Cardiomyopathies."
- **Braunwald's Heart Disease, 13e** — "The Dilated, Restrictive, and Infiltrative Cardiomyopathies" (AHA/ESC classification, ARVC Task Force criteria), "Cardiac Amyloidosis," and "Hypertrophic Cardiomyopathy."
- **CMDT 2026** — "Heart Failure & Cardiomyopathy" (current GDMT, mavacamten, restrictive-vs-constrictive "square-root" sign).

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Peripartum cardiomyopathy

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Cardiomyopathy* denotes primary disease of the heart muscle itself, traditionally excluding myocardial dysfunction arising from coronary, valvular, hypertensive or congenital disease (though common usage now admits ischaemic, valvular and hypertensive "cardiomyopathy"). It is classified by **morphology and function** into three classic phenotypes — hypertrophic (HCM), dilated (DCM) and restrictive (RCM) — with arrhythmogenic cardiomyopathy (ACM/ARVC) and left ventricular non-compaction (LVNC) as evolving fourth/fifth categories, and increasingly by **aetiology** (genetic vs acquired). *Peripartum cardiomyopathy (PPCM)* is a distinct acquired DCM developing toward the end of pregnancy or in the months after delivery.

A. Classification of cardiomyopathy

1. Morphological / functional classification (the traditional working scheme; WHO 1995):

Phenotype	Defining criteria	Key features / mimics
Hypertrophic (HCM)	Septal/wall thickness ≥15 mm (men), ≥13 mm (women); LVEF normal/high, usually >0.60; LV cavity ≤normal	Asymmetric septal, sigmoid, concentric or apical patterns; distinguish from athlete's heart, hypertension, aortic stenosis; mimicked by storage diseases — *Anderson-Fabry* (GLA), *PRKAG2*, *Danon* (LAMP2) and amyloid
Dilated (DCM)	LVEF ≤0.50 (most present ≤0.40) ± LV dilation (LVEDD/LVEDV increased)	Convergent end-phenotype of many injuries; functional MR; ~⅓ of recent-onset cases recover ("HFimpEF")
Restrictive (RCM)	Functional diagnosis: moderate-severe diastolic dysfunction / raised filling pressures; LVEF mildly reduced	Least common; marked **biatrial enlargement**, right-heart failure dominates; marked wall thickening suggests **amyloidosis**, storage/metabolic disease
Arrhythmogenic (ACM-LV / ACM-RV = ARVC)	DCM-type morphology with ventricular arrhythmias *out of proportion* to dysfunction; ARVC by *2010 modified Task Force criteria*	LGE patterns on CMR; ICD considered even at LVEF >0.35; sarcoid/Chagas can mimic
LV non-compaction (LVNC) — trait	Non-compacted : compacted myocardium ratio >2.3	May overlay HCM/DCM/dystrophies; trabeculation can be physiological in pregnancy/athletes

2. Aetiological classification of DCM (Harrison Table 269-1) — a high-yield framework:

- **Inflammatory / infective** — viral (coxsackie, adenovirus, COVID-19, HIV), parasitic (*Trypanosoma cruzi* — Chagas), bacterial (diphtheria), spirochaetal (Lyme), rickettsial (Q fever).
- **Non-infective inflammatory** — sarcoidosis, giant-cell & eosinophilic myocarditis, collagen-vascular disease, checkpoint-inhibitor myocarditis, transplant rejection.
- **Toxic** — alcohol (commonest toxin), catecholaminergic stimulants (cocaine, amphetamines), chemotherapy (anthracyclines, trastuzumab), hydroxychloroquine/chloroquine, anabolic steroids, heavy metals (lead, mercury, cobalt).

- **Metabolic** — thiamine/selenium (Keshan)/carnitine deficiency, Ca^{2+}/PO_4^{3-}/Mg^{2+} depletion, thyroid disease, phaeochromocytoma, diabetes, obesity, haemochromatosis.
- **Genetic / familial** — ~30% of DCM; autosomal-dominant predominantly; *TTN* truncations, *LMNA*, *MYH7*, *TNNT2*, dystrophinopathies (Duchenne/Becker), mitochondrial (Kearns-Sayre).
- **Miscellaneous (overlap)** — **peripartum**, tachycardia-induced (uncontrolled SVT, high PVC burden), LVNC, arrhythmogenic.

> A **two-hit model** is increasingly recognised — a genetic predisposition is unmasked by an acquired trigger (infection, toxin, **pregnancy**, tachycardia). The pragmatic clinical split remains **primary** (genetic, mixed, acquired) vs **secondary** (systemic-disease) cardiomyopathy.

B. Peripartum cardiomyopathy — definition & risk factors

- **Definition:** PPCM is a **diagnosis of exclusion** — *de novo* LV systolic dysfunction (**LVEF ≤0.45**) presenting in the **last month of pregnancy or within ~5–6 months postpartum**, with no other identifiable cause of heart failure; **most cases present within the first 2 weeks after delivery**.
- **Incidence: 1:1000 to 1:4000 deliveries** in the USA; striking geographic/ethnic variation — close to **1% of deliveries in parts of Nigeria** (highest in Hausa & Fulani) vs ~1 in 15,000 in Japan.
- **Risk factors:**
  - **Older maternal age**; **increased parity / multiparity**.
  - **Multiple (twin) gestation**.
  - **Hypertensive disorders of pregnancy / pre-eclampsia** — present in *up to half* of cases.
  - **Black / African ancestry** — risk ~**four-fold higher** in Black women, with slower and less complete recovery.
  - **Malnutrition** and **tocolytic therapy** for premature labour.
  - **Genetic susceptibility** — **TTN truncating variants in ~15%** (overall pathogenic/likely-pathogenic truncations ~15% — similar to non-PPCM DCM), predicting poorer recovery.
- **Pathogenesis ("vasculo-hormonal" model):** late-gestation **oxidative stress** drives **antiangiogenic signalling** — high **soluble FLT1 (sFLT1)**, an inhibitor of VEGF (also elevated in pre-eclampsia) — together with **cathepsin-D–mediated cleavage of prolactin** into a toxic **16-kDa prolactin fragment** that promotes **endothelial and cardiomyocyte apoptosis**. This is the rationale for **bromocriptine** (prolactin suppression).

C. Clinical presentation, diagnosis & management

- **Presentation:** typically the **syndrome of congestion** — exertional dyspnoea, orthopnoea, fatigue, pedal/abdominal oedema — easily mis-attributed to normal late pregnancy. **Atrial and ventricular arrhythmias** occur; **LV thrombus / systemic or pulmonary embolism** (especially LVEF <0.35); rarely cardiogenic shock.
- **Diagnostic clues & work-up:** raised **BNP/NT-proBNP** and **troponin**, elevated central venous pressure, and **echocardiography (LVEF ≤0.45)** is usually sufficient. **CMR** may help in complex cases — **gadolinium should be avoided** antepartum. **Always exclude** pulmonary embolism, spontaneous coronary artery dissection and other de-novo cardiomyopathies (familial DCM, HCM, LVNC, ARVC). **Genetic testing** is reasonable (informs prognosis and family screening).

- **Management:**
  - **Diuresis** with loop diuretics to restore euvolaemia (use cautiously).
  - **Antepartum: RAS inhibitors (ACEi/ARB/ARNI), aldosterone antagonists and SGLT2i are contraindicated** (fetotoxic). Afterload reduction with **hydralazine + nitrate**; **digoxin** and **β-blockers (metoprolol preferred over carvedilol)** for rate/arrhythmia control; close maternal-fetal medicine collaboration with a plan for emergency delivery.
  - **Postpartum:** full guideline-directed therapy for HFrEF — **metoprolol, enalapril/captopril/lisinopril and spironolactone** are compatible with breastfeeding (avoid eplerenone, ARNI, SGLT2i, DOACs while breastfeeding).
  - **Anticoagulation** for ~6 weeks if **LVEF <0.35** or marked dilation (once obstetric bleeding settles).
  - **Bromocriptine** — *class IIb* in ESC HF guidelines (with anticoagulation); **not routinely recommended** by the 2022 AHA/ACC/HFSA guideline; large RCT ongoing.
  - **Wearable cardioverter-defibrillator** is reasonable when LVEF <0.35, given early arrhythmic risk; **breastfeeding is now generally encouraged** where fluid balance permits.

D. Prognosis of peripartum cardiomyopathy

- **Recovery is comparatively favourable:** LVEF improves to **≥0.50 in 50–80%**, usually within **6 months**. In the North American **IPAC** study ~**70%** had LVEF >0.50 at 1 year; the ESC EORP registry showed recovery in ~**66%**.
- **One-year mortality:** ~**4–11%** in the USA (higher in Black women), ~**8%** in the ESC EORP registry, and reported **up to two-fold higher in Africa**.
- **Predictors of poor recovery / adverse outcome:**
  - **LVEF <0.30** at presentation; **LV end-diastolic dimension ≥6.0 cm**.
  - **Black race**; **presentation >6 weeks after delivery**.
  - Elevated **natriuretic peptides, troponin and sFLT1**; **positive genetic testing (e.g., TTN)**.
- **Subsequent pregnancies** carry substantial risk of relapse and death — **contraindicated where there is any residual LV dysfunction** (mWHO class IV); recurrence risk correlates with the degree of recovery. PPCM is the **4th commonest indication for cardiac transplantation in women** in the USA (~5%), with post-transplant outcomes similar to other indications.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Morphological classification montage** — four LV cross-sections side by side, labelled: *HCM* (thick asymmetric septum, small slit-like cavity), *DCM* (globular dilated thin-walled LV), *RCM* (normal-sized cavity with grossly dilated **biatrial** chambers), *ARVC/ACM* (dilated, fibro-fatty right ventricle). Annotate LVEF and wall-thickness criteria.
- **PPCM "vasculo-hormonal" pathogenesis flowchart** — labels: *Late pregnancy/puerperium → Oxidative stress* → two arrows to *sFLT1 (anti-VEGF)* and *Cathepsin-D cleaves prolactin → 16-kDa prolactin fragment → Endothelial + cardiomyocyte apoptosis / microvascular dysfunction → LV systolic dysfunction (LVEF ≤45%)*; side-box *Genetic susceptibility — TTN truncating variant (~15%)*; timeline bar *last trimester → 5–6 months postpartum (peak: first 2 weeks)*.

Clinical / Diagnostic significance

- Distinguishing the **phenotype** guides initial work-up, while **aetiology** (especially genetic vs acquired) drives family screening, ICD decisions and prognosis.
- In a peripartum woman with new heart failure, **PPCM is the commonest cause** but remains a **diagnosis of exclusion** — rule out PE, coronary dissection and unmasked familial/structural disease.
- **sFLT1, BNP/troponin and TTN status** are emerging prognostic biomarkers; **avoid gadolinium** and **RAS blockade/SGLT2i antepartum**.
- Counsel against further pregnancy if LV function does not fully normalise; document contraception.

High-yield exam pointers

- Three classic phenotypes = **HCM, DCM, RCM**; add **ARVC/ACM** and **LVNC**; HCM wall ≥15 mm (M)/≥13 mm (W), DCM LVEF ≤0.40 for therapy & ≤0.30–0.35 for primary-prevention ICD.
- **Amyloidosis** = commonest RCM; **alcohol** = commonest toxic DCM; **TTN** = commonest DCM gene.
- PPCM = **LVEF ≤0.45**, last month of pregnancy to ~5 months postpartum, **peak in first 2 weeks after delivery**; incidence **1:1000–1:4000** (USA).
- Risk factors: **older age, multiparity, twins, pre-eclampsia/HTN, Black race (4×), malnutrition, tocolytics, TTN variant**.
- Pathogenesis: **16-kDa prolactin fragment + sFLT1** → "vasculo-hormonal" injury → rationale for **bromocriptine**.
- **No ACEi/ARB/ARNI/MRA/SGLT2i before delivery**; use **hydralazine-nitrate, β-blocker, digoxin, diuretic**; anticoagulate if **LVEF <0.35**.
- Recovery (LVEF ≥0.50) in **50–80%**; 1-year mortality **4–11%**; poor prognosis if **LVEF <0.30, LVEDD ≥6 cm, Black race, late presentation, high sFLT1/troponin**.
- Subsequent pregnancy **contraindicated with residual LV dysfunction**; 4th commonest transplant indication in women.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Classification of Cardiomyopathy" (morphological classification, Table 266-1; initial evaluation) and "Dilated Cardiomyopathies" (aetiological Table 269-1; Peripartum Cardiomyopathy section — incidence, risk factors, sFLT1/16-kDa prolactin, TTN, management, prognosis); "Genetic Cardiomyopathies".
- **Braunwald's Heart Disease, 13e** — "The Dilated, Restrictive, and Infiltrative Cardiomyopathies" (PPCM genetics, bromocriptine class IIb/AHA stance, recovery ~50%, transplant data) and "Pregnancy and Heart Disease" (risk factors, IPAC ~70% recovery & predictors, ESC EORP 8% 1-yr mortality, mWHO contraindication, drug safety in lactation).
- **CMDT 2026** — "Heart Failure & Cardiomyopathy" (dilated cardiomyopathy epidemiology/work-up, LV-thrombus anticoagulation, referral thresholds).

Coverage note: The corpus grounds the morphological and aetiological classifications fully; the formal **AHA 2006 (primary genetic/mixed/acquired vs secondary)** and **ESC MOGE(S)** nomenclature are universally accepted but are referenced only implicitly in this corpus, so they are mentioned briefly rather than tabulated.

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Conducting system of the heart and electrocardiogram

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — The **cardiac conduction system** is the network of specialized, automatic and rapidly-conducting myocardial fibres that initiates each heartbeat and delivers the impulse in an orderly sequence from atria to ventricles, ensuring coordinated, synchronous mechanical contraction. The **electrocardiogram (ECG/EKG)** is the noninvasive graphical recording of the depolarization (stimulation) and repolarization (recovery) electrical activity of the working atrial and ventricular myocardium, detected by metallic electrodes on the limbs and chest wall. Because the cardiac depolarization and repolarization wavefronts have direction and magnitude, they can be represented as **vectors**, and the surface ECG is the summed projection of these vectors onto standardized leads.

Anatomy and sequence of the conduction system

The electrical currents that spread through the heart are produced by three components: **cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself**. The orderly route of a normal impulse is:

- **Sinoatrial (SA) node** — the dominant pacemaker, situated at the lateral junction of the **superior vena cava and right atrium**; possesses spontaneous **automaticity** and is richly innervated by autonomic fibres for dynamic heart-rate control.
- **Atrial myocardium** — depolarization spreads across the right then the left atrium via **preferential conduction pathways**, inducing atrial systole; inscribes the **P wave**.

- **Atrioventricular (AV) node** — the AV nodal and His-bundle areas together form the **AV junction**; conduction here is deliberately **slow**, providing physiologic AV synchrony (the PR interval). In normal hearts the AV node is the **only electrical connection** between atria and ventricles.
- **Bundle of His → right and left bundle branches** — the His bundle bifurcates; the main left bundle fans out into **left anterior and left posterior fascicles**.
- **Purkinje fibres** — an endocardial network that rapidly and synchronously activates both ventricles. Depolarization then spreads through the ventricular wall from **endocardium to epicardium**, triggering coordinated ventricular contraction.

Structure	Property / role	Conduction velocity
SA node	Primary pacemaker; *If* (funny) current automaticity; autonomic control	Nodal (slow)
Atrial myocardium	Inscribes P wave; atrial systole	0.3–0.4 m/s
AV node	Slow conduction → AV delay (PR interval); sole AV connection	Slow
His–bundle branches–fascicles	Rapid transmission to ventricles	High
Purkinje fibres	Endocardial, synchronizes ventricular activation	**2–3 m/s**

Conduction is faster in Purkinje fibres (2–3 m/s) than in myocardial cells (0.3–0.4 m/s), partly due to different connexins in their gap junctions.

Cellular electrophysiology, automaticity and autonomic control

The cardiac **action potential (AP)** drives all electrophysiologic behaviour and has five phases (0–4): **rapid upstroke, early repolarization, plateau, late repolarization, and diastole.** Ionic currents flux through voltage-gated channels and gap-junction (connexin) complexes:

Current	Gene	Protein	Principal AP role
I_Na	SCN5A	Nav1.5	Phase 0 upstroke (atrial/ventricular)
I_Ca-L	CACNA1C	Cav1.2	Plateau (phase 2); phase 0 of **nodal** tissue
I_to	KCND3 / KCNIP2	Kv4.3 / KChIP2	Phase 1 early repolarization
I_Kr	KCNH2 / KCNE2	HERG / MiRP-1	Phase 3 repolarization
I_Ks	KCNQ1 / KCNE1	KVLQT1 / minK	Phase 3 repolarization
I_K1	KCNJ2	Kir2.1	Phase 4 — sets **resting membrane potential**
I_Kur	KCNA5	Kv1.5	Atrial repolarization

Current	Gene	Protein	Principal AP role
I_f (funny)	—	Semiselective Na/Ca channel	SA-node **phase 4 automaticity**; target of **ivabradine**

- **Automaticity** = spontaneous phase-4 depolarization; a normal property of the SA node, AV node and His-Purkinje system. In the SA node the **Na/Ca *If* current** drives phase 4; the normal range of SA automaticity is **30–220 beats/min**. The **intrinsic heart rate (IHR)** is the native SA rate without autonomic input.
- **Autonomic modulation:** parasympathetic vagal tone releases acetylcholine → opens **I_KACh** (G-protein mediated) → K^+ efflux hyperpolarizes nodal cells → slows phase 4. Sympathetic catecholamines act via **β1 receptors** → activate L-type Ca channels → enhance phase 4 → faster rate (with exercise the PR interval physiologically shortens).
- **Escape rhythm:** if a proximal pacemaker fails, a more distal automatic focus may take over to maintain cardiac output. Mutations in **K-channel** subtypes (e.g., delayed closing) prolong the QT and cause inherited **long-QT syndromes**.

Genesis of the normal ECG — correlation of conduction events with waveforms

Each ECG deflection corresponds to a phase of the simultaneously-obtained ventricular AP: **phase 0 ↔ onset of QRS; plateau phase 2 ↔ isoelectric ST segment; active repolarization phase 3 ↔ T wave.**

ECG component	Electrical event	AP phase	Normal value
P wave	Atrial depolarization (vector down & leftward → +ve in II, –ve in aVR)	Atrial phase 0	≤2.5 mm tall
PR interval	Atrial→ventricular delay, mostly AV-nodal conduction	—	**120–200 ms**
QRS complex	Ventricular depolarization	Phase 0	**100–110 ms or less**
J point	Junction of QRS end and ST start	—	—
ST segment	Early ventricular repolarization (plateau)	Phase 2	Isoelectric
T wave	Ventricular repolarization (epicardium→endocardium)	Phase 3	Concordant with QRS (within ~45°)
QT interval	Ventricular depolarization + repolarization	Phases 0–3	QTc ≤**450 ms (men)**, ≤**460 ms (women)**
U wave	Late repolarization deflection	—	≤1 mm

- Atrial repolarization (ST-Ta) is usually too small to detect; it may emerge in **acute pericarditis, atrial infarction and AV block**.
- **QRS septal vectors:** vector 1 = septal depolarization (left→right, anterior) gives a small **septal r in V1** and **septal q in V6**; vector 2 = dominant LV (left & posterior) gives the **S wave in V1** and **R wave in V6**. The **transition zone** (R ≈ S) is usually **V3–V4**.

- **Rate-correction (QTc):** classic Bazett **QTc = QT/√RR** (in seconds); the **Framingham** formula QTc = QT + 0.154 (1000 – RR) in ms.

The 12-lead ECG: leads, calibration and axis

- **12 leads = 6 limb (frontal plane, hexaxial reference) + 6 chest/precordial (horizontal plane).** Each lead is like a different "camera angle" viewing the same depolarization/repolarization. An upright deflection occurs when the wavefront travels **toward** the positive pole of a lead.
- **Calibration:** recorded on 1-mm^2 grid at 25 mm/s — smallest 1-mm horizontal box = **40 ms (0.04 s)**, heavy lines every **200 ms (0.20 s)**; vertically **1 mV = 10 mm**.
- **Heart rate:** 300 ÷ number of large (0.20 s) boxes between R waves, or 1500 ÷ number of small boxes.
- **Mean QRS axis:** normal **–30° to +100°**; more negative than –30° = **left axis deviation**, more positive than +90 to +100° = **right axis deviation**.
- Supplementary leads: **V3R–V6R** (right ventricular infarction), and posterior **V7 (midaxillary), V8 (posterior axillary), V9 (posterior scapular)** for posterolateral infarction.

Conduction abnormalities and key ECG correlates

- **Complete bundle branch block:** QRS **≥120 ms**; incomplete **110–120 ms**. **RBBB** — terminal vector right & anterior → **rSR′ in V1, qRS in V6**. **LBBB** — vector left & posterior → wide **QS in V1, monophasic R in V6**; often marks coronary, hypertensive, aortic valve disease, or cardiomyopathy. Both cause **secondary ST-T changes** (T wave opposite to terminal QRS = appropriate discordance).
- **Fascicular blocks (hemiblocks):** do not greatly widen QRS but shift the axis — **left anterior fascicular block** (axis more negative than –45°, commonest cause of marked LAD); **left posterior fascicular block** (axis > +110–120°, rare).
- **Pre-excitation:** wide QRS via a bypass tract (Wolff-Parkinson-White) — a non-conduction-delay cause of QRS prolongation.
- **Metabolic/drug effects: hyperkalemia** — peaked/tented T → wide QRS → loss of P → sine-wave → asystole; **hypokalemia** — prominent **U waves**, long QT; **hypocalcemia** prolongs / **hypercalcemia** shortens QT; **hypothermia** — **Osborn (J) wave**; **digitalis** — ST "scooping," short QT.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Cardiac conduction system (schematic, after Fig. 247-1):** label **SA node, right atrium (RA), left atrium (LA), AV node, AV junction, His bundle, right bundle branch, left bundle branch, ventricular septum, Purkinje fibres, RV, LV, ventricular myocardium**, with directional arrows showing impulse sequence.
- **Diagram 2 — Basic ECG waveforms/intervals (after Fig. 247-2):** label **P wave, QRS complex, T wave, U wave, J point, PR interval, QRS interval, ST segment, QT interval** (and note the RR interval). Optionally align below it the AP phases 0–4 to show ST↔phase 2 and T↔phase 3.

Clinical / Diagnostic significance

- The ECG is **immediately available, noninvasive and inexpensive** — central to diagnosing **arrhythmias, conduction disturbances and myocardial ischaemia/infarction**, and may reveal life-threatening **electrolyte disturbances, drug toxicity** and susceptibility to **sudden cardiac arrest**.
- The 12-lead resting ECG is the **cornerstone** of arrhythmia evaluation; if active arrhythmia is captured a definitive diagnosis is made. As it samples only ~6 s, transient arrhythmias need **ambulatory monitoring** (Holter, event/patch recorders) or provocation, and **invasive EP study** for mechanism/ablation.
- ECG localization of ischaemia: **anterior (V1–V6, I, aVL); inferior (II, III, aVF); right ventricular (right-sided leads); posterior (reciprocal ST depression V1–V3).**
- ECG **voltage criteria** for LVH/RVH have low sensitivity; echocardiography and cardiac MRI give more definitive anatomic/functional data.

High-yield exam pointers

- Impulse order: **SA node → atria → AV node → His → bundle branches → fascicles → Purkinje → ventricular myocardium.**
- **AV node = only normal electrical atria-to-ventricle connection**; its slow conduction creates the **PR interval (120–200 ms)**.
- **P wave = atrial depolarization; QRS = ventricular depolarization; ST-T-U = ventricular repolarization;** atrial repolarization is normally hidden in QRS.
- AP correspondence: **phase 0 → QRS, phase 2 → ST, phase 3 → T wave;** I_K1 sets resting potential, I_f drives SA automaticity (ivabradine target).
- Paper: **1 small box = 40 ms, 1 large = 200 ms, 1 mV = 10 mm;** rate = 300/large boxes.
- Normal QRS axis **−30° to +100°**; QRS **≥120 ms = complete BBB**; **RBBB rSR′ in V1**, **LBBB QS in V1/R in V6**.
- QTc upper limits **450 ms (men), 460 ms (women)**; **Bazett QTc = QT/√RR.**
- Hyperkalemia sequence: **tented T → wide QRS → flat P → sine wave → asystole.**

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 247 "Electrocardiography"** (Goldberger) and **Ch 250 "Principles of Clinical Cardiac Electrophysiology"** (Sauer, Koplan, Zei). **Coverage note:** The provided chapters describe conduction anatomy functionally but do **not** give the nodal **blood supply** (SA-nodal/AV-nodal arteries), the named **internodal/Bachmann interatrial tracts**, or the classic resting **escape pacemaker hierarchy** (SA 60–100, AV junction 40–60, ventricular 30–40 /min) — these are added only where universally-accepted standard internal medicine and are flagged here as outside the supplied text (Harrison gives the dynamic SA range of 30–220 /min and the general "escape rhythm" concept instead).

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Constrictive pericarditis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Constrictive pericarditis (CP) is the end-stage of a chronic inflammatory process in which a rigid, thickened, fibrotic and often calcified pericardium encases the heart, obliterating the pericardial cavity and limiting diastolic filling of the ventricles. It is the prototype of a *surgically curable* cause of right-heart failure / diastolic heart failure. *(Note: the 2019 paper printed the topic as "conservative pericarditis" — a near-universal transcription error for constrictive pericarditis, which is the only recognised clinical entity and is answered here.)*

Etiology and Classification

CP results when healing of fibrinous/serofibrinous pericarditis or resorption of a chronic effusion is followed by obliteration of the pericardial cavity by granulation tissue that contracts into a firm, sometimes calcific, scar. Constriction may evolve over weeks–months but typically takes years.

Group	Causes
Idiopathic / viral	Commonest cause in the developed world; risk after viral/idiopathic pericarditis <1%
Post-surgical	After cardiac surgery of any type (common in transient/reversible CP)
Post-radiation	Mediastinal irradiation (breast cancer, lymphoma) — poor surgical prognosis
Tuberculous	Leading cause in the developing world (India), sub-Saharan Africa; risk after purulent bacterial pericarditis 20–30%, after immune/neoplastic 2–5%
Connective tissue / autoimmune	RA, SLE, scleroderma, sarcoidosis
Others	Chronic renal failure on dialysis (uremic), neoplasm, trauma with organised clot, asbestosis, drug-induced, *Mulibrey nanism* (familial, AR)

Harrison's clinical-temporal classification of pericarditis places constriction in the **subacute (6 wks–6 months, effusive-constrictive or constrictive)** and **chronic (>6 months, constrictive or adhesive)** categories.

Pathophysiology — the hallmark physiology

- **Impaired filling:** Ventricular filling is *unimpeded in early diastole* but stops abruptly when the elastic limit of the rigid pericardium is reached (≈ entire stroke volume enters in early diastole). Contrast with tamponade, where filling is impeded *throughout* diastole.
- **Equalisation of pressures:** Ventricular end-diastolic, mean atrial, pulmonary venous and systemic venous pressures are all elevated and **equal to within ≤5 mmHg** of one another (typically ~20–25 mmHg).
- **Dissociation of intrathoracic and intracardiac pressures:** The stiff pericardium prevents transmission of the inspiratory fall in intrathoracic pressure to the cardiac chambers. On inspiration, the pressure drop reaches the pulmonary veins but **not** the LA/LV, reducing the pulmonary-vein-to-LA gradient → ↓ left-heart filling.
- **Enhanced ventricular interdependence:** Because total cardiac volume is fixed by the shell, inspiratory ↓ LV filling permits ↑ RV filling with a **leftward septal shift** ("septal bounce"); the reverse occurs in expiration. This is the basis of all the respirophasic Doppler signs.
- Systolic function is usually preserved ("pure" constriction); advanced disease may extend fibrosis into the myocardium (mixed constriction–restriction / myopericarditis), worsening prognosis.

Clinical Features

- **Symptoms:** Insidious fatigue, weakness, exertional dyspnoea, orthopnoea; progressive systemic venous congestion — raised abdominal girth, ascites (often *out of proportion to peripheral oedema*), congestive hepatomegaly/jaundice, anasarca, muscle wasting and cachexia in end-stage disease.
- **Jugular venous pulse:** Markedly elevated, with a **prominent, rapid y descent** and a normal x descent → **M- or W-shaped** waveform; fails to fall (or rises) on inspiration = **Kussmaul's sign**.
- **Pericardial knock:** Early diastolic sound at LSB/apex, slightly *earlier and higher-pitched* than an S3, from abrupt cessation of ventricular filling.
- **Pulsus paradoxus:** Present in only about **one-third** of cases (unlike tamponade, where it is the rule).
- **Other signs:** Distant heart sounds, *Broadbent's sign* (systolic apical retraction), hepatomegaly with pulsatile veins, splenomegaly, pleural effusions, stigmata of cardiac cirrhosis (spider naevi, palmar erythema). Atrial fibrillation is common.
- A common pitfall is mistaking CP for **hepatic cirrhosis** (ascites + hepatomegaly); inspection of the distended neck veins distinguishes them.

Investigations

- **ECG:** Non-specific — low-voltage QRS, diffuse T-wave flattening/inversion; **atrial fibrillation in ~one-third**.

- **Chest X-ray:** Normal or slightly enlarged heart; **pericardial calcification** (best seen in lateral view) — most frequent in tuberculous CP but neither sensitive nor specific; pleural effusions common.
- **Echocardiography–Doppler (first-line):** Pericardial thickening; **septal "bounce"**; dilated IVC/hepatic veins with blunted respiratory variation; abrupt halt of early LV filling. Doppler: respiratory variation in **mitral E ≥25%** (↑ on early expiration), tricuspid/mitral flows ~180° out of phase, hepatic-vein **expiratory diastolic flow reversal**, mitral E deceleration time usually <160 ms.
- **Tissue Doppler / strain:** *Annulus reversus* — medial (septal) mitral-annular **e′ > lateral e′**; preserved/increased medial e′ (>8 cm/s) favours constriction over restriction; *strain reversus* (preserved longitudinal, reduced circumferential strain).
- **CT / CMR:** CT is most accurate for **pericardial thickness** (normal <2 mm) and calcification; thickening **>4 mm** supports the diagnosis, but pericardium is of **normal thickness in ~20–28% of CP** — so normal thickness does *not* exclude it. CMR with T2-STIR/late gadolinium enhancement detects active pericardial inflammation (predicts response to anti-inflammatory therapy / transient CP).
- **Cardiac catheterisation (confirmatory in equivocal cases):** Elevated and equalised diastolic pressures; **"square-root" / dip-and-plateau** sign; RVEDP >⅓ of RV systolic pressure; **discordance** of RV and LV systolic pressures with respiration (RV rises as LV falls) and a **systolic area index >1.1**; low pulmonary artery pressure. **BNP is normal/low in CP but elevated in restriction.**

Constriction vs Restriction vs Tamponade

Feature	Constrictive pericarditis	Restrictive cardiomyopathy	Cardiac tamponade
Pulsus paradoxus	~⅓ of cases (+)	Usually absent	Marked (+++)
JVP y descent	**Prominent** (M/W shape)	Variable	Absent/blunted (x prominent)
Kussmaul's sign	Present (+++)	±	Absent
Pericardial knock	Present	Absent	Absent
S3	Absent	Present	Absent
RV–LV diastolic pressures	Equal (≤5 mmHg apart)	LV higher by ≥3–5 mmHg	Equalised
Filling pressure >25 mmHg / severe PHT	Uncommon	Common	—
Respiratory flow variation	Exaggerated, discordant	Normal/concordant	Exaggerated
Pericardium	Thickened ± calcified	Normal	Effusion present
Septal bounce	Present	Absent	—

Feature	Constrictive pericarditis	Restrictive cardiomyopathy	Cardiac tamponade
Tissue Doppler e′ / BNP	e′ increased; BNP normal	e′ reduced; BNP high	—

Variants

- **Effusive-constrictive pericarditis (ECP):** Tense effusion *plus* visceral pericardial constriction. Constrictive physiology is unmasked **after pericardiocentesis** — defined as failure of RA pressure to fall by ≥50% to <10 mmHg once intrapericardial pressure is reduced to ~0. Commonest causes: idiopathic, malignancy, radiation, post-pericardiotomy, TB. Often needs wide excision of *both* visceral and parietal pericardium.
- **Transient / reversible constriction:** Subacute inflammatory CP (esp. early post-cardiac surgery) that resolves over 3–6 months; ~60% avoid surgery with anti-inflammatory therapy (NSAID + colchicine + prednisone ± IL-1 antagonist), guided by CMR late-gadolinium enhancement and raised hsCRP.

Treatment

- **Surgical pericardiectomy (decortication) is the only definitive cure** and should be as complete as possible (median sternotomy ± cardiopulmonary bypass; "waffle" procedure for dense epicardial involvement). Perform **early**, before myocardial atrophy/cachexia set in; benefit accrues over weeks–months.
- **Pre-operative coronary angiography** in patients **>50 years** to exclude CAD.
- **Operative mortality 5–15%** (up to ~20% in some series), highest with radiation-induced disease, renal/hepatic dysfunction, reduced LVEF, low serum sodium and NYHA class IV.
- **Medical / bridging therapy:** Salt restriction and aggressive **diuresis** (loop diuretics ± thiazide ± aldosterone antagonist) for volume overload; rate control with digoxin if AF (avoid drugs that slow the compensatory tachycardia). Treat the **specific cause** — e.g. anti-tuberculous chemotherapy for tuberculous CP, with pericardiectomy if constriction persists.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **JVP waveform in CP:** a venous pressure tracing showing a **prominent, steep y descent** with normal x descent giving an **M/W contour**; label *a wave, x descent, v wave, y descent (deep), Kussmaul's sign (inspiratory rise).*
- **Ventricular pressure tracing:** RV/LV diastolic curves showing the **"square-root" (dip-and-plateau) sign** with **equalised, elevated end-diastolic pressures**; label *early diastolic dip, diastolic plateau, elevated & equal EDP, respiratory discordance of RV/LV systolic peaks.*

Clinical / Diagnostic significance

- CP is one of the few **reversible/curable** causes of refractory right heart failure — always distinguish it from restrictive cardiomyopathy and cirrhosis, because management diverges completely.

- In India and the developing world, **tuberculosis remains a leading cause**; calcific ("armoured heart") constriction is classically tuberculous.
- A multimodality approach (echo-Doppler → CT/CMR → catheterisation) is needed; no single test is definitive, and normal pericardial thickness does not exclude CP.
- Anti-inflammatory therapy can reverse *transient* inflammatory constriction and spare some patients surgery — identify them with CMR (LGE) and hsCRP.

High-yield exam pointers

- **Pathognomonic triad:** raised JVP with prominent y descent + Kussmaul's sign + pericardial knock.
- **"Square-root" sign** (dip-and-plateau) and **equalisation of diastolic pressures (≤5 mmHg)** on catheterisation.
- **Ventricular interdependence / septal bounce** with respirophasic discordance is the unifying mechanism — yields **systolic area index >1.1**.
- Pulsus paradoxus in only ~⅓ of CP (contrast tamponade) — *low-yield to expect it*.
- **Annulus reversus** (medial e′ > lateral e′) and **normal/elevated e′ with normal BNP** favour CP over restriction.
- **Pericardial calcification** = most often TB; thickening >4 mm supportive but absent in 20–28%.
- **Pericardiectomy** = only cure; **coronary angiography if >50 y**; mortality ~5–15%, worst with prior radiation.
- **Effusive-constrictive PCarditis:** constriction revealed *after* draining the effusion.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Pericardial Disease" (chronic constrictive pericarditis; effusive-constrictive and tuberculous pericardial disease).
- Braunwald's Heart Disease, 13e — "Pericardial Diseases" (pathophysiology of ventricular interdependence, echo-Doppler/tissue-Doppler criteria, invasive haemodynamics, pericardiectomy outcomes, effusive-constrictive and transient constriction).
- CMDT 2026 — "Constrictive Pericarditis" (essentials of diagnosis, current diuretic/surgical management, risk of constriction by aetiology).

Coverage note: The exam printed the topic as "conservative pericarditis," which is not a recognised entity; per the spec note this is a typo for **constrictive pericarditis**, and the answer is grounded accordingly. The corpus covers the topic in depth across all three texts; no fabrication was required.

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Cor pulmonale

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Cor pulmonale* ("pulmonary heart") is **right ventricular (RV) enlargement — hypertrophy and/or dilatation — progressing to right heart failure, caused by pulmonary hypertension that arises from primary disorders of the respiratory system, lung parenchyma, pulmonary vasculature, chest wall or ventilatory control.** By convention it **excludes** RV dysfunction secondary to left heart disease or congenital heart disease. As Braunwald frames it, "cor pulmonale, decompensated right heart failure, is the end-stage result of severe RV–pulmonary arterial (RV–PA) uncoupling." It is the common terminal pathway of advanced chronic lung disease, most often **COPD**, and carries a poor prognosis once overt RV failure supervenes.

Etiology and classification

- **Acute cor pulmonale** — sudden RV pressure overload and dilatation, classically from **massive/sub-massive pulmonary embolism**; also severe acute lung injury/ARDS. (Acute RV strain pattern, no time for hypertrophy.)
- **Chronic cor pulmonale** — slow RV hypertrophy then failure from sustained pulmonary hypertension. The underlying causes map largely onto **WSPH Group 3 (PH due to lung disease/hypoxia)** and **Group 4 (chronic thromboembolic PH)**.

Mechanism / category	Representative causes
Obstructive airway disease	**COPD/emphysema (commonest cause)**, severe chronic asthma, bronchiectasis, cystic fibrosis
Restrictive / parenchymal (ILD)	Idiopathic pulmonary fibrosis, sarcoidosis, pneumoconioses, post-TB fibrosis
Chest-wall / neuromuscular	Kyphoscoliosis, thoracoplasty, obesity-hypoventilation, neuromuscular weakness
Hypoventilation / sleep-disordered breathing	Obstructive sleep apnoea, central hypoventilation syndromes
Chronic hypoxia without lung disease	Prolonged high-altitude residence
Pulmonary vascular disease	Pulmonary arterial hypertension (Group 1), **CTEPH/recurrent PE (Group 4)**, schistosomiasis, sickle-cell disease

- In COPD, cor pulmonale "typically occurs in individuals who have marked decreases in **FEV_1 (<25% of predicted) and chronic hypoxaemia (PaO_2 <55 mmHg)**" (Harrison). Severe PH in lung disease is uncommon: ~90% of COPD patients have mPAP >20 mmHg but only ~5% exceed 35 mmHg.

Pathophysiology

- **Alveolar hypoxia** is the central driver: it triggers **hypoxic pulmonary vasoconstriction** (a reflex diverting blood from poorly-ventilated alveoli), which when chronic and global raises **pulmonary vascular resistance (PVR)**.

- Sustained hypoxaemia, acidosis and hypercapnia, plus **destruction/obliteration of the pulmonary capillary bed** (emphysema, fibrosis, embolic webs) and vascular remodelling (intimal fibrosis, medial hypertrophy), further increase PVR and pulmonary artery pressure.
- **Secondary erythrocytosis** (chronic hypoxia) raises blood viscosity, adding to RV load.
- Pulmonary hypertension is now defined hemodynamically as a **mean PA pressure (mPAP) >20 mmHg** at rest (lowered from the older ≥25 mmHg at the 2018 Sixth World Symposium); pre-capillary PH additionally requires **PVR >2 Wood units with PA wedge pressure ≤15 mmHg**.
- Rising **RV afterload** → compensatory **RV hypertrophy** → progressive **RV dilatation** → loss of RV –PA coupling → falling RV output, septal flattening (D-shaped LV), functional **tricuspid regurgitation** and systemic venous congestion = clinical right heart failure.

Clinical features

- **Symptoms** — exertional dyspnoea and fatigue dominate early; as RV fails, **dependent (pedal) oedema, abdominal bloating/distension** (congestive hepatomegaly, ascites), exertional chest pain, and **pre-syncope/syncope** appear (advanced disease). Symptoms of the underlying lung disease (cough, sputum, wheeze) coexist.

Sign	Underlying basis
Loud / palpable P2, accentuated pulmonic component of S2	Elevated pulmonary artery pressure
Left parasternal heave / RV lift	RV hypertrophy & pressure overload
Right-sided S3 (± S4) gallop	RV dysfunction / decreased compliance
Raised JVP with prominent *a* wave; large *v* wave if TR	Systemic venous congestion
Pansystolic tricuspid regurgitant murmur (louder on inspiration — *Carvallo's sign*)	RV/tricuspid annular dilatation
Tender, pulsatile hepatomegaly, ascites, pedal oedema	Right heart failure / congestion
Central cyanosis, clubbing (in ILD/bronchiectasis)	Hypoxaemia / underlying lung disease

- Harrison: *symmetric* pedal oedema "may suggest cor pulmonale," whereas asymmetric oedema points to DVT; the syndrome presents "with abdominal bloating or distention and pedal edema."

Investigations

- **ECG** — signs of RV hypertrophy with strain: **peaked (tall) R waves in V1, ST-segment depression in V2–V3** (strain), **P pulmonale** (P wave **>3 mm / tall peaked in II, III, aVF**), **right axis deviation** and **RBBB**; the acute PE pattern is S1Q3T3 with sinus tachycardia.
- **Chest X-ray** — enlarged central/proximal pulmonary arteries with peripheral "pruning," RV enlargement, and **obliteration of the retrosternal space** on the lateral film; features of the underlying lung disease (hyperinflation in COPD, fibrosis in ILD).
- **Echocardiography (key initial screening test)** — estimated PA systolic pressure >35 mmHg / **tricuspid regurgitant jet velocity >2.8 m/s** suggests PH; **RV hypertrophy and dilatation, RA enlargement, interventricular septal flattening in diastole** (pressure overload); agitated-saline "bubble" study to exclude intracardiac shunt.
- **BNP / NT-proBNP** — correlate with RV dysfunction and prognosis.

- **PFT + ABG** — characterise obstructive vs restrictive disease, document hypoxaemia/hypercapnia; an **isolated low DLCO** is typical of pulmonary vascular involvement.
- **V/Q scan or CT pulmonary angiography** — screen for **CTEPH**; nocturnal oximetry/polysomnography for OSA.
- **Right heart catheterisation** — *gold standard* to confirm and classify PH (mPAP >20 mmHg, pre-capillary pattern PVR >2 WU, PAWP ≤15 mmHg).

Management

- **Treat the underlying disorder** — this is the cornerstone:
  - **COPD**: smoking cessation, inhaled bronchodilators (LABA/LAMA) ± ICS triple therapy, pulmonary rehabilitation; treat exacerbations.
  - **ILD**: disease-specific therapy; **OSA/hypoventilation**: CPAP/NIV; **CTEPH**: lifelong anticoagulation + **pulmonary endarterectomy** (curative in suitable cases), or **riociguat**/balloon pulmonary angioplasty if inoperable.
- **Long-term oxygen therapy (LTOT)** — the single most important measure in chronic hypoxaemic cor pulmonale; reverses hypoxic pulmonary vasoconstriction and **reduces mortality, the benefit being proportional to hours/day used**. Prescribe for **resting PaO_2 ≤55 mmHg or SaO_2 ≤88%**, OR **PaO_2 56–59 mmHg / SaO_2 89% with evidence of cor pulmonale** (dependent oedema, **P pulmonale on ECG**, or **haematocrit >56%**). In acute illness, target SaO_2 **88–92%** to avoid CO_2 retention.
- **Diuretics** (± **mineralocorticoid-receptor antagonist**) and a **low-salt diet** for congestion/oedema — used cautiously to avoid excessive preload reduction and prerenal azotaemia.
- **Therapeutic phlebotomy** for symptomatic severe secondary erythrocytosis (Hct >56%).
- **Caveat on PAH-specific vasodilators** — prostanoids, ERAs, PDE5 inhibitors are *not* routinely beneficial in Group 3 (lung-disease) cor pulmonale and may worsen V/Q matching; inhaled iloprost gave only modest benefit in ILD-PH and a COPD-PH trial was stopped early. They are reserved for Group 1 PAH/selected Group 4 disease at expert centres.
- **Lung or heart–lung transplantation** in refractory end-stage disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flowchart (label each box):** *Chronic lung disease / alveolar hypoxia → Hypoxic pulmonary vasoconstriction + capillary-bed destruction + vascular remodelling + erythrocytosis → ↑ Pulmonary vascular resistance → Pulmonary hypertension (↑ RV afterload) → RV hypertrophy → RV dilatation → Right ventricular failure (cor pulmonale) → Raised JVP, tender hepatomegaly, ascites, pedal oedema, tricuspid regurgitation.*
- **ECG of RV hypertrophy / strain (label):** *Tall R wave in V1, deep S wave in V6, right axis deviation, P pulmonale (tall peaked P >2.5–3 mm in II), ST-T "strain" in V1–V3, RBBB pattern.*

Clinical / Diagnostic significance

- Cor pulmonale is the chief cardiovascular complication of advanced chronic lung disease and a **marker of poor prognosis**; its appearance signals the need to optimise oxygenation and reassess the underlying disorder.
- Distinguishing cor pulmonale (Group 3/4 PH) from PH due to **left heart disease (Group 2)** and from **pulmonary arterial hypertension (Group 1)** is essential, because management diverges sharply — LTOT and treating the lung disease for cor pulmonale versus PAH-targeted vasodilators for Group 1.
- **Symmetric** pedal oedema with raised JVP in a known COPD/ILD patient should prompt evaluation for cor pulmonale rather than being dismissed; an absolutely normal echocardiogram makes significant PH unlikely.

High-yield exam pointers

- **Definition stresses the cause:** RV failure from a *pulmonary/respiratory* cause — left heart and congenital disease are *excluded*.
- **COPD is the commonest cause of chronic cor pulmonale**; **massive PE** is the classic cause of **acute** cor pulmonale.
- **Hypoxic pulmonary vasoconstriction** is the central mechanism; chronic hypoxia + capillary loss + remodelling → ↑PVR → PH → RV failure.
- **PH now = mPAP >20 mmHg** (revised 2018 WSPH); pre-capillary PH adds PVR >2 WU, PAWP ≤15 mmHg; **RHC is the gold standard**.
- **Cardinal signs:** loud P2, left parasternal heave, raised JVP, tricuspid regurgitant murmur, tender pulsatile hepatomegaly, pedal oedema.
- **ECG:** P pulmonale (P >3 mm in II/III/aVF), tall R in V1, right axis deviation, RV strain; **echo** shows RV dilatation/hypertrophy and septal flattening.
- **LTOT reduces mortality** in hypoxaemic cor pulmonale (PaO_2 ≤55 mmHg / SaO_2 ≤88%, or ≤59/89% with cor pulmonale signs); benefit is dose-dependent on hours/day.
- **Do not** give PAH-specific vasodilators routinely in lung-disease cor pulmonale; **treat the underlying disease + oxygen + diuretics**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pulmonary Hypertension" (definition, hemodynamics, WSPH classification, ECG/CXR/echo/RHC, treatment of PH due to lung disease & CTEPH); "Chronic Obstructive Pulmonary Disease" (cor pulmonale in COPD, FEV_1/PaO_2 thresholds, oxygen therapy and mortality benefit); "Approach to the Patient with Disease of the Respiratory System" (cor pulmonale symptoms, symmetric oedema); "Interstitial Lung Disease" and "Heart Failure: Pathophysiology and Diagnosis" (cor pulmonale among causes of right heart failure).
- **Braunwald's Heart Disease, 13e** — "Pulmonary Hypertension" (RV–PA uncoupling definition of cor pulmonale, physical-examination findings of right-sided pressure/volume overload, Group 3 lung-disease PH, TR velocity threshold).
- **CMDT 2026** — "Pulmonary Disorders" (LTOT prescribing criteria including P pulmonale and haematocrit thresholds; P-pulmonale definition).

Coverage note: The corpus has no chapter titled "Cor Pulmonale"; the entity is covered within the Pulmonary Hypertension, COPD and respiratory-approach chapters. Universally-accepted standard points not separately spelled out in these chapters (e.g., *Carvallo's sign* for inspiratory accentuation of the TR murmur, the S1Q3T3 pattern of acute PE) are included as established textbook medicine.

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Conducting system of the heart — complete heart block

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — The cardiac conduction system is a network of specialised, predominantly non-contractile myocytes that generate and propagate the electrical impulse responsible for the orderly, sequential contraction of the atria and ventricles. It comprises the **sinoatrial (SA) node** (the natural pacemaker), the **atrial preferential/internodal pathways**, the **atrioventricular (AV) node**, the **bundle of His**, the **right and left bundle branches**, and the terminal **Purkinje network**. *Complete (third-degree) heart block* is the most severe AV conduction disturbance, in which no atrial impulse reaches the ventricles, producing complete AV dissociation with a ventricular rate slower than the atrial rate and a constant risk of syncope (Stokes-Adams attacks) and asystolic death.

Anatomy and physiology of the SA node and atrial conduction

- **SA node** — a cigar-shaped cluster of small fusiform pacemaker cells in the *sulcus terminalis (crista terminalis)* on the epicardial surface at the **right atrial–superior vena cava junction**, enveloping the SA nodal artery within a protective extracellular matrix that insulates it from the hyperpolarising atrium.
- **Blood supply** — SA nodal artery arises from the **right coronary artery (RCA) in 55–60%** and the **left circumflex (LCx) in 40–45%**.
- **Pacemaker physiology** — nodal cells have no true resting potential; they exhibit spontaneous **phase 4 (diastolic) depolarisation** driven by the *funny current (I_f)* plus T- and L-type calcium

currents. Phase 0 upstroke is slow and **calcium-mediated** (fast Na^+ channels absent). Intrinsic discharge rate **60–100 beats/min**, dominant because phase 4 is steepest here.

- **Autonomic control** — at rest the node is under vagal (parasympathetic) predominance; after complete autonomic blockade the **intrinsic heart rate ≈ 118.1 − (0.57 × age)** beats/min (~100–110/min in young adults).
- **Atrial spread** — the impulse spreads to the AV node by **preferential intra-atrial pathways** of higher conduction velocity than ordinary atrial muscle. The **Bachmann bundle** carries activation from the right to the left atrium. The classic three *internodal tracts* — **anterior (Bachmann), middle (Wenckebach) and posterior (Thorel)** — are traditional eponyms; their existence as discrete insulated tracts remains debated, with preferential conduction now attributed to fibre orientation in atrial myocardium.

Structure and physiology of the AV node and His–Purkinje system

- **AV node** — a small structure (~**1 × 3 × 5 mm**) beneath the right atrial endocardium at the apex of the **triangle of Koch**, bounded by the **coronary sinus ostium (posteriorly)**, the **septal tricuspid annulus (anteriorly)** and the **tendon of Todaro (superiorly)**.
- **Zones** — transitional (atrionodal) cells, the compact node, and the penetrating His bundle. Two functional inputs exist in many people: a **slow pathway** (inferior nodal extension) and a **fast pathway** (the substrate for AV nodal re-entry tachycardia).
- **Slow conduction / "gatekeeper" role** — compact-node cells sit at ~−60 mV, have slow phase 0 (<10 V/s) mediated by **L-type Ca^{2+} current (I_Ca-L)**, sparse gap junctions (predominantly **connexin-40**) and **decremental conduction**. This creates the physiological AV delay (compact node velocity <10 cm/s vs ~35 cm/s in atrial muscle), allowing atrial systole to complete ventricular filling and protecting the ventricle from rapid atrial rates. Intrinsic AV-junctional escape rate **20–60/min**.
- **Blood supply** — AV nodal artery from the **RCA in 80–90%** and LCx in ~10% (matching coronary dominance); the bundle branches have dual supply from **LAD septal perforators** (LBB, proximal RBB) and the posterior descending artery.
- **His bundle (penetrating AV bundle)** — pierces the central fibrous body/annulus fibrosus and runs along the ventricular septum; insulated from working myocardium.
- **Bundle branches** — **right bundle branch (RBB)**, a discrete cord reaching the **moderator band**; **left bundle branch (LBB)**, a broad subendocardial sheet dividing into **anterior and posterior fascicles**.
- **Purkinje network** — ramifies over both ventricular endocardia; **fastest conduction in the heart (1–3 m/s)**, with rapid phase 0, prolonged plateau and modest automaticity (escape ~20–40/min).
- **Autonomic note** — the AV node is richly innervated by sympathetic and parasympathetic fibres; the **His bundle and distal system are not influenced by autonomic tone**.

ECG correlation of the conduction sequence

ECG component	Electrical event	Normal value
P wave	SA node firing → atrial depolarisation (RA then LA)	<120 ms; upright in II, inverted in aVR
PR interval	Onset of atrial to onset of ventricular depolarisation (mostly AV-nodal delay)	**120–200 ms**
PR segment	AV nodal + His conduction delay	isoelectric
QRS complex	His–Purkinje → ventricular depolarisation	**≤100–110 ms**
ST-T-U	Ventricular repolarisation	—

- Invasive **His-bundle electrogram** intervals: **AH interval** (AV-nodal conduction) normally **<130 ms**; **HV interval** (His-Purkinje conduction) normally **≤55 ms**. A prolonged HV (>100 ms) carries ~10% annual risk of complete AV block.

Complete (third-degree) heart block — definition and classification

- **Definition** — complete interruption of AV conduction; atria and ventricles are driven by independent pacemakers (**AV dissociation**) with the **atrial rate exceeding the ventricular (escape) rate**. *Complete AV block always implies AV dissociation, but not all AV dissociation is complete block.*
- **Level of block determines escape characteristics:**

Feature	Block in AV node / proximal His	Infra-Hisian (distal) block
Typical setting	Often **congenital**, inferior MI, drug/vagal, Lyme	Usually **acquired**, anterior MI, sclerodegenerative
Escape focus	Junctional, near His	Ventricular (Purkinje)
QRS	**Narrow**	**Wide**
Escape rate	40–60/min, more stable	**<40/min, unreliable**
His electrogram	Each ventricular beat **preceded** by His deflection; P not followed by His	P **followed** by His; escape **not** preceded by His
Response to atropine/exercise	Improves	No improvement
Prognosis	Better	Worse, risk of asystole

Aetiology, clinical features and diagnosis of complete heart block

- **Idiopathic fibrosis/sclerosis (~50% of acquired block)** — *Lev's disease* (proximal bundle-branch fibrosis/calcification, elderly, related to aortic/mitral annular calcification) and *Lenègre's disease* (distal sclerodegeneration in younger patients); accelerated familial forms link to **SCN5A** mutations (also cause LQT3).

- **Ischaemic** — AV block complicates 10–25% of acute MI; **inferior MI** → nodal block, narrow stable escape, usually reversible; **anterior MI** → distal/infra-nodal block, wide unstable escape, high mortality.
- **Iatrogenic/drugs** — beta blockers, verapamil/diltiazem, digoxin; valve surgery, **TAVR**, alcohol septal ablation, catheter ablation.
- **Infective/infiltrative/autoimmune** — Lyme carditis (*Borrelia burgdorferi*), endocarditis with **perivalvular abscess**, viral myocarditis, **Chagas' disease**, cardiac **sarcoidosis**, **amyloidosis**, SLE/RA/scleroderma.
- **Congenital** — maternal SLE/anti-Ro antibodies, complex congenital heart disease (TGA, ostium primum ASD, endocardial cushion defects).
- **Neuromuscular** — myotonic dystrophy, Kearns-Sayre syndrome, Lamin A/C cardiomyopathy.
- **Clinical features** — fatigue, exertional intolerance, dyspnoea, presyncope and **Stokes-Adams syncope/convulsions**; sudden death from asystole. Signs: **variable-intensity S_1**, **intermittent cannon "a" waves** in the JVP (atrium contracting against a closed AV valve), wide pulse pressure and variable systolic BP.
- **Investigations** — 12-lead ECG (AV dissociation, atrial rate > ventricular rate, P waves marching through independent QRS); ambulatory/Holter or mobile telemetry for intermittent block; **echocardiography** for structural disease; **electrophysiology study with His-bundle recording** to localise block; **cardiac MRI / FDG-PET** for sarcoid/amyloid (especially age ≤60); Lyme serology, electrolytes, TSH and drug review for reversible causes.

Management of complete heart block

- **Acute** — identify and reverse causes (stop AV-blocking drugs, correct electrolytes/ischaemia, treat hypoxia/sleep apnoea). For symptomatic/haemodynamically unstable block: **atropine 0.5 mg IV** (effective only for nodal block), then **isoproterenol, dopamine or epinephrine** infusion; **transcutaneous pacing** (cathode patch over apex anteriorly, anode posteriorly) as a bridge; **transvenous temporary pacing** for reliability when escape is slow or wide-complex.
- **Definitive — permanent pacemaker (PPM)** is the only reliable therapy. Acquired **third-degree (and Mobitz II) AV block is a Class I indication regardless of symptoms** when not reversible/physiological. A **dual-chamber (DDD) device** is preferred to preserve AV synchrony.
- **Physiologic / conduction-system pacing** — in patients with **LVEF <50%** likely to need ventricular pacing **>40%** of the time, use **His-bundle or left bundle branch area pacing**, or **cardiac resynchronisation therapy (CRT)**, to avoid pacing-induced heart failure.
- **In acute MI** — pace for persistent 2nd/3rd-degree block or transient high-grade block with new bundle branch block; transient inferior-MI nodal block usually needs no permanent device.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Conduction system of the heart (coronal heart outline).** Labels: *SA node (at RA–SVC junction)*, *Bachmann bundle*, *anterior/middle/posterior internodal tracts*, *AV node (triangle of Koch — coronary sinus ostium, tendon of Todaro, septal tricuspid annulus)*, *bundle of His*, *right bundle branch → moderator band*, *left bundle branch with anterior and posterior fascicles*, *Purkinje fibres*.
- **Diagram 2 — ECG strip of complete heart block.** Labels: *regular P waves (atrial rate)*, *regular but slower QRS (ventricular escape)*, *no fixed PR relationship = AV dissociation*, *P waves "marching through" QRS*, plus a **JVP tracing showing intermittent cannon "a" waves**.

Clinical / Diagnostic significance

- The **physiological AV-nodal delay** times atrial against ventricular contraction (optimising filling) and shields the ventricle during atrial tachyarrhythmias — its decremental property is exploited by AV-nodal blocking drugs for rate control.
- **Dual blood supply** explains clinical patterns: SA/AV nodes are RCA-dependent, so inferior MI causes (usually reversible) nodal block, whereas anterior (LAD) MI damaging the His-Purkinje system causes dangerous infranodal block.
- **QRS width + escape rate localise the block** and predict stability — a wide, slow escape mandates urgent pacing.
- Distinguishing **congenital** (narrow, faster escape, rate rises with exercise) from **acquired** (wide, slow escape, no exercise response) CHB guides prognosis and urgency of pacing.
- Always exclude **reversible causes** (drugs, ischaemia, hyperkalaemia, hypothyroidism, Lyme, high vagal tone) before committing to a permanent device.

High-yield exam pointers

- **SA node = pacemaker (60–100/min); AV junction 40–60/min; Purkinje 20–40/min** — hierarchy of subsidiary pacemakers.
- **Triangle of Koch** = coronary sinus ostium + tendon of Todaro + septal tricuspid annulus → AV node landmark.
- Normal **PR 120–200 ms; AH <130 ms; HV ≤55 ms; QRS ≤110 ms**.
- *Lev's disease* = proximal/calcific (old); *Lenègre's disease* = distal sclerodegenerative (young); **SCN5A** = progressive familial heart block (+LQT3).
- CHB = **AV dissociation with atrial rate > ventricular rate**; hallmark sign = **cannon "a" waves** and **variable S_1**.
- **Narrow QRS escape = nodal, stable, atropine-responsive; wide QRS escape = infranodal, unstable, atropine-resistant.**
- **Atropine works only for nodal block**; for infranodal/unstable block use isoproterenol + temporary pacing.
- Acquired **third-degree / Mobitz II AV block = Class I indication for permanent pacing irrespective of symptoms.**

- **Inferior MI** block = nodal, reversible; **anterior MI** block = infranodal, high mortality, needs pacing.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "The Bradyarrhythmias: Disorders of the Sinoatrial Node" and "The Bradyarrhythmias: Disorders of the Atrioventricular Node" (AV node anatomy, triangle of Koch, AH/HV intervals, aetiology and pacing indications); "Electrocardiography" (P/PR/QRS intervals, conduction sequence).
- **Braunwald's Heart Disease, 13e** — "Bradyarrhythmias and Atrioventricular Block" (classification of AV block, levels and His-electrogram correlation in complete heart block, AV dissociation, cannon a waves) and "Mechanisms of Cardiac Arrhythmias" / "Electrocardiography" (SA node automaticity, Bachmann bundle, nodal conduction velocities).
- **CMDT 2026** — "Disorders of Cardiac Rhythm" (current management of AV block, atropine/isoproterenol/pacing, pacemaker nomenclature and indications).
- *Coverage note:* the named internodal tracts (anterior/Bachmann, middle/Wenckebach, posterior/Thorel) are classic teaching; modern texts (Braunwald) regard discrete insulated internodal tracts as controversial, favouring preferential atrial conduction — presented here with that caveat.

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Mitral stenosis — anatomy and management

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The **mitral (left atrioventricular) valve** is not a simple flap but a functional **"mitral apparatus"** comprising six integrated components — the *annulus, two leaflets, two commissures, chordae tendineae, papillary muscles and the supporting left atrial/ventricular myocardium* — whose coordinated action permits unobstructed diastolic LA-to-LV filling and competent systolic closure. **Mitral stenosis (MS)** is obstruction to LV inflow at valve level producing a diastolic LA-to-LV pressure gradient — the hemodynamic hallmark. The normal orifice is **4–6 cm²**; obstruction becomes significant at **<~2 cm²** and "severe" at **<1.5 cm²**, when an LA pressure of ~25 mmHg is needed to maintain output.

Structure of the mitral valve apparatus

Component	Key anatomical features	Relevance in MS
Annulus	Saddle-/D-shaped fibrous ring at the LA–LV junction; anterior part is in fibrous continuity with the aortic valve, posterior part is muscular; contracts in systole to reduce orifice	**Mitral annular calcification** with extension onto leaflets is a recognised cause of obstruction
Leaflets (2)	**Anterior (aortic/septal)** — larger, semicircular, guards ~two-thirds of the orifice area; **Posterior (mural)** — smaller, quadrangular, with scallops	Rheumatic **diffuse leaflet thickening** + calcification produces the **funnel-shaped, "fish-mouth" valve**

Component	Key anatomical features	Relevance in MS
Commissures (2)	Anterolateral and posteromedial junctions where the two leaflets meet	**Commissural fusion** is the cardinal rheumatic lesion; splitting it is the basis of *commissurotomy*
Chordae tendineae	Fibrous cords from papillary muscle tips to leaflets (marginal/primary, intermediate, basal)	**Fusion and shortening of chordae** create *subvalvular* stenosis; surgery must "loosen subvalvular fusion"
Papillary muscles (2)	Anterolateral and posteromedial; arise from LV wall, anchor the chordae and prevent leaflet prolapse	Scarring of the subvalvular apparatus reduces suitability for balloon commissurotomy
LA & LV myocardium	The atrial and ventricular walls form the muscular base of the apparatus	LA dilatation/AF promote appendage thrombus; LV EF is preserved in pure MS

- The valve functions as a *unit*: leaflet closure depends on annular size, chordal restraint and papillary-muscle/LV-wall integrity acting together.
- In rheumatic disease the inflammatory injury simultaneously affects **leaflets, commissures and the subvalvular apparatus** — the wider the involvement, the less amenable the valve is to balloon therapy.

Etiology and pathology of Mitral Stenosis

Major causes (Table 274-1)
Rheumatic fever — the leading cause worldwide
Congenital — parachute valve, cor triatriatum
Severe mitral annular calcification with leaflet involvement
SLE, rheumatoid arthritis
Left atrial myxoma
Infective endocarditis with large vegetations

- **Rheumatic fever** is by far the commonest cause; **pure or predominant MS** occurs in ~40% of patients with rheumatic heart disease and a history of rheumatic fever, while lesser MS may accompany MR and aortic disease.
- Incidence has **fallen in temperate, middle-/high-income countries** but MS **remains a major problem in low-income regions** — sub-Saharan Africa, **India**, Southeast Asia and Oceania.
- **Pathology:** chronic inflammation → diffuse leaflet thickening with fibrosis and calcific deposits → **commissural fusion**, **fusion and shortening of chordae tendineae**, rigid cusps and narrowing at the apex of the funnel-shaped ("fish-mouth") valve. Later changes are aggravated by altered-flow trauma. Calcification immobilises leaflets and narrows the orifice further; thrombus/embolism may arise from the calcific valve or, more often in **AF**, from the dilated **LA appendage**.

Pathophysiology

- A reduced orifice obliges flow only across an **abnormally raised LA–LV gradient**; elevated pulmonary venous and PA wedge pressures reduce pulmonary compliance → **exertional dyspnea**.
- **Tachycardia** (especially rapid AF) shortens diastole disproportionately, raising the transvalvular gradient and LA pressure for any given output — explaining decompensation with fever, exercise, anemia, pregnancy and thyrotoxicosis.
- **LV diastolic pressure and EF remain normal** in isolated MS.
- **Pulmonary hypertension** results from (1) passive backward transmission of LA pressure, (2) reactive pulmonary arteriolar constriction ("second stenosis"), (3) interstitial edema of vessel walls, and (4) end-stage obliterative vascular changes → RV enlargement, secondary **TR/PR** and right heart failure.

Clinical features

Symptoms — Latent period of ~2 decades after rheumatic carditis; disability typically in the **fourth decade**.

- Progressive **exertional dyspnea**, then **orthopnea** and **paroxysmal nocturnal dyspnea**.
- Onset of **persistent AF** marks a turning point and accelerates symptom progression.
- **Hemoptysis** from rupture of pulmonary–bronchial venous connections (pulmonary venous hypertension); rarely fatal.
- **Recurrent pulmonary emboli** (often from RA mural thrombus) — important late morbidity/mortality.
- **Pulmonary infections** (bronchitis, bronchopneumonia, lobar pneumonia).
- **Systemic embolization** (incidence 10–20%) — commoner with AF, age >65, and reduced CO; may be the presenting feature even in mild MS.
- **Ortner's (cardiovocal) syndrome** — hoarseness from compression of the left recurrent laryngeal nerve by an enlarged LA/PA.

Signs

- **Inspection/palpation: malar flush ("mitral facies")** with pinched, blue facies in severe MS; prominent jugular **a waves** (in sinus rhythm with severe pulmonary hypertension/TS); a **parasternal lift** (RV enlargement); rarely a diastolic thrill at the apex in left lateral position.
- **Auscultation (the diagnostic quartet): loud (accentuated) S1**; **loud P2** with closely split S2 when PAP is high; **opening snap (OS)** best heard in expiration at or just medial to the apex, following A2 by 0.05–0.12 s; and a **low-pitched, rumbling mid-diastolic murmur** at the apex (left lateral position, accentuated by exercise) with **presystolic accentuation** in sinus rhythm.
- The **A2–OS interval varies inversely with severity**, and murmur duration correlates with severity when CO is preserved.
- **Associated murmurs:** functional **TR** with **Carvallo's sign** (louder on inspiration); **Graham Steell murmur** of pulmonary regurgitation in severe pulmonary hypertension. With very low CO, findings may vanish — **"silent MS."**

Investigations

- **ECG: P mitrale** (broad notched P, LA enlargement); tall peaked P in II and upright in V1 with pulmonary hypertension/TS; **right-axis deviation and RV hypertrophy** in severe pulmonary hypertension; AF common.
- **Echocardiography (investigation of choice): TTE** with color/spectral Doppler gives the **E and A wave** inflow velocities, peak/mean gradients, **mitral valve area**, leaflet calcification/restriction, subvalvular distortion, associated MR, PA systolic pressure (from TR jet) and suitability for balloon valvotomy. The **"echo score"** (leaflet thickening, calcification, mobility, subvalvular thickening) predicts PMBC success — a **lower score = better outcome**. **TEE** is performed to **exclude LA/appendage thrombus** before PMBC.
- **Chest X-ray:** straightening of the upper-left cardiac border, prominent main PAs, dilated upper-lobe veins, posterior esophageal displacement by the enlarged LA, and **Kerley B lines** when mean LA pressure exceeds ~20 mmHg.
- **Cardiac catheterization:** reserved for clinical–echo discrepancy; CT coronary angiography or invasive angiography screens for CAD before intervention.

Management

Medical

- **Secondary prophylaxis** with penicillin against group A streptococcus; infective-endocarditis prophylaxis only in high-risk patients.
- **Symptom control:** sodium restriction and **low-dose diuretics**.
- **Rate control of AF: beta blockers, non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)**, or **digitalis glycosides**.
- **Anticoagulation: vitamin K antagonist (warfarin, INR 2–3)** indefinitely for MS with AF, prior thromboembolism or LA thrombus. **DOACs are contraindicated** — a randomized trial showed **higher mortality with rivaroxaban than warfarin** in rheumatic MS with AF.
- **Cardioversion** for recent-onset AF after ≥3 weeks of therapeutic anticoagulation (or after heparin + TEE if urgent); rarely sustained in severe MS with large LA or AF >1 year.

Mechanical relief of obstruction (symptomatic NYHA II–IV, severe MS, orifice <~1 cm^2/m^2 BSA or <1.5 cm^2):

Procedure	Indication / requirements
Percutaneous mitral balloon commissurotomy (PMBC)	Procedure of choice for pliable, minimally calcified valves; needs little commissural calcium, unscarred subvalvular apparatus, **no LA thrombus** and **MR ≤2+/4+**. Inoue balloon via transseptal puncture; event-free survival **80–90% over 3–7 years** in patients <45 y. Preferred in **pregnancy** (TEE-guided, minimal radiation)
Open surgical commissurotomy	When PMBC unsuitable/failed or restenosis; on bypass — split commissures, free subvalvular fusion of papillary muscles/chordae, debulk calcium, remove atrial thrombi; perioperative mortality ~2%
Mitral valve replacement (MVR)	Significant associated MR, severely distorted/calcified valve; **chordal attachments preserved** to protect LV function; perioperative mortality 2–5%

- **Success criterion** (any commissurotomy): **≥50% fall in mean gradient and doubling of valve area**.
- In **asymptomatic** patients, intervene only if recurrent systemic embolization or severe pulmonary hypertension (PA systolic **>50 mmHg at rest or >60 mmHg with exercise**).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Mitral valve apparatus (LV opened, "surgeon's view"):** label *mitral annulus, anterior (aortic) leaflet, posterior (mural) leaflet, anterolateral commissure, posteromedial commissure, chordae tendineae, anterolateral papillary muscle, posteromedial papillary muscle, LA, LV wall.*
- **Auscultation timing strip of MS:** label *loud S1, A2, opening snap (OS), mid-diastolic rumble, presystolic accentuation* — with the **A2–OS interval** marked (shorter interval = more severe).

Clinical / Diagnostic significance

- The diagnostic auscultatory triad — **loud S1 + opening snap + presystolic-accentuated diastolic rumble** — localises the lesion at the bedside; a **short A2–OS interval** flags severe disease.
- **Echo + echo score** is decisive: it both grades severity and selects patients for **PMBC vs surgery**; mandatory **TEE** rules out LA thrombus pre-procedure.
- **AF and the dilated LA appendage** drive thromboembolism — hence lifelong **warfarin (not DOACs)**.
- Distinguish MS from **MR, the Austin Flint murmur of AR** (softens with amyl nitrite, no presystolic accentuation), **tricuspid stenosis, ASD** and **LA myxoma** (positional murmur, systemic features, IL-6 elevation).

High-yield exam pointers

- Normal MV area **4–6 cm²**; severe MS **<1.5 cm²**; very severe **<1 cm²**; LA pressure ~25 mmHg sustains output in severe MS.
- **Rheumatic fever** is the leading cause; pure MS in ~**40%** of RHD.
- Lesion quartet: **commissural fusion, leaflet thickening/calcification, chordal fusion-shortening, fish-mouth orifice.**
- **Ortner's syndrome** = hoarseness from left recurrent laryngeal nerve compression; **Carvallo's sign** = inspiratory accentuation of TR.
- **P mitrale** on ECG; **Kerley B lines** when mean LA pressure >20 mmHg.
- **A2–OS interval inversely proportional** to MS severity.
- **PMBC** = treatment of choice for pliable valves; needs no LA thrombus and MR ≤2+; success = 50% gradient fall + doubling of area.
- **Avoid DOACs** (rivaroxaban increased mortality vs warfarin); PMBC preferred in pregnancy.

SOURCE & COVERAGE

Harrison 22e — Ch 274 "Mitral Stenosis" (etiology, pathology, pathophysiology, clinical features, investigations, management; Table 274-1; Figs. 274-1 to 274-4). **Coverage note:** Ch 244 "Basic Biology of the Cardiovascular System" covers cardiovascular embryology/biology and Doppler, **not** the detailed mitral valve apparatus anatomy. The six-component structural description (annulus, anterior/posterior leaflets, anterolateral/posteromedial commissures, chordae tendineae, anterolateral/posteromedial papillary muscles, supporting myocardium) is **universally accepted standard anatomy**; its individual elements — leaflets, commissures, chordae tendineae, papillary muscles, annular calcification and the subvalvular apparatus — are explicitly named in Ch 274 within the rheumatic-pathology and surgical sections, but the integrated anatomical map is supplied from standard textbook anatomy rather than the provided chapters.

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Diastolic heart failure

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — *Diastolic heart failure*, in current nomenclature **heart failure with preserved ejection fraction (HFpEF)**, is the clinical syndrome of heart failure (breathlessness, fatigue, fluid retention) occurring with a left-ventricular ejection fraction (LVEF) **>40%** (HFpEF strictly defined as LVEF **≥50%**; LVEF 41–49% is now termed **HF with mildly reduced EF, HFmrEF**). The cardinal haemodynamic abnormality is **elevated LV end-diastolic and left-atrial pressure** at rest or on exertion, owing to impaired myocardial relaxation and reduced LV chamber compliance ("a stiff ventricle") despite a normal-sized, non-dilated cavity. It accounts for **about half of all symptomatic HF**, is increasing in prevalence with population ageing, and carries morbidity and hospitalisation rates approaching those of HFrEF.

Definitions, classification and nomenclature

- The pathophysiologic definition of HF — *"inability of the heart to pump blood at a rate commensurate with the body's needs, or to do so only at the cost of high filling pressures"* — makes **no assumption about EF**; HFpEF is HF with this physiology but normal EF.
- **EF-based phenotypes (universal framework):** HFrEF (LVEF ≤40%); **HFmrEF** (41–49%); **HFpEF** (≥50%); and HF with improved EF (previously ≤40%, now >40%).
- The older dichotomy of "systolic" vs "diastolic" HF is imprecise because **most HF patients have both systolic and diastolic abnormalities** — many HFpEF patients have subclinical longitudinal systolic dysfunction (reduced global longitudinal strain) despite normal EF.
- **Clinical sub-phenotypes (Braunwald):** "garden-variety" HFpEF (hypertension/diabetes/obesity/CKD), CAD-HFpEF, right-heart-failure HFpEF, atrial-fibrillation–predominant, HCM-like, high-output, and valvular HFpEF — useful because management and prognosis differ.

Epidemiology and risk factors

- ~64 million people live with HF worldwide; of these **~50% have HFpEF** and **10–25% HFmrEF**.
- Prevalence rises with age and is **higher in women** at any age; men predominate at lower EFs.
- **Independent risk factors for HFpEF:** advancing age, **hypertension**, **obesity** (high body-mass index / visceral adiposity), **diabetes mellitus**, **atrial fibrillation**, chronic kidney disease and prior myocardial infarction. Higher BMI and AF associate more strongly with HFpEF, whereas prior MI, male sex and LV hypertrophy associate more with HFrEF.
- **Atrial fibrillation** is the commonest arrhythmia — present in **20–40%** at presentation and occurring in two-thirds at some point.
- **Prognosis:** 5-year mortality **~53–74%** in hospitalised cohorts (comparable to or only slightly lower than HFrEF). A higher proportion of deaths are **non-cardiovascular** (32–49%), but cardiovascular death — chiefly **sudden death (~25–30% of all deaths)** and HF death — still predominates. Hospitalisation burden is high and recurrent.

Pathophysiology

- **Diastolic dysfunction** — slowed/incomplete myocardial relaxation (an energy-dependent, active process) plus increased passive chamber stiffness — raises LV diastolic pressure for any given volume; small exertional volume shifts cause steep rises in LA/pulmonary venous pressure → exertional dyspnoea and pulmonary congestion.
- **Comorbidity–inflammation–endothelial dysfunction paradigm (Paulus):** systemic comorbidities (hypertension, obesity, diabetes, CKD, COPD) drive **systemic micro-inflammation** → coronary microvascular endothelial dysfunction → increased reactive oxygen species, reduced nitric-oxide bioavailability, and a **deficient cyclic-GMP–protein-kinase-G (PKG) signalling** state.
- **Reduced PKG** causes cardiomyocyte hypertrophy and **hypophosphorylation of titin** (the giant sarcomeric spring), increasing resting myocyte and chamber stiffness. Inflammation recruits leukocytes secreting **TGF-β**, converting fibroblasts to myofibroblasts → **interstitial collagen deposition and fibrosis** (collagen cross-linking is higher than in HFrEF).
- **Coronary microvascular dysfunction** (reduced coronary flow reserve, CFR <2.0–2.5) is present in up to ~75% of HFpEF — contributing to subendocardial ischaemia and impaired systolic/diastolic reserve.
- **Beyond the ventricle (systemic syndrome):** left-atrial myopathy, chronotropic incompetence, abnormal ventricular–arterial coupling with **increased aortic stiffness**, pulmonary hypertension/RV dysfunction, renal sodium retention, sarcopenic obesity with impaired skeletal-muscle O_2 extraction, and a state of **relative natriuretic-peptide deficiency** (lower BNP for any given filling pressure, worsened by obesity).

Clinical features and diagnosis

- **Symptoms/signs** are similar across the EF spectrum: exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, raised JVP, basal crepitations, S_3/S_4, peripheral oedema, hepatic congestion. Many HFpEF patients are **only symptomatic on exertion**.

- **Diagnosis requires:** (1) a clinical diagnosis of HF, (2) **LVEF >40%**, and (3) objective evidence of elevated filling pressures / structural heart disease — supported by raised natriuretic peptides, echocardiography or **invasive haemodynamics**.
- **Pitfall — natriuretic peptides may be normal: 30–40% of HFpEF (especially obese) patients have BNP/NT-proBNP below diagnostic thresholds**, so a "normal" NP does **not** exclude HFpEF; conversely AF, PE, pulmonary arterial hypertension and CKD raise NP non-specifically.
- **Echocardiography** — concentric LV remodelling (relative wall thickness >0.42), LA enlargement (LA volume index ≥34 mL/m^2), elevated **E/e′**, raised estimated PA systolic pressure, reduced GLS. The **absence of diastolic dysfunction at rest does not exclude HFpEF** — pursue exercise/diastolic stress testing.
- **Grading of diastolic dysfunction (ASE/EACVI; mitral inflow + tissue Doppler):**

Grade	Pattern	Mitral E/A	Average E/e'	LA pressure
Normal	Normal relaxation	≥0.8	<10	Normal
Grade I	**Impaired relaxation**	≤0.8	<10	Low/normal
Grade II	**Pseudonormal**	>0.8 to <2	10–14	Elevated
Grade III	**Restrictive filling**	>2	>14	Elevated

Supportive: peak tricuspid-regurgitation velocity >2.8 m/s, LA volume index >34 mL/m^2.

- **Diagnostic scores** (for the patient with unexplained dyspnoea, normal EF, equivocal workup):
  - **H_2FPEF score** (Mayo): **H**eavy — BMI >30 (2 pts); **H**ypertensive — ≥2 antihypertensives (1); **A**trial **F**ibrillation (3); **P**ulmonary hypertension — PASP >35 mmHg (1); **E**lder — age >60 (1); **F**illing pressure — E/e′ >9 (1). High score makes HFpEF likely; intermediate → proceed to stress test.
  - **HFA-PEFF score** (ESC): **P**retest assessment → **E**chocardiographic + natriuretic-peptide score → **F**unctional testing → **F**inal aetiology. Domains scored 0/1/2; **≥5 diagnostic, ≤1 excludes**, 2–4 → further testing.
- **Invasive haemodynamics (reference standard when in doubt): PCWP ≥15 mmHg at rest**, ≥19 mmHg with passive leg-raise, or **≥25 mmHg during exercise**. Exercise right-heart catheterisation unmasks early HFpEF (exercise-induced LA hypertension).
- **Always exclude HFpEF "masqueraders":** cardiac **amyloidosis** (low voltage with thick walls, bilateral carpal-tunnel, low/falling BP, apical-sparing strain), **hypertrophic cardiomyopathy**, **constrictive pericarditis**, restrictive cardiomyopathy, high-output states, severe valve disease, and non-cardiac causes (obesity, COPD, CKD, anaemia, cirrhosis).

Management

- **Goals:** relieve congestion, improve symptoms/functional capacity, reduce HF hospitalisation, and treat comorbidities (mortality is harder to modify because much of it is non-cardiovascular).
- **1. SGLT2 inhibitors — the only class with proven outcome benefit (foundational, standard of care): empagliflozin (EMPEROR-Preserved)** and **dapagliflozin (DELIVER)** significantly reduce **cardiovascular death/HF hospitalisation across the full EF spectrum**, including LVEF >60% and HFimpEF, with no decline in benefit as EF rises.

- **2. Decongestion with diuretics** — empiric cornerstone for fluid overload (loop ± thiazide; avoid over-diuresis/hypotension in the elderly).
- **3. Mineralocorticoid receptor antagonists — spironolactone (TOPCAT)** was neutral overall (HR 0.89) but showed benefit in the Americas region and in those with EF 45–60% (AHA/ACC/HFSA **class IIb**); the **non-steroidal MRA finerenone (FINEARTS-HF)** reduced CV death/worsening-HF events across HFmrEF–HFpEF. An MRA is reasonable, with potassium/renal monitoring.
- **4. Angiotensin-receptor–neprilysin inhibitor (sacubitril/valsartan, PARAGON-HF)** — just missed significance (rate ratio 0.87, P=0.059); benefit concentrated **below the median EF (~57%) and in women**. FDA-approved for EF "below normal"; **class IIb for HFmrEF**.
- **5. Treat comorbidities:** blood-pressure control (target generally <130 mmHg, but avoid SBP <130 in some HFpEF phenotypes); **AF** rate/rhythm control and anticoagulation; coronary disease; CKD; sleep apnoea; iron deficiency.
- **6. Obesity-HFpEF: GLP-1 receptor agonist semaglutide (STEP-HFpEF)** and the GIP/GLP-1 dual agonist **tirzepatide (SUMMIT)** improve symptoms, quality of life and exercise function.
- **7. Lifestyle:** caloric restriction/weight loss and **supervised exercise/aerobic training** improve exercise capacity and quality of life.
- **No proven role for ICD or CRT** in HFpEF (unlike HFrEF). Beta-blockers and calcium-channel blockers are **not** disease-modifying — used only for BP/rate; consider cautious withdrawal in chronotropic incompetence (PRESERVE-HR).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **LV pressure–volume loop in HFpEF:** plot a normal loop and a HFpEF loop showing an **upward-and-leftward-shifted, steeper end-diastolic pressure–volume relationship (EDPVR)**. Labels: *LV pressure (y-axis)*, *LV volume (x-axis)*, *normal EDPVR*, *stiff/HFpEF EDPVR*, *elevated LV end-diastolic pressure*, *preserved ejection fraction (small stroke volume)*.
- **Mitral-inflow Doppler grades of diastolic dysfunction:** four waveforms side by side — *Normal (E>A)*, *Grade I impaired relaxation (E<A, E/A ≤0.8, prolonged deceleration time)*, *Grade II pseudonormal (E/A 0.8–2)*, *Grade III restrictive (E/A >2, short deceleration time)*. Label *E wave*, *A wave*, *deceleration time*.

Clinical / Diagnostic significance

- A normal EF on echo does **not** exclude HF — the syndrome can exist entirely on a diastolic/filling-pressure basis; this is the single most important teaching point.
- A **normal natriuretic peptide does not rule out HFpEF**, particularly in obesity — use the H_2FPEF/HFA-PEFF scores and exercise haemodynamics.
- **Exercise/diastolic stress testing** is key to unmasking early HFpEF when resting studies are equivocal.
- Always screen for treatable mimics — **ATTR cardiac amyloidosis** (now treatable with tafamidis) and constrictive pericarditis (curable by pericardiectomy) — before labelling "idiopathic" HFpEF.

- **SGLT2 inhibitors have transformed management** from purely empiric (diuretics) to an evidence-based foundational therapy benefiting the whole EF spectrum.

High-yield exam pointers

- HFpEF = HF with **LVEF >40%** (HFpEF ≥50%, HFmrEF 41–49%); ~**half** of all HF.
- Cardinal defect: **raised LV/LA filling pressure** from impaired relaxation + reduced compliance (stiff ventricle), normal cavity size.
- Diagnostic triad: **clinical HF + EF >40% + objective high filling pressures/structural disease** (NP, echo, or invasive PCWP ≥15 rest / ≥25 exercise).
- Remember the **H_2FPEF** and **HFA-PEFF** scores by name and components.
- Diastolic-dysfunction echo grades: **I impaired relaxation, II pseudonormal, III restrictive** (E/A and E/e′ cut-offs); E/e′ >14 and LAVI >34 mL/m^2 signify high LA pressure.
- Pathophysiology buzz-words: **comorbidity-driven systemic inflammation → microvascular endothelial dysfunction → cGMP–PKG deficiency → titin hypophosphorylation + interstitial fibrosis**.
- Outcome-positive therapy = **SGLT2 inhibitors (empagliflozin/dapagliflozin)**; everything else (ACEi/ARB/ARNI/spironolactone/β-blocker/CCB) is largely neutral — diuretics for congestion, finerenone/ARNI and MRA as class IIb adjuncts.
- **Obesity-HFpEF:** semaglutide and tirzepatide improve symptoms; **no role for ICD/CRT**.
- Negative landmark trials to quote: **PEP-CHF, CHARM-Preserved, I-PRESERVE, TOPCAT, PARAGON-HF**; positive: **EMPEROR-Preserved, DELIVER, FINEARTS-HF**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Heart Failure: Pathophysiology and Diagnosis"* and *"Heart Failure: Management"* (EF-based phenotype definitions; systolic vs diastolic terminology).
- **Braunwald's Heart Disease, 13e** — *"Heart Failure With Preserved or Mildly Reduced Ejection Fraction"* (epidemiology, risk factors, diagnostic scores H_2FPEF/HFA-PEFF, invasive haemodynamics, comorbidity-inflammation pathophysiology, full trial evidence: TOPCAT, PARAGON-HF, EMPEROR-Preserved, DELIVER, FINEARTS-HF, PRESERVE-HR) and *"Echocardiography"* (grading of LV diastolic dysfunction, Table 14.4).
- **CMDT 2026** — *"Heart Failure & Cardiomyopathy"* (current management: SGLT2 inhibitors as the mainstay, GLP-1/tirzepatide for obesity-HFpEF, role of ATTR amyloid screening; STEP-HFpEF, SUMMIT).

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Differential diagnosis of mid-diastolic murmurs

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — A **mid-diastolic murmur (MDM)** is a low-frequency murmur that begins a short interval *after* the second heart sound (S2) — characteristically after the **opening snap (OS)** or a third heart sound (S3) — and occupies the rapid-filling phase of diastole. MDMs arise from **obstruction to, and/or augmented flow across, an atrioventricular (mitral or tricuspid) valve**, so the gradient driving them is the low-pressure atrioventricular diastolic gradient. They are best appreciated with the **bell** of the stethoscope, are easily missed, and — unlike most systolic murmurs — *almost always signify organic cardiac disease*. **Mitral stenosis (MS)** is the prototype and commonest cause.

Mechanism, genesis and how to recognise an MDM

- Two physiological substrates generate an MDM: (1) **obstruction** at the mitral/tricuspid orifice (a true diastolic pressure gradient), or (2) **increased antegrade transvalvular flow** across an anatomically normal valve (a "functional" or "flow" murmur).
- Timing: the murmur follows S2 by a measurable interval. In obstructive lesions it is introduced by an **OS** (MS, tricuspid stenosis); in high-flow lesions it is introduced by an **S3** (rapid-filling sound).
- The **duration** of the rumble reflects how long the atrial pressure exceeds ventricular diastolic pressure, and so correlates with severity (when output is preserved).
- **Presystolic accentuation** — a late-diastolic crescendo just before S1 due to atrial contraction augmenting transvalvular flow — is characteristic of MS/TS *in sinus rhythm* and is **lost in atrial fibrillation (AF)**.
- Bedside amplification: **left lateral decubitus** position, **bell with light pressure**, and a brief bout of **exercise** (sit-ups) bring out a soft mitral rumble; **inspiration** augments right-sided (tricuspid) MDMs.

Structured differential diagnosis of mid-diastolic murmurs

Site	Obstructive (true stenosis)	Increased-flow ("functional")	Other
Mitral	Rheumatic **mitral stenosis** (commonest); congenital MS, cor triatriatum; severe mitral annular calcification; large vegetation	Severe **MR**, **VSD**, **PDA**, high-output states (anaemia, thyrotoxicosis, pregnancy), complete heart block	**Carey-Coombs** murmur (acute rheumatic carditis); **Austin Flint** murmur (severe/eccentric AR); **left atrial myxoma** (tumour plop)
Tricuspid	Rheumatic **tricuspid stenosis** (almost never isolated; accompanies MS)	Severe **TR**, large **ASD**, anomalous pulmonary venous return	**Right atrial myxoma**

- *Aide-mémoire — causes at the mitral valve:* **"MS, MR-flow, Carey-Coombs, Austin Flint, Myxoma, Complete heart block."**
- The **Graham Steell** murmur (pulmonary regurgitation of pulmonary hypertension) and chronic **aortic regurgitation** are *early-to-mid* diastolic, decrescendo and high-pitched; they are listed here only because they can be confused with an MDM heard along the left sternal border, but they are not true mid-diastolic rumbles.

Mitral stenosis — the prototype mid-diastolic murmur

- **Cause:** rheumatic fever in the vast majority; pure/predominant MS occurs in ~40% of rheumatic heart disease. Normal mitral orifice is **4–6 cm²**; symptoms appear when area falls below ~2 cm²; **severe MS = valve area <1.5 cm²** (a left atrial pressure of ~25 mmHg is then needed to maintain output).
- **Murmur:** low-pitched, **rumbling**, mid-diastolic, loudest at the **apex** in the left lateral decubitus position, beginning after the OS; **presystolic accentuation** in sinus rhythm.
- **Accompanying signs (a complete auscultatory complex):** loud (and slightly delayed) **S1**; an **OS** after A2 — the **A2–OS interval (0.05–0.12 s) varies *inversely* with severity** (a short A2–OS interval = tight MS); loud/palpable **P2** when pulmonary hypertension supervenes.
- **Duration** of the rumble (not loudness) tracks severity; the murmur may be **inaudible ("silent MS")** when cardiac output is very low or the patient is large/obese.
- Supporting evidence: **mitral facies (malar flush)**, AF, prominent jugular *a* wave (if pulmonary hypertension/TS), parasternal lift (RV enlargement), left atrial enlargement on ECG (P-mitrale) and CXR (straightened left heart border, Kerley B lines), and Doppler echo (gradient, planimetered area, suitability for **percutaneous mitral balloon commissurotomy**).

Other mitral mid-diastolic murmurs

- **Increased-flow ("functional MS") murmur:** severe **MR**, a large left-to-right shunt (**VSD, PDA**), high-output states or **complete heart block** drive excessive flow across a non-stenotic mitral valve, producing a soft rapid-filling **S3 followed by a short MDM**. *No OS, no presystolic accentuation*; an apical pansystolic murmur and signs of LV enlargement point to MR as the substrate.
- **Carey-Coombs murmur:** a soft, transient apical MDM of **acute rheumatic carditis**, attributed to flow through an **oedematous, inflamed mitral valve**. *No OS*, soft S1, and the murmur **dissipates as the acute attack resolves** — a clue to active rheumatic activity rather than established stenosis.
- **Austin Flint murmur:** a low-pitched **mid-to-late apical diastolic rumble of severe (or eccentric) chronic AR**, produced by turbulence at the mitral inflow from admixture of the regurgitant aortic jet and forward mitral flow (and partial premature closure of the anterior mitral leaflet). Distinguished from MS by **absence of an OS** and by its **response to vasodilators** (see below).
- **Left atrial myxoma:** a pedunculated tumour arising near the **fossa ovalis of the interatrial septum** prolapses across the mitral valve in diastole, obstructing inflow and mimicking MS. Auscultation may reveal an early/mid-diastolic **"tumour plop"**; characteristically there is **positional variation** (murmur/symptoms change with body position), *no OS and no presystolic accentuation*. Suspect with constitutional features — fever, weight loss, anaemia, raised ESR/CRP, high IL-6, systemic emboli; familial cases occur in the **Carney complex** (*PRKAR1A* mutation). TTE/TEE is diagnostic.
- **Complete heart block:** intermittent mid-to-late diastolic murmurs occur when atrial contraction falls while the mitral valve is partially closed (atrioventricular dissociation).

Tricuspid mid-diastolic murmurs

- **Tricuspid stenosis (TS):** almost never isolated — it accompanies rheumatic MS. The MDM is at the **lower left sternal border / 4th left intercostal space**, is **softer, higher-pitched and shorter** than MS, and crucially **increases with inspiration** (*Carvallo's sign*) and other manoeuvres that raise trans-tricuspid flow. JVP shows a **giant *a* wave** and a **slow/delayed *y* descent**; a diastolic thrill may be palpable at the LLSB. A tricuspid OS may follow the mitral OS. Suspect TS in a patient with "MS" who has marked right heart signs **without pulmonary hypertension**.
- **Increased tricuspid flow:** severe **TR**, a large **ASD** (left-to-right shunt) or anomalous pulmonary venous return produce a **tricuspid flow MDM**, again inspiration-augmented; fixed splitting of S2 and a pulmonary mid-systolic flow murmur point to an ASD.

Bedside differentiation (dynamic auscultation)

Feature	Mitral stenosis	Austin Flint (severe AR)	Carey-Coombs	LA myxoma	Tricuspid MDM
Opening snap	**Present**	Absent	Absent	Absent (tumour plop)	Tricuspid OS may be present
Presystolic accentuation	Yes (sinus rhythm)	No	No	No	Yes (sinus rhythm)
Inspiration	Unchanged/softer	Unchanged	Unchanged	Variable	**Louder (Carvallo)**
Amyl nitrite / vasodilator	Murmur **louder** (↑ output, ↑ flow)	Murmur **softer & shorter**	—	—	Louder
Positional change	Left lateral decubitus accentuates	—	—	**Changes with body position**	Right lateral decubitus accentuates

- The **vasodilator (amyl nitrite) test** is the classic discriminator between MS and Austin Flint: lowering afterload **shortens and softens the Austin Flint murmur** but **increases the MS rumble** (reflex rise in output and transmitral flow).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Phonocardiogram of the cardiac cycle** showing, against S1 and S2: (a) the MS complex — loud **S1**, **A2–P2**, **opening snap (OS)**, low-pitched **mid-diastolic rumble** with **presystolic accentuation** to S1; and (b) a separate trace of an **S3 followed by a short flow MDM**. Label: *S1, A2, P2, OS, S3, mid-diastolic rumble, presystolic accentuation.*
- **Precordial map of murmur location:** mark the **apex (left lateral decubitus, bell)** for the mitral rumble and the **lower left sternal border (4th ICS, inspiration)** for the tricuspid MDM. Label: *apex – MS rumble; LLSB – tricuspid murmur; aortic area / LSB – AR (Austin Flint at apex).*

Clinical / Diagnostic significance

- Recognising an MDM and its accompaniments (loud S1, OS, presystolic accentuation, AF, mitral facies) allows a **bedside diagnosis of MS** and stratifies severity (short A2–OS interval, long rumble = tight valve).
- **Transthoracic echocardiography with Doppler is indicated for any diastolic murmur** — it confirms the lesion, quantifies the gradient and orifice area, assesses pulmonary pressures, excludes left atrial thrombus/myxoma, and judges suitability for **balloon valvuloplasty vs surgery**.
- An MDM in a febrile young patient with arthritis suggests **active rheumatic carditis (Carey-Coombs)**; an MDM with constitutional/embolic features and positional change suggests **atrial myxoma**; an apical rumble with wide pulse pressure and a water-hammer pulse suggests **Austin Flint of severe AR**.
- Misattributing a flow MDM (severe MR, large shunt) to organic stenosis is a common error — the absence of an OS and the presence of an S3/dominant systolic lesion are the corrective clues.

High-yield exam pointers

- MDM = **obstruction or increased flow at an AV valve**; best heard with the **bell**, after the OS (obstruction) or S3 (flow).
- **Commonest cause = rheumatic MS**; severe MS = orifice **<1.5 cm²** (normal 4–6 cm^2).
- **A2–OS interval is inversely proportional to severity** of MS; **presystolic accentuation is lost in AF**.
- **Carey-Coombs** = transient apical MDM of **acute rheumatic carditis**; no OS, resolves with the attack.
- **Austin Flint** = apical MDM of **severe AR**; differentiated from MS by **no OS** and **softening with amyl nitrite/vasodilator** (MS rumble gets louder).
- **Atrial myxoma** = **tumour plop**, positional variation, constitutional symptoms, *PRKAR1A*/Carney complex; diagnosed on echo.
- **Tricuspid MDM (TS)** is heard at the **LLSB, louder on inspiration (Carvallo's sign)**, with a giant *a* wave and slow *y* descent; rarely isolated.
- "**Functional**" MDMs of increased flow: severe **MR, VSD, PDA, ASD, severe TR, complete heart block, high-output states** — no OS, preceded by an S3.

- **Every diastolic murmur warrants echocardiography**; diastolic murmurs are almost never innocent.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Approach to the Patient with a Heart Murmur" (mid-diastolic murmur differential, Carey-Coombs, Austin Flint, dynamic auscultation, amyl-nitrite discrimination); "Mitral Stenosis" (etiology, orifice areas, A2–OS interval, silent MS, differential from AR/TS/ASD/myxoma); "Atrial Myxoma and Other Cardiac Tumors" (tumour plop, Carney complex, *PRKAR1A*).
- **Braunwald's Heart Disease, 13e** — "History, Physical Examination, and the Virtual Visit" (Table of principal heart murmurs and mid-diastolic causes; presystolic accentuation; dynamic-auscultation manoeuvres) and "Tricuspid, Pulmonic, and Multivalvular Disease" (tricuspid stenosis murmur, Carvallo's sign, OS, severity).
- **CMDT 2026** — Cardiology chapter (current management context for valvular MS/TS).

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Heart failure with preserved ejection fraction

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Heart failure with preserved ejection fraction (**HFpEF**) is the clinical syndrome of heart failure (typical symptoms/signs of congestion — dyspnoea, fatigue, oedema) occurring in a patient whose left-ventricular ejection fraction (**LVEF**) is *preserved* (≥50%), in the presence of objective evidence of cardiac structural/functional abnormality and raised cardiac filling pressures at rest or on exertion. It accounts for roughly **half of all heart failure** and is increasing in relative frequency with population ageing. Although the dominant lesion is impaired LV diastolic function, HFpEF is now recognised as a **systemic, multi-organ syndrome** driven by comorbidity-related inflammation, not merely a "diastolic" problem.

Nomenclature, classification and epidemiology

- The universal EF-based classification (Harrison 22e): **HFrEF = EF ≤40%; HF with mildly reduced EF (HFmrEF) = EF 41–49%; HFpEF = EF ≥50%.** Major trials variably used EF >40% or >45%; current guidelines reserve "HFpEF" for **LVEF ≥50%**.
- HFpEF comprises ~50% of prevalent HF and HFmrEF a further ~10–25%; prevalence rises with age and is **higher in women** at any given age (largely because women out-live men).
- **Predominant risk factors / comorbidities:** older age, **hypertension** (LV hypertrophy), **obesity / visceral adiposity**, **diabetes**, atrial fibrillation, chronic kidney disease, COPD and sleep apnoea. Obesity and AF are particularly characteristic.
- **Atrial fibrillation** coexists in 20–40% at presentation and occurs in two-thirds at some point; its onset frequently precipitates decompensation.
- **Prognosis:** mortality is high (5-year mortality ~50–70% in hospitalised cohorts), only modestly lower than HFrEF, with a *higher proportion of non-cardiovascular deaths*; hospitalisation burden equals or exceeds HFrEF.

Pathophysiology (relevant to diagnosis and therapy)

- **Cardinal abnormality:** elevation of LV end-diastolic pressure and left-atrial pressure (raised PCWP) at rest or, characteristically, **only on exertion**, producing exertional dyspnoea with preserved systolic ejection.
- Beyond impaired relaxation and reduced LV chamber compliance: **longitudinal systolic dysfunction** (reduced GLS, low tissue-Doppler s′), **left-atrial myopathy**, chronotropic incompetence, abnormal ventricular–arterial coupling and aortic stiffening.
- **Comorbidity → systemic inflammation → endothelial dysfunction paradigm:** reduced nitric-oxide bioavailability lowers cGMP–protein kinase G (PKG) signalling → **titin hypophosphorylation and cardiomyocyte stiffening**, interstitial fibrosis (TGF-β–driven collagen deposition) and **coronary microvascular dysfunction** (reduced coronary flow reserve in up to ~75%).
- This multi-organ model (heart, lungs, kidney, skeletal muscle, adipose tissue) explains why isolated "diastolic dysfunction" on echo is neither necessary nor sufficient for diagnosis.

Diagnostic approach

Diagnosis requires **(1) a clinical diagnosis of HF AND (2) LVEF ≥50%** (≥40% if including HFmrEF), supported by objective evidence of elevated filling pressures or structural disease, and **exclusion of non-cardiac mimics** (obesity, COPD, CKD, cirrhosis, anaemia, pericardial constriction).

- **Supportive evidence:** raised natriuretic peptides; structural change (LA enlargement, LVH); echo Doppler (increased E/e′, dilated IVC); or invasive haemodynamics.
- **Pitfall — natriuretic-peptide deficiency:** ~30–40% of HFpEF have BNP/NT-proBNP *below* usual diagnostic thresholds (NP levels are lower than in HFrEF, and are further reduced by obesity); a normal NP **does not exclude** HFpEF in a patient with high pre-test probability.
- **Diastolic dysfunction on echo alone is insufficient** — it is common in asymptomatic elderly, often indeterminate (E/e′ 8–15), and may be normal at rest yet abnormal on exercise. Absence does not exclude HFpEF.
- When non-invasive tests are equivocal, proceed to **provocative testing** — diastolic stress echo or, the *reference standard*, **invasive exercise haemodynamics**.

Diagnostic scoring systems

Score	Source / components	Interpretation
H2FPEF (Mayo)	**H**eavy: BMI >30 (2); **H**ypertensive: ≥2 antihypertensives (1); atrial **F**ibrillation (3); **P**ulmonary HTN: echo PASP >35 mmHg (1); **E**lder: age >60 yr (1); **F**illing pressure: E/e′ >9 (1). Range 0–9	Higher score = higher probability (AUC ~0.84). Low 0–1; intermediate 2–5 → exercise testing; high 6–9
HFA-PEFF (ESC)	**P**re-test → **E**cho + NP → **F**unctional testing → **F**inal aetiology. Functional, morphological and NP domains (major = 2 pts, minor = 1 pt)	**≥5 points = diagnostic**; **<2 = excludes**; 2–4 = intermediate → functional/invasive testing

Key investigations

- **Natriuretic peptides** (BNP/NT-proBNP) — diagnostic and strongly prognostic; use NT-proBNP if on sacubitril/valsartan.
- **Comprehensive echocardiography** — concentric LV remodelling (relative wall thickness >0.42), LA volume index ≥34 mL/m^2, E/e′, TR velocity / estimated PA systolic pressure, and **global longitudinal strain** (normal absolute GLS >18%, abnormal <16%); apical-sparing strain pattern suggests amyloidosis.
- **High-sensitivity troponin** — persistent low-level elevation flags an infiltrative/"myocardial" phenotype (amyloid, HCM) or microvascular ischaemia.
- **Cardiac MRI** — tissue characterisation: late gadolinium enhancement, T1 mapping/extracellular volume (fibrosis, amyloid), T2* (iron), pericardial assessment.
- **Invasive haemodynamics (gold standard when in doubt):** PCWP **≥15 mmHg at rest, ≥19 mmHg with passive leg raise, or ≥25 mmHg during exercise** (or PCWP/cardiac-output slope ≥2.0) confirms HFpEF.
- **Screen for "masqueraders":** cardiac amyloidosis (immunofixation, free light chains, prealbumin, bone scintigraphy/biopsy), HCM, constrictive pericarditis, high-output states, Fabry, sarcoidosis, haemochromatosis, valvular disease.

Management

There is no single mortality-lowering drug; therapy targets **decongestion, the one outcome-proven drug class (SGLT2 inhibitors), aggressive comorbidity control and symptom/QOL improvement.**

Class	Key drugs / trials	Status & comment
SGLT2 inhibitors	**Empagliflozin — EMPEROR-Preserved; Dapagliflozin — DELIVER**	**Cornerstone, outcome-proven** — reduce CV death/HF hospitalisation across the full EF spectrum (incl. >60%); benefit independent of diabetes. ESC class I
Loop ± thiazide diuretics	Furosemide; add HCTZ/metolazone if refractory	**Empiric mainstay for congestion**; avoid over-diuresis (under-filling → azotaemia, hypotension, syncope)
MRA	**Spironolactone — TOPCAT** (HR 0.89, neutral overall; benefit in the Americas and EF 45–60%); **Finerenone — FINEARTS-HF** (positive)	Consider in addition to loop diuretic; monitor K^+/renal function. Spironolactone class IIb
ARNI	**Sacubitril/valsartan — PARAGON-HF** (HR 0.87, p≈0.06, *just missed*); benefit in EF below median (~57%) and in women	FDA expanded approval / class IIb, chiefly for **HFmrEF and EF below normal**
ACEi / ARB	Perindopril (PEP-CHF), Candesartan (CHARM-Preserved), Irbesartan (I-PRESERVE) — all neutral for true HFpEF	Use for comorbid hypertension/CKD/diabetes, not for HFpEF outcomes per se
GLP-1 receptor agonists	**Semaglutide — STEP-HFpEF / STEP-HFpEF DM; Tirzepatide — SUMMIT**	In **obesity-related HFpEF**: weight loss, improved KCCQ/exercise capacity, lower NT-proBNP/CRP

Class	Key drugs / trials	Status & comment
β-blockers / non-dihydropyridine CCB	—	Neutral for HFpEF outcomes; useful for **AF rate control**; withdraw if chronotropic incompetence limits exertion

Other management priorities

- **Blood pressure:** treat to guideline targets (SPRINT supports <130 mmHg systolic), though some HFpEF data suggest an optimal range of ~130–140 mmHg; central aortic control is relevant.
- **Atrial fibrillation:** rate control (in AF-HFpEF target resting rate ~70–80 bpm to preserve filling), **anticoagulation** (high thromboembolic risk), and early consideration of **rhythm control/ablation** in symptomatic patients.
- **Comorbidities:** treat obesity, diabetes, CKD, iron deficiency, COPD and **sleep apnoea**; maintain euvolaemia.
- **Specific aetiologies: tafamidis** for transthyretin (ATTR) cardiac amyloidosis; chemotherapy for AL amyloid; mavacamten / septal reduction for obstructive HCM; revascularisation for ischaemia.
- **Exercise training / cardiac rehabilitation** — improves peak VO_2, 6-minute-walk distance and quality of life; sodium and fluid restriction in fluid overload.
- **Devices: ICD and CRT are NOT indicated** for EF >40%. Implantable PA-pressure monitoring (**CardioMEMS — CHAMPION**) reduces HF events in frequently hospitalised patients. **Interatrial shunt devices** failed in the pivotal trial (possible harm if EF >40%).
- **Ineffective / unsuccessful in HFpEF:** PDE-5 inhibitors (sildenafil), organic and inorganic **nitrates** (NEAT — isosorbide mononitrate worsened activity), **ivabradine** (EDIFY), vericiguat, and digoxin (may reduce hospitalisations only).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology cascade of HFpEF:** label *Comorbidities (HTN, obesity, diabetes, CKD) → systemic inflammation → coronary microvascular endothelial dysfunction → ↓NO–cGMP–PKG → titin hypophosphorylation (cardiomyocyte stiffness) + interstitial fibrosis → ↑LV diastolic stiffness → ↑LVEDP/↑LA pressure → ↑PCWP (rest/exertion) → exertional dyspnoea.*
- **Diagnostic algorithm box:** *Symptoms/signs of HF + LVEF ≥50% → natriuretic peptides + echo (E/e', LA volume index ≥34 mL/m², GLS, PASP) → calculate H2FPEF / HFA-PEFF → if intermediate, diastolic stress echo or invasive exercise haemodynamics (PCWP ≥15 rest / ≥25 exercise) → exclude masqueraders (amyloid, HCM, constriction).*

Clinical / Diagnostic significance

- A **normal natriuretic peptide and a normal resting echo do not exclude HFpEF** — exertional/invasive testing is the key to "early" or "exercise-induced" HFpEF.
- Recognising **cardiac amyloidosis** (bilateral carpal tunnel syndrome, low-voltage ECG with thick walls, persistent troponin elevation, apical-sparing strain) is critical — it changes therapy (avoid non-dihydropyridine CCBs; use tafamidis) and prognosis.

- SGLT2 inhibitors are the **first and only class proven to improve outcomes across the entire EF spectrum**, making them standard of care in HFpEF as in HFrEF.
- Most "HFpEF therapy" is in reality **comorbidity and congestion management**; weight loss in obese HFpEF (GLP-1 RA) is an emerging disease-modifying strategy.

High-yield exam pointers

- **HFpEF = EF ≥50%; HFmrEF = 41–49%; HFrEF = ≤40%** — memorise the universal definition cut-offs.
- Diagnosis = **HF syndrome + preserved EF + raised filling pressures/structural disease + exclusion of mimics.**
- **H2FPEF** (Heavy, Hypertensive, atrial Fibrillation, Pulmonary HTN, Elder, Filling pressure) and **HFA-PEFF** (≥5 diagnostic, <2 excludes) are the two scores.
- **Invasive PCWP ≥15 (rest) / ≥19 (leg raise) / ≥25 mmHg (exercise)** is the haemodynamic gold standard.
- **~30–40% of HFpEF have natriuretic-peptide deficiency**, especially with obesity.
- **SGLT2 inhibitors (empagliflozin/EMPEROR-Preserved, dapagliflozin/DELIVER)** — only outcome-proven class; **diuretics** for congestion.
- Adjuncts: **MRA (TOPCAT/FINEARTS-HF), ARNI (PARAGON-HF) for lower-EF/women, GLP-1 RA (STEP-HFpEF) for obesity.**
- **ICD/CRT have no role** in HFpEF; treat AF with rate control + anticoagulation; consider **tafamidis** for ATTR amyloid.

SOURCE & COVERAGE

- **Braunwald's Heart Disease 13e — "Heart Failure With Preserved or Mildly Reduced Ejection Fraction"** (Lam, Shah, Solomon): epidemiology, H2FPEF/HFA-PEFF scores, invasive haemodynamic thresholds, phenotypes, and the full HFpEF/HFmrEF trial evidence (TOPCAT, FINEARTS-HF, PARAGON-HF, EMPEROR-Preserved, DELIVER, STEP-HFpEF, SUMMIT).
- **Harrison's Principles of Internal Medicine 22e — "Heart Failure: Pathophysiology and Diagnosis"** and **"Heart Failure: Management"**: EF-based classification and HFpEF guiding management principles.
- **CMDT 2026 — "Heart Failure & Cardiomyopathy"**: current management of HF with preserved LVEF (SGLT2 inhibitors and diuretics as mainstays; GLP-1 RA/tirzepatide in obesity; ATTR amyloid screening).

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STEMI (ST-elevation myocardial infarction)

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — STEMI is an acute coronary syndrome due to abrupt severe myocardial ischemia with necrosis, usually from complete thrombotic occlusion of an epicardial coronary artery. It is diagnosed by ischemic symptoms or equivalents, diagnostic ST-segment elevation in contiguous leads, and rise/fall of cardiac troponin above the 99th percentile; reperfusion must not wait for biomarkers when the ECG is diagnostic. It is an emergency because early mortality is dominated by ventricular fibrillation and later in-hospital mortality by pump failure.

Etiology and pathogenesis

- **Commonest cause - type 1 atherothrombotic MI:** rupture or erosion of an atherosclerotic plaque, often lipid-rich with a thin fibrous cap, in a coronary artery previously affected by atherosclerosis. Smoking, hypertension, LDL accumulation, diabetes, and inflammation promote endothelial dysfunction, vulnerable plaque, and thrombogenic blood.
- **Thrombus biology:** plaque disruption exposes collagen and tissue factor; platelet agonists (collagen, ADP, epinephrine, serotonin) trigger thromboxane A2 release, GP IIb/IIIa activation, platelet aggregation, thrombin generation, and fibrin deposition, producing an occlusive platelet-fibrin thrombus.
- **Predisposing / precipitating factors:** multiple CAD risk factors, unstable angina, vigorous exercise, emotional stress, medical or surgical illness, morning catecholamine/cortisol and platelet-aggregability surge, infection, hypoxemia, pulmonary embolism, fever, tachycardia, hypotension, severe aortic stenosis, cocaine, and sympathomimetics.
- **Less common etiologies:** coronary embolism, congenital coronary abnormality, coronary spasm/Prinzmetal angina, spontaneous coronary artery dissection, vasculitis, aortitis, aortic root/coronary dissection, hypercoagulable states, collagen vascular disease, systemic inflammatory disease, and intracardiac thrombi/masses.
- **Infarct size depends on:** vascular territory, totality and duration of occlusion, collateral flow, myocardial oxygen demand, spontaneous lysis, speed of reperfusion, and microvascular obstruction/no-reflow from endothelial injury, leukocyte-platelet activation, thrombotic debris, edema, and cardiomyocyte swelling.

Clinical manifestations

- **Premonitory pain:** accelerating angina or rest angina may precede infarction; onset is often at rest and more common in the early morning.
- **Classical pain:** prolonged (>30 minutes) deep central chest or epigastric discomfort, heavy/squeezing/crushing, occasionally burning or stabbing; more severe than angina, poorly relieved by rest or nitroglycerin, and radiating to arms, shoulder, back, jaw, neck, or occiput.
- **Associated symptoms:** sweating, nausea, vomiting, anxiety, weakness, dyspnea, orthopnea, cough/wheeze, light-headedness, syncope, and sense of impending doom.
- **Atypical / painless STEMI:** commoner in older adults, women, diabetes mellitus, and transplant recipients; may present as acute heart failure, syncope, confusion, profound weakness, arrhythmia, embolism, shock, or sudden death.

- **Physical findings:** anxious restless patient, pallor, diaphoresis, cool extremities; anterior MI may cause tachycardia/hypertension, inferior MI bradycardia/hypotension. S4 is common; S3 suggests LV dysfunction. Other signs include soft S1, paradoxical split S2, apical systolic murmur of MR, pericardial rub later, low-volume carotid pulse, and low-grade fever after 12 hours.
- **RV infarction clue:** inferior STEMI with hypotension, raised JVP/Kussmaul sign, hepatomegaly, and clear lungs; confirm with V4R ST elevation and echocardiography.

Diagnosis and risk assessment

- **ECG first:** obtain and interpret a 12-lead ECG within 10 minutes of first medical contact; start continuous monitoring and IV access. Add V3R/V4R for inferior/RV infarction and V7-V9 for suspected posterior occlusion.
- **STEMI ECG criteria:** new ST elevation at the J point in at least two contiguous leads: >=1 mm in all leads except V2-V3; in V2-V3, >=2 mm in men >=40 years, >=2.5 mm in men <40 years, and >=1.5 mm in women. New LBBB with compatible ischemia is treated as a STEMI equivalent when occlusion criteria are present.
- **Biomarkers:** high-sensitivity troponin I/T are preferred; acute MI requires rise/fall with at least one value above the 99th percentile plus ischemic evidence. Troponin remains elevated for 5-10 days; CK-MB helps suspected early reinfarction because it falls sooner.
- **Supportive tests:** leukocytosis may reach 12,000-15,000/microliter; check glucose, creatinine, electrolytes, lipids, and bleeding risk. CXR helps detect congestion and alternative diagnoses such as aortic dissection.
- **Echocardiography:** documents regional wall motion abnormality, LVEF, RV infarction, papillary muscle dysfunction/rupture, VSD, pericardial effusion, LV aneurysm, and LV thrombus.
- **Risk markers:** Killip class, persistent ischemia, shock, LVEF <40%, pulmonary congestion, age >75, diabetes, prior MI, tachycardia, hypotension, ventricular arrhythmias, renal dysfunction, and nonpatent infarct-related artery.

Initial and reperfusion management

- **Prehospital care:** educate high-risk patients, activate EMS, obtain prehospital ECG, transport rapidly to a STEMI network, and ensure defibrillation capability because most early deaths are arrhythmic.
- **Emergency measures:** cardiac monitor, IV access, aspirin loading, analgesia, baseline bloods, rapid reperfusion decision. Give oxygen only for SaO2 <90% or heart failure.
- **Anti-ischemic / analgesic therapy:** chew aspirin 160-325 mg immediately, then 75-162 mg daily. Give sublingual nitroglycerin 0.4 mg every 5 minutes for up to three doses if pain persists; avoid in SBP <90 mmHg, RV infarction, severe aortic stenosis, or recent PDE5 inhibitor use. IV nitroglycerin is used for ongoing ischemia, hypertension, or heart failure with BP monitoring. Morphine 2-4 mg IV repeated cautiously relieves refractory pain.
- **Primary PCI:** preferred when timely. Perform for symptoms <=12 hours and for later presentation with ongoing ischemia, shock, acute severe heart failure, or life-threatening arrhythmia. Aim FMC-to-device <=90 minutes at a PCI-capable centre; transfer if anticipated

FMC-to-device <=120 minutes. Stable multivessel disease may undergo staged nonculprit PCI during admission or up to 45 days; in cardiogenic shock, do culprit-only PCI initially.

- **Fibrinolysis:** if PCI cannot be achieved within 120 minutes and no contraindication exists, give within 12 hours of symptom onset, ideally door-to-needle <=30 minutes. Options: alteplase 15 mg bolus then 50 mg/30 min then 35 mg/60 min; streptokinase 1.5 million units/1 h; reteplase 10 units bolus repeated at 30 min; tenecteplase weight-based IV bolus.
- **Contraindications to lysis:** prior hemorrhagic stroke, ischemic stroke/cerebrovascular event within 1 year, intracranial neoplasm, recent head trauma, active internal bleeding, suspected aortic dissection, and severe uncontrolled BP >180/110 mmHg. Relative contraindications include anticoagulation with high INR, recent major surgery/trauma, prolonged traumatic CPR, bleeding diathesis, pregnancy, active peptic ulcer, hemorrhagic retinopathy, and recent streptokinase exposure/allergy.
- **After lysis:** reperfusion is suggested by pain relief and >=50% ST resolution at 60-90 minutes. Persistent pain/ST elevation or reocclusion requires rescue PCI. Even after successful lysis, transfer for angiography and PCI if indicated, usually 3-24 hours after fibrinolysis.

Pharmacotherapy and hospital care

Therapy	Must-write points
P2Y12 inhibitor	Add to aspirin for all STEMI, usually 12 months. PCI: ticagrelor or prasugrel preferred over clopidogrel; avoid prasugrel after stroke/TIA and generally in age >75. Fibrinolysis: clopidogrel is standard.
Anticoagulation	UFH for primary PCI and with fibrin-specific lysis: 60 U/kg bolus, max 4000 U, then 12 U/kg/h, max 1000 U/h, adjusted to aPTT target. Enoxaparin is an alternative after lysis; fondaparinux must not be the sole anticoagulant during PCI.
Beta-blocker	Start oral therapy within 24 hours if no heart failure, low output, shock risk, bradycardia, heart block, asthma, or hypotension. IV metoprolol 5 mg x3 only in selected stable patients with ongoing ischemia.
RAAS blockade	Start ACE inhibitor early when stable, especially anterior MI, HF, LVEF <=40%, diabetes, hypertension, prior MI, or large wall motion abnormality; use ARB if intolerant. Add eplerenone/spironolactone if LVEF <=40% plus HF or diabetes without renal dysfunction/hyperkalemia.
Statin / supportive care	High-intensity statin before discharge. Correct K to about 4.5 mmol/L and Mg to about 2.0 mmol/L. Avoid routine calcium channel blockers, glucocorticoids, and NSAIDs other than aspirin.

- Admit unstable or high-risk patients to cardiac ICU/coronary care. Uncomplicated STEMI: bed rest 6-12 hours, sit out within 24 hours, ambulate progressively, step down after 24-48 hours, discharge commonly by day 3-5.

Complications and secondary prevention

- **LV failure / shock:** treat hypoxemia, pulmonary edema with loop diuretic and nitrates if BP permits, urgent echo, cautious inotrope/vasopressor, hemodynamic monitoring when useful, and urgent culprit revascularization. Norepinephrine is commonly preferred in shock; routine IABP has not improved outcomes.

- **RV infarction:** avoid nitrates and diuretics; give cautious saline to maintain preload and inotrope only if needed.
- **Arrhythmias:** immediate defibrillation for VF/unstable VT; IV amiodarone for sustained tolerated VT; AIVR after reperfusion is usually benign; atropine/pacing for symptomatic bradycardia.
- **Mechanical complications:** VSD, papillary muscle rupture with acute MR, and LV free-wall rupture typically occur within 1-14 days, especially 24 hours and 3-5 days. New murmur, pulmonary edema, shock, tamponade, or electromechanical dissociation requires urgent echo and surgical/interventional management.
- **Pericarditis / thrombus / aneurysm:** post-MI pericarditis is treated with high-dose aspirin; avoid early NSAIDs/steroids. Large anterior MI with LV thrombus needs therapeutic anticoagulation for about 3 months. True LV aneurysm causes HF, embolism, arrhythmias; pseudoaneurysm requires repair.
- **Secondary prevention:** lifelong aspirin, DAPT for 12 months if bleeding risk allows, high-intensity statin, beta-blocker at least 1 year, ACE inhibitor/ARB and aldosterone antagonist when indicated, smoking cessation, BP/diabetes/lipid control, cardiac rehabilitation, LVEF assessment in all, and delayed ICD consideration if severe LV dysfunction persists after reassessment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **ACS pathogenesis flowchart:** vulnerable plaque -> rupture/erosion -> platelet activation -> thromboxane A2 + GP IIb/IIIa aggregation -> thrombin/fibrin -> occlusive thrombus -> ST elevation -> necrosis.
- **STEMI reperfusion algorithm:** suspected STEMI -> ECG within 10 minutes -> primary PCI if FMC-device <=90/120 minutes -> fibrinolysis if PCI delayed and no contraindication -> rescue PCI if failed reperfusion at 60-90 minutes -> routine angiography 3-24 hours after successful lysis.

Clinical / Diagnostic significance

- Chest pain with diaphoresis for >30 minutes is STEMI until proved otherwise; epigastric "gas" pain in a high-risk patient is dangerous.
- Do not wait for troponin before reperfusion when the ECG is diagnostic.
- Inferior STEMI with hypotension and clear lungs suggests RV infarction; nitrates can cause collapse.
- Failed lysis or recurrent ST elevation mandates rescue PCI.
- New murmur with pulmonary edema or shock after MI suggests papillary muscle rupture or VSD.
- Killip class, LVEF, shock, persistent ischemia, age, diabetes, and ventricular arrhythmias guide prognosis.

High-yield exam pointers

- STEMI is usually **plaque rupture/erosion with occlusive platelet-fibrin thrombus**.

- **Time is muscle:** primary PCI preferred; fibrinolysis only when timely PCI is unavailable and safe.
- **ECG:** ST elevation in two contiguous leads; remember higher V2-V3 cutoffs.
- **Aspirin immediately:** chew 160-325 mg, then add P2Y12 inhibitor plus anticoagulation.
- **No routine oxygen** when saturation is normal.
- **Avoid nitrates** in RV infarction, hypotension, severe aortic stenosis, and recent PDE5 inhibitor use.
- **Failed lysis:** persistent pain/ST elevation at 60-90 minutes or <50% ST resolution -> rescue PCI.
- **Killip IV = cardiogenic shock** and needs urgent revascularization.
- **Discharge drugs:** DAPT, statin, beta-blocker, ACE inhibitor/ARB, aldosterone antagonist when indicated, and rehabilitation.

SOURCE & COVERAGE

Harrison 22e — "ST-Segment Elevation Myocardial Infarction"; "Ischemic Heart Disease"; Braunwald's Heart Disease 13e — "ST-Elevation Myocardial Infarction Pathophysiology and Clinical Evolution"; "ST-Elevation Myocardial Infarction: Management"; CMDT 2026 — "Coronary Artery Disease, Valvular Disease, & Other Key Topics in Cardiology".

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Early invasive strategy in non-ST-elevation ACS

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) encompasses unstable angina (UA, no necrosis) and non-ST-segment elevation myocardial infarction (NSTEMI, troponin-positive necrosis) and arises from a supply–demand mismatch driven most often by non-occlusive coronary thrombosis on a fissured/eroded plaque. An **early (routine) invasive strategy** means that, after starting anti-ischaemic and antithrombotic therapy, the patient is taken for **coronary angiography within 24 h** (and within 2 h if very high-risk), followed by revascularisation (PCI or CABG) guided by the coronary anatomy. This is contrasted with an **ischaemia-guided (selective) strategy** in which angiography is reserved for spontaneous or provoked ischaemia. The central exam concept is that strategy is *risk-matched*: invasive management benefits high-risk patients, whereas low-risk patients do equally well with an initially conservative approach.

Three Management Strategies — Definitions

Strategy	What it means	Whom it suits
Immediate invasive	Angiography **<2 h**, as soon as possible	Very-high-risk (haemodynamic/electrical instability)
Early invasive (routine)	Angiography **within 24 h** of presentation, then PCI/CABG/medical therapy per anatomy	High-risk stable patients (NSTEMI, GRACE >140, dynamic ECG)

Strategy	What it means	Whom it suits
Delayed invasive	Angiography **25–72 h**	Intermediate-risk after stabilisation
Ischaemia-guided (selective/conservative)	Medical therapy first; angiography only for recurrent rest pain, ST/biomarker change, haemodynamic instability, or positive non-invasive stress/CT	Non-high-risk, low TIMI/GRACE, troponin-negative

Pathophysiological Rationale & Evidence Base

- The **culprit lesion** in NSTE-ACS is typically an eccentric stenosis with scalloped/overhanging edges and a narrow neck, often a lipid-rich plaque with a thin fibrous cap (rupture) or a proteoglycan-rich eroded plaque with a platelet-rich white thrombus. At angiography ~35% have three-vessel disease, 25% two-vessel, 20% single-vessel, <10% left-main and ~10% no critical epicardial stenosis.
- An invasive strategy allows **direct identification and treatment of the culprit (and significant non-culprit) lesions**, plaque stabilisation by stenting, and complete revascularisation — addressing the unstable substrate that medical therapy alone cannot.
- **Trial evidence:** multiple randomised trials and meta-analyses show that, compared with a conservative/selective approach, an early invasive strategy **reduces composite cardiovascular endpoints, recurrent MI and length of stay** — with the benefit **concentrated in high-risk patients** (multiple risk factors, ST-segment deviation, positive biomarkers). A meta-analysis of 13 RCTs (≈11,972 patients) of early vs delayed angiography showed a **significant long-term reduction in MI but no overall mortality difference**; in the pre-specified subgroup with **GRACE score >140**, early invasive management significantly reduced MACE, whereas low-GRACE patients showed no clear benefit.
- **Timing within the invasive arm:** two studies comparing immediate invasive intervention (median 1.4 and 4.7 h) with delayed intervention (median 61 and 62 h) reduced death or new MI, with the **greatest benefit in high-risk-score patients**. For the broad NSTEMI population the survival benefit of "very early" over "early/delayed" timing is modest; risk score, not the clock alone, drives urgency.
- **Long-term "catch-up":** in long-term follow-up of the *ICTUS* trial (out to ~10 years), the early-invasive advantage over a selective strategy was no longer apparent, partly because of catch-up revascularisation in the selective arm — emphasising that selective management is a legitimate option in non-high-risk patients.

Risk Stratification — the Trigger for Strategy Selection

Strategy is selected by formal risk scoring plus clinical features. Early risk assessment identifies those who derive the greatest benefit from an early invasive approach.

- **TIMI risk score (0–7):** age ≥65 y; ≥3 CAD risk factors; known coronary stenosis ≥50%; ST-segment deviation on presenting ECG; ≥2 anginal episodes in prior 24 h; aspirin use in prior 7 days; elevated cardiac biomarkers. Higher score → higher 14-day risk of death/MI/urgent revascularisation (≈5% at 0–1 rising to ≈41% at 6–7).

- **GRACE risk score** (best discrimination; applies with or without ST elevation): age, Killip class, systolic BP, ST-segment deviation, cardiac arrest at presentation, serum creatinine, elevated CK-MB/troponin, and heart rate. A **GRACE score >140** is a key trigger for early invasive management.
- **HEART pathway** (History, ECG, Age, Risk factors, Troponin): identifies a low-risk group (HEART 0–3 with negative serial troponins, NPV ~99.6%) suitable for early discharge, versus HEART ≥4 / troponin-positive needing cardiology admission.

Selection, Timing and Staging of the Invasive Strategy

Risk tier	Defining features	Recommended timing
Very high risk (≥1)	Cardiogenic shock / unstable haemodynamics; acute HF from ongoing ischaemia; cardiac arrest after presentation; life-threatening arrhythmia; mechanical complication of MI; angina refractory to medical therapy; recurrent dynamic ischaemic ECG changes	**Immediate invasive (<2 h)**
High risk (≥1)	Confirmed NSTEMI; **GRACE >140**; transient ST-segment elevation; dynamic ST- or T-wave changes	**Early invasive (<24 h)**
Non-high risk	None of the above	**Selective invasive** — clinical/non-invasive assessment, then angiography only if ischaemia confirmed

- **Culprit-lesion PCI** is performed (CABG if anatomy unfavourable, e.g. complex multivessel/left-main or mechanical complications such as VSD or papillary-muscle rupture, where surgery is preferred).
- **Non-culprit / multivessel disease:** complete revascularisation (single-stage during index PCI, or staged within ~45 days) should be considered in the absence of cardiogenic shock, severe comorbidity (e.g. AKI) or unfavourable anatomy; a **Heart Team** decides PCI vs CABG for complex anatomy.
- **CABG-favouring factors:** diabetes mellitus, LVEF <35%, contraindication to DAPT, diffuse in-stent restenosis, heavy calcification, inability to achieve complete revascularisation, or concomitant valve/aortic surgery.
- **Vascular access: radial access is the default (Class I)** to reduce bleeding.

Peri-procedural Pharmacotherapy (Optimise Before/During the Cath)

- **Antiplatelet:** aspirin loading 150–325 mg (then 75–100 mg/day) **plus** a P2Y12 inhibitor. **Ticagrelor** (180 mg load, 90 mg bd) benefits patients managed conservatively *or* invasively; **prasugrel** (60 mg load, 10 mg/day) is given **once coronary anatomy is known (post-angiography)** when PCI is planned and is contraindicated after prior stroke/TIA; **clopidogrel** (300–600 mg load) when potent agents are unsuitable or anticoagulation is also needed. Contemporary guidance discourages **routine P2Y12 pretreatment** before angiography in patients planned for early invasive management with unknown anatomy.

- **Anticoagulant:** UFH, enoxaparin, bivalirudin (used at/just before PCI) or fondaparinux (best for conservatively-managed, high bleeding risk — needs supplemental UFH at PCI to avoid catheter thrombosis).
- **GP IIb/IIIa inhibitors** (eptifibatide, tirofiban): reserved for bail-out / high thrombus burden, not routine.
- **Anti-ischaemic & secondary prevention:** nitrates, beta-blockers (target HR 50–60/min), high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) ± ezetimibe/PCSK9 to LDL-C <55 mg/dL, ACE-I/ARB; DAPT generally 12 months (modulated by ischaemic vs bleeding risk).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Risk-stratified strategy/timing flow-chart (Fig. 285-4 style):** Box "NSTE-ACS" → three branches: **Very high risk** (shock/HF/arrest/arrhythmia/mechanical complication/refractory angina/dynamic ECG) → *Immediate invasive <2 h*; **High risk** (NSTEMI / GRACE >140 / transient ST-elevation / dynamic ST-T) → *Early invasive <24 h*; **Non-high risk** → *Selective invasive*. Downstream labels: "Culprit-lesion PCI (CABG if unfavourable anatomy)", "Evaluation of non-culprit lesion", "Staged vs single-stage PCI", "Medical management". Label the GRACE >140 cut-off.
- **Spectrum-of-ACS diagram:** clinical presentation → **ECG** (Normal / ST-depression / ST-elevation) → **hs-cTn** (non-elevated vs rise-and-fall) → final diagnosis **UA / NSTEMI / STEMI**. Labels: UA, NSTEMI, STEMI, hs-cTn, ST-segment depression.

Clinical / Diagnostic significance

- **Diagnosis** rests on history (rest pain >10 min, recent-onset, or crescendo), ECG (new ST-depression in ~⅓; deep symmetrical T-inversions ≥0.3 mV) and a **rise-and-fall of high-sensitivity troponin** (distinguishes NSTEMI from UA); the 0/1-h rapid rule-out algorithm accelerates triage. Distinguish **myocardial injury** (troponin >99th percentile without ischaemia — sepsis, CKD, HF, PE, myocarditis, Takotsubo) from true **type 1 MI**.
- **Management pearl:** match invasiveness to risk — invasive strategy for high-risk substrate, selective for low-risk. Always exclude life-threatening mimics (aortic dissection, PE, tamponade) before committing to the cath lab.
- Women, older adults, and patients with diabetes or CKD are **under-treated** despite higher risk and benefit from invasive care; meta-analysis supports early intervention in the elderly.

High-yield exam pointers

- Early/routine invasive = **angiography within 24 h** then revascularisation; **immediate = <2 h** for very-high-risk; **selective/ischaemia-guided** for non-high-risk.
- **GRACE score >140** is the pivotal numeric trigger for an early invasive strategy; benefit of invasive care is **proportional to baseline risk**.
- Invasive strategy reduces **recurrent MI, refractory ischaemia, MACE and length of stay**, but **not overall mortality** in unselected patients.
- **Very-high-risk = immediate (<2 h):** shock, refractory angina, acute HF from ischaemia, life-threatening arrhythmia, mechanical complication, recurrent dynamic ECG changes.

- **Radial access (Class I)** to cut bleeding; avoid routine GP IIb/IIIa and routine P2Y12 pretreatment before known anatomy.
- **Prasugrel only after angiography** when PCI planned; contraindicated with prior stroke/TIA. **Ticagrelor** works in both conservative and invasive pathways.
- Consider **complete revascularisation** (single-stage or staged ≤45 days) in multivessel disease without shock/AKI; **Heart Team** for complex/left-main → CABG, especially with diabetes or LVEF <35%.
- *ICTUS* long-term data show the early-invasive edge narrows over years due to **catch-up revascularisation** in the selective arm.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)" (risk scores, invasive vs conservative strategy, Fig. 285-4 selection/timing, antithrombotic regimens).
- **Braunwald's Heart Disease, 13e** — "Non-ST Elevation Acute Coronary Syndromes" (Invasive vs Conservative Management; timing meta-analyses and GRACE >140 subgroup; ICTUS 10-year catch-up; ACC/AHA vs ESC triage; revascularisation/Heart Team).
- **CMDT 2026** — "Coronary Artery Disease… Key Topics in Cardiology" (early invasive algorithm, GRACE/TIMI scoring, drug doses, indications for catheterisation, Table 10–8).
- *Coverage note:* the corpus supports the strategy, timing tiers, risk scores and pooled/meta-analytic evidence in full; among individual landmark timing/strategy trials, only *ICTUS* is named explicitly (the older FRISC-II, TACTICS-TIMI 18 and RITA-3 trials that historically established routine-invasive benefit are universally accepted standard cardiology but are not separately detailed in the available chapters).

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Heart failure — emerging therapies

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Over the past five decades, management of heart failure (HF) has evolved from a *renocentric* (diuretics) and *hemodynamic* model (digoxin, inotropes) to an era of **disease-modifying therapy** built on neurohormonal antagonism and, more recently, metabolic and device-based strategies. The contemporary pharmacologic backbone of HF with reduced ejection fraction (HFrEF) comprises **four foundational pillars** — RAAS blockade (including **ARNI**), evidence-based **beta blockers**, **mineralocorticoid receptor antagonists (MRAs)** and **SGLT-2 inhibitors** — onto which newer agents (vericiguat, omecamtiv mecarbil, ivabradine) and novel strategies (rapid in-hospital sequencing, transcatheter valve repair, remote haemodynamic monitoring) are layered. This answer covers the emerging drugs, devices and care-delivery strategies that now modify the natural history of HF.

Foundational "four pillars" of modern HFrEF therapy

- The sequential addition of each class produces a **progressive, incremental decline in mortality** (Fig. 265-3): ACEI/ARB → beta blocker → MRA → ARNI (in place of ACEI/ARB) → SGLT-2 inhibitor → balanced vasodilators (hydralazine–isosorbide dinitrate in selected populations, e.g. African Americans).
- These four classes now **form the pillars of pharmacotherapy**, facilitating stabilisation and even *reverse remodelling*, reducing symptoms, hospitalisations and both pump-failure and arrhythmic deaths.
- **Add-on agents** (ivabradine, vericiguat) further reduce HF hospitalisation but do **not** substantially lower mortality. Further "stacked" neurohormonal blockade (ACEI + ARB + MRA together; aliskiren — *ATMOSPHERE*; endothelin antagonists; moxonidine) is ineffective or harmful — there is a **ceiling of benefit** of RAAS inhibition.

Drug class	Representative agent	Initiation → target dose	Key trial(s)
ARNI	Sacubitril–valsartan (LCZ696)	100 mg bid → 200 mg bid	PARADIGM-HF; PIONEER-HF
SGLT-2 inhibitor	Dapagliflozin / Empagliflozin	10 mg qd → 10 mg qd	DAPA-HF; EMPEROR-Reduced
sGC stimulator	Vericiguat	2.5 mg qd → 10 mg qd	VICTORIA
Myosin activator	Omecamtiv mecarbil	25 mg bid → up to 50 mg bid (plasma-guided)	GALACTIC-HF; COSMIC-HF
If-channel inhibitor	Ivabradine	— (added if HR >70, sinus rhythm)	SHIFT

ARNI and soluble guanylyl cyclase stimulation

- **Angiotensin receptor–neprilysin inhibitor (ARNI):** sacubitril–valsartan combines an **AT1-receptor blocker** with **neprilysin inhibition**, which raises circulating **natriuretic peptides** (and other vasoactive peptides), promoting natriuresis, vasodilation and anti-remodelling.

- In **PARADIGM-HF** (8399 HFrEF patients), sacubitril–valsartan vs enalapril gave a **20% reduction in CV death/HF hospitalisation** and a **16% reduction in all-cause mortality**, with lower hyperkalaemia and renal dysfunction but more symptomatic hypotension.
- Guidelines now advocate **switching to ARNI** in symptomatic HFrEF tolerating ACEI/ARB; up-front use in *de novo* HF is increasingly considered. **Contraindicated** with prior angioedema; allow a **36-h washout** from an ACEI (excess bradykinin → angioedema, as seen with omapatrilat in *OVERTURE*). An ARB leaves the ACE-bradykinin pathway intact, hence lower angioedema risk.
- **Vericiguat** is a novel oral **soluble guanylyl cyclase (sGC) stimulator** that enhances cyclic-GMP/NO signalling (directly stimulates and sensitises sGC to endogenous NO). In **VICTORIA** (5050 patients, LVEF <45%, recent worsening HF), it produced a **modest 10% relative risk reduction** in CV death/HF hospitalisation, driven principally by reduced HF hospitalisation — a useful **adjunct** in high-risk, recently-decompensated HFrEF.

SGLT-2 inhibition and metabolic strategies

- **SGLT-2 inhibitors** (dapagliflozin, empagliflozin) are the most recent pillar; their cardiac benefit is **independent of glycaemic (HbA1c) lowering** and of diabetes status (SGLT-2 is itself a *novel biologic target* in HF).
- **DAPA-HF** (4744 HFrEF) — dapagliflozin 10 mg gave a **26% reduction** in worsening HF/CV death, consistent with and without diabetes. **EMPEROR-Reduced** (3730, EF ≤40%) — empagliflozin gave a **25% reduction** in CV death/HF hospitalisation.
- Benefit now extends across the EF spectrum: **EMPEROR-PRESERVED** and **DELIVER** show reduced CV death/HF hospitalisation in **HFpEF/HF with LVEF >40%** — the first clearly effective disease-modifying drug class in HFpEF.
- **Other metabolic/inflammatory targets: GLP-1 receptor agonists** (e.g. liraglutide) do not worsen HF and **improve QOL in obese HFpEF irrespective of diabetes**; IV **iron** (ferric carboxymaltose — FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN) corrects iron deficiency and improves symptoms/functional capacity (oral iron ineffective); anti-inflammatory therapy (anti-TNF infliximab/etanercept) **failed**, while IL-1β blockade (**canakinumab, CANTOS**) reduced HF hospitalisation post-MI in post-hoc analysis.

Novel inotropy and heart-rate modification

- **Omecamtiv mecarbil** — a **selective cardiac myosin activator** that prolongs the ejection period and increases fractional shortening **without raising myocardial oxygen demand** or intracellular calcium (distinct from classic inotropes). In **GALACTIC-HF** (8256, EF ≤35%) it gave a **14% reduction** in the composite of CV death/first HF event, driven by HF events (**no effect on CV death alone**); a signal of greater benefit in advanced HF (lower EF, higher natriuretic peptides).
- **Calcium sensitisers — levosimendan** (also a PDE-3 inhibitor/vasodilator) for acute decompensated HF: in **SURVIVE/REVIVE II** it did **not** reduce mortality; not approved in the USA but used elsewhere. *Routine long-term/short-term inotropes (e.g. milrinone, OPTIME-CHF) remain discouraged* — reserved as bridge to LVAD/transplant or palliation.
- **Ivabradine** — selective **If-current inhibitor** of the SA node; lowers heart rate without affecting contractility or vascular tone. **SHIFT** (NYHA II–III, sinus rhythm, HR >70/min): reduced CV

death/HF hospitalisation proportional to heart-rate reduction. Considered as **adjunct/alternative** in patients still symptomatic on GDMT, in sinus rhythm, with HR >70/min.

Emerging therapies and strategies in HFpEF

- **SGLT-2 inhibitors** (EMPEROR-PRESERVED, DELIVER) — reduce HF hospitalisation; now the cornerstone of HFpEF therapy.
- **ARNI — PARAGON-HF** (4822, LVEF ≥45%) showed a 13% reduction that **narrowly missed significance (p = 0.06)**; benefit greatest in those with **lower (mildly reduced) EF and in women**. Now approved across the full EF spectrum, greatest benefit when LVEF is below normal (PARAGLIDE-HF — benefit confined to EF ≤60%).
- **MRAs** — spironolactone (TOPCAT/ALDO-DHF) improved diastolic indices but not hard outcomes; the non-steroidal MRA **finerenone (FINEARTS-HF)** and **SPIRRIT-HFpEF** are evaluating this further.
- **Ineffective in HFpEF:** ACEIs/ARBs (except for prevention), digoxin (may cut hospitalisation), beta/calcium-channel blockers (useful only for rate control in AF), **PDE-5 inhibitor sildenafil**, and nitrates (NEAT-HFpEF, INDIE-HFpEF). Strategy emphasis: decongestion (avoiding excessive preload reduction → underfilling, azotaemia, syncope), BP control, maintaining sinus rhythm (AF ablation), and treating comorbidity (obesity, sleep apnoea, CKD, iron deficiency).

Strategies: in-hospital initiation, rapid sequencing and remote monitoring

- **Pre-discharge / in-hospital initiation: PIONEER-HF** (sacubitril–valsartan started before discharge) and **EMPULSE** (empagliflozin in hospitalised HF across EF spectrum) improved natriuretic peptides and clinical outcomes — institute GDMT *before discharge* to improve adherence.
- **Rapid sequencing / intensive titration: STRONG-HF** showed that aggressive up-titration to guideline targets **within 2 weeks of discharge** plus frequent follow-up to 2 months cut all-cause mortality and HF readmission at 180 days (benefit regardless of EF) — most readmissions occur in the first 2 weeks.
- **Remote haemodynamic monitoring:** implantable **pulmonary-artery pressure sensor (CardioMEMS)** reduced HF hospitalisations by up to 39% (CHAMPION); **GUIDE-HF** was neutral overall (confounded by COVID-19) but positive in pre-pandemic analysis. Telemonitoring of weight/vitals and intrathoracic impedance have **not** improved outcomes.

Device, surgical, cellular and gene-based advances

- **Cardiac resynchronisation therapy (CRT):** biventricular pacing via coronary sinus restores synchronous contraction; mortality benefit in CARE-HF, RAFT, MADIT-CRT — greatest with **QRS >149 ms and LBBB**. **Conduction-system / left-bundle-branch-area pacing** is an evolving alternative (evidence still less certain).
- **ICD** for primary prevention of sudden cardiac death — NYHA II–III, **LVEF ≤35%** (≤30% post-MI), on optimal therapy, no benefit within 40 days of MI; uncertain benefit in non-ischaemic cardiomyopathy (DANISH).

- **Cardiac contractility modulation (CCM):** non-excitatory RV-septal stimulation during the refractory period — improves symptoms/QOL in **EF 25–45% with narrow QRS** (not CRT-eligible); no proven mortality benefit, not yet guideline-endorsed.
- **Neuromodulation devices** (vagal nerve stimulation — INOVATE-HF/ANTHEM-HFrEF; baroreflex activation; renal denervation) have **largely failed** in large trials.
- **Transcatheter edge-to-edge mitral repair (MitraClip)** for functional MR: **COAPT** (positive — fewer hospitalisations and deaths) vs **MITRA-FR** (neutral); benefit depends on MR being disproportionate to LV dilation.
- **Surgical:** CABG for ischaemic cardiomyopathy (STICH — long-term benefit), AF catheter ablation (CASTLE-AF), and advanced therapies — **LVAD and cardiac transplantation** (detailed in Chap. 271).
- **Cellular and gene-based therapy (investigational):** bone-marrow/cardiac-derived and mesenchymal precursor cells (DREAM-HF negative) and **SERCA2a gene transfer** via AAV1 (CUPID — confirmatory trial failed) remain experimental.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Mortality-staircase (Fig. 265-3 style):** an X–Y plot with *risk of mortality* descending stepwise. Label, top→bottom: **Placebo → ACE inhibitor/ARB → Beta-blockers (carvedilol, metoprolol succinate, bisoprolol) → Mineralocorticoid receptor antagonist → ARNI (instead of ACEI/ARB) → SGLT-2 inhibitor → balanced vasodilators**; side-box "add-on, hospitalisation-only: Ivabradine, Vericiguat, Omecamtiv mecarbil"; "Ineffective/harmful: Endothelin antagonists, Moxonidine, Xamoterol, oral inotropes".
- **Neurohormonal target schematic:** a cardiomyocyte/vasculature with arrows to drug targets — **AT1 receptor (ARB)**, **neprilysin (sacubitril) → ↑natriuretic peptides**, **sGC/cGMP (vericiguat)**, **SGLT-2 (gliflozins)**, **cardiac myosin (omecamtiv)**, **SA-node If current (ivabradine)**, **mineralocorticoid receptor (MRA/finerenone)**.

Clinical / Diagnostic significance

- **Sequence flexibly, titrate fully:** CIBIS-III showed order of ACEI vs beta blocker initiation does not matter — what matters is achieving target doses of all four pillars; GDMT is widely **under-dosed/under-utilised**.
- **ARNI** needs a 36-h ACEI washout and is avoided with prior angioedema; monitor BP (hypotension), K+ and renal function.
- **SGLT-2 inhibitors** are now started early and across the EF spectrum regardless of diabetes — a practice-changing shift; watch for genital mycotic infection, volume depletion and (rare) euglycaemic ketoacidosis.
- **Functional MR** with refractory symptoms → consider transcatheter repair (COAPT-type patients); refractory advanced HF → MCS/transplant referral.
- **Transitional care** (pre-discharge GDMT, STRONG-HF rapid titration, early follow-up, CardioMEMS in selected NYHA III) reduces the high (~50% at 6 months) readmission rate.

High-yield exam pointers

- **Four pillars of HFrEF:** ARNI/RAAS-blocker, beta blocker, MRA, **SGLT-2 inhibitor** — each adds incremental mortality benefit.
- **PARADIGM-HF:** sacubitril–valsartan → 20% ↓ CV death/HF hospitalisation, 16% ↓ all-cause mortality; target **200 mg bid**, 36-h ACEI gap, contraindicated if prior angioedema.
- **DAPA-HF (26% ↓)** and **EMPEROR-Reduced (25% ↓)**; HFpEF benefit in **EMPEROR-PRESERVED & DELIVER**.
- **Vericiguat** = oral **sGC stimulator** (VICTORIA, modest 10% RRR, HF-hospitalisation driven).
- **Omecamtiv mecarbil** = selective **cardiac myosin activator** (GALACTIC-HF, 14% ↓, no effect on CV death alone, no ↑O2 demand).
- **Ivabradine** = **If-current** SA-node inhibitor (SHIFT; HR >70, sinus rhythm).
- **HFpEF:** SGLT-2i effective; ARNI borderline (PARAGON-HF p = 0.06); finerenone (FINEARTS-HF) and GLP-1 agonists (obesity) emerging; sildenafil/nitrates ineffective.
- **Strategies:** in-hospital initiation (PIONEER-HF, EMPULSE), rapid up-titration (STRONG-HF), MitraClip (COAPT), CardioMEMS, CRT (QRS >149 ms + LBBB), ICD (LVEF ≤35%).

> **SOURCE & COVERAGE**
>
> Harrison's Principles of Internal Medicine, 22e — **Ch 265 "Heart Failure: Management"** (primary); with brief reference to **Ch 264 "Heart Failure: Pathophysiology and Diagnosis"** (SGLT-2 as a novel biologic target). LVAD and cardiac transplantation are cross-referenced by Harrison to **Ch 271** (not provided here). *Coverage note:* this answer is fully grounded in the provided chapters; specific drug doses are taken from Table 265-2. Advanced mechanical circulatory support/transplant details fall outside the supplied text (Ch 271) and are therefore summarised only at the level Ch 265 provides.

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Endomyocardial fibrosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Endomyocardial fibrosis (**EMF**, *Davies' disease*) is a progressive **fibrotic obliterative disease of the ventricular apices and subvalvular apparatus** that produces a **restrictive cardiomyopathy (RCM)**. It is a member of the *endomyocardial diseases* — a group unified pathologically by **dense fibrosis of the endocardium**, of which the temperate-zone counterpart is **Löffler (eosinophilic) endocarditis**. First described in Uganda in 1948, EMF is one of the **commonest causes of RCM worldwide** and a major cause of heart failure in tropical Africa, the South Asian subcontinent (notably Kerala, India) and Brazil. The dominant haemodynamic lesion is **impaired diastolic filling of a non-compliant ventricle with preserved or near-preserved ejection fraction**.

Etiopathogenesis and epidemiology

- **Cause remains unknown.** No single unifying infectious, environmental or genetic mechanism has been established; several hypotheses coexist.

- **Eosinophil hypothesis (unifying concept):** EMF is regarded as the **end-stage fibrotic phenotype** that pathologically resembles eosinophilic (Löffler) endocarditis. Toxic **eosinophil granule cationic proteins** are thought to damage the endocardium and drive fibrosis. *However*, peripheral or cardiac-tissue **eosinophilia is seldom demonstrable in established tropical EMF** — distinguishing it from frank hypereosinophilic disease.
- **Environmental hypothesis:** exposure to **cerium** (a rare-earth element abundant in affected soils) has been implicated; dietary and infectious (helminthic/filarial) cofactors have been proposed but not confirmed.
- **Geography:** tropical and subtropical regions — **sub-Saharan Africa (Uganda, Nigeria, Mozambique)**, the South Asian subcontinent and Brazil; sporadic cases occur in temperate climates.
- **Epidemiology:** a **community prevalence of ~20% has been reported in rural Mozambique**, with **male predominance (≈23% vs 17% in females)** and **family clustering**. Age shows a **bimodal peak** — onset in the **first decade**, and again in the **second to fourth decades**.

Pathology and natural history

- Hallmark is **dense, white, glistening fibrous tissue obliterating the apex of the right and/or left ventricle**, extending onto the **inflow tract and the chordae/papillary muscles** (subvalvular apparatus) while characteristically **sparing the outflow tracts**.
- **Apical obliteration** by fibrosis (± superimposed mural thrombus) reduces cavity volume and produces restriction; tethering of the AV-valve apparatus produces **mitral and/or tricuspid regurgitation**. The atria dilate, often massively.
- **Three pathological stages** (best characterised in eosinophilic/Löffler disease, the temperate analogue, and applied to the endomyocardial-disease spectrum):

Stage	Pathological process	Clinical correlate
1. Acute necrotic	Eosinophil infiltration of myocardium, degranulation and **myocardial necrosis/inflammation**	Often few/no symptoms; biomarkers ± raised, CMR may show inflammation
2. Intermediate (thrombotic)	**Mural thrombus** layered over damaged endocardium, favouring the apices; risk of embolism	Chest pain, dyspnoea, AV-valve regurgitation, systemic/cerebral emboli
3. Fibrotic	**Diffuse endocardial scarring → restrictive cardiomyopathy**, subvalvular scarring impairing valve mobility	Established RCM with biventricular congestion

- **Anatomical patterns of EMF:** *right-ventricular* (RV apical obliteration → severe TR, gross ascites, raised JVP), *left-ventricular* (LV apical obliteration → MR, pulmonary congestion), and *biventricular* (commonest, ~50%).

Tropical EMF versus Löffler (eosinophilic) endocarditis

Feature	Tropical EMF (Davies')	Löffler endocarditis
Geography / climate	Tropics (Africa, S. Asia, Brazil)	Temperate / developed countries

Feature	Tropical EMF (Davies')	Löffler endocarditis
Age, sex	Children & young adults; M>F	Adults (typically male)
Eosinophilia	Usually **absent / not demonstrable**	**Hypereosinophilia present** (AEC >1500/μL ≥1 month, often ≥6 months)
Underlying cause	Unknown (cerium, ?infective)	Helminth/parasitic infection, allergy/drug reaction, **eosinophilic leukaemia/malignancy**, idiopathic **HES**; myeloproliferative HES may respond to **tyrosine-kinase inhibitors**
Course	Indolent, chronically progressive	More aggressive (acute necrotic → thrombotic → fibrotic)
Common end-point	**Restrictive cardiomyopathy with apical fibrosis & AV regurgitation**	Same fibrotic RCM end-stage

Clinical features

- Symptoms of **restrictive physiology** dominate, frequently **right-sided**: exertional dyspnoea, **paroxysmal nocturnal dyspnoea**, fatigue, peripheral oedema and **prominent ascites** (a feature common to all endomyocardial diseases, often out of proportion to peripheral oedema).
- **Signs: raised JVP with rapid/steep Y descent and a positive Kussmaul sign** (inspiratory rise in JVP); a **fourth heart sound (S4)** is more typical than S3 in sinus rhythm; murmurs of **mitral and/or tricuspid regurgitation**; **atrial fibrillation** is common; hepatomegaly and dependent oedema. The apex beat is **less displaced than in DCM and less forceful than in HCM**.
- **Complications:** congestive heart failure, AF and other arrhythmias, mural thrombus with **systemic/pulmonary embolism**, AV-valve regurgitation, pericardial effusion, and **sudden cardiac death**.

Investigations and diagnosis

- **ECG:** non-specific — low-voltage complexes, T-wave inversion, atrial enlargement, **atrial fibrillation**, conduction abnormalities.
- **Chest radiograph:** cardiomegaly from biatrial enlargement; pericardial effusion; occasionally **apical/endocardial calcification**.
- **Echocardiography (key test): obliteration of the ventricular apex** by fibrous tissue ± thrombus, **apical/subvalvular AV-apparatus involvement**, AV-valve regurgitation, **gross biatrial enlargement**, restrictive transmitral inflow (tall E, short deceleration time) and preserved/near-normal systolic function.
- **Cardiac MRI:** demonstrates apical fibrosis and **subendocardial late gadolinium enhancement**; detects thrombus and inflammation in the eosinophilic phase.
- **Cardiac catheterisation:** elevated and equalised end-diastolic pressures with a **"dip-and-plateau" (square-root sign)** ventricular pressure tracing; **pulmonary arterial pressure is raised**.
- **Endomyocardial biopsy:** more useful in RCM than in DCM/HCM to confirm an infiltrative/fibrotic aetiology; shows endocardial fibrosis (and eosinophilic infiltration in the active eosinophilic phase).

- **Crucial differential — RCM vs constrictive pericarditis** (both present with right-heart dominance):

Feature	Restrictive cardiomyopathy (EMF)	Constrictive pericarditis
Respiratory ventricular interaction	**Absent / not accentuated**	**Accentuated** (interdependence)
Pulmonary artery pressure	**Elevated** (high PCWP)	Usually **normal**
Pericardium	Normal	Thickened ± calcified
BNP / NT-proBNP	**High**	Relatively low/normal
Septal motion / CMR	Apical fibrosis, LGE	Pericardial thickening, septal bounce

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Four-chamber heart in EMF** — label: *fibrous obliteration of LV apex*, *fibrous obliteration of RV apex*, *mural thrombus over endocardium*, *tethered mitral and tricuspid subvalvular apparatus → MR/TR*, *grossly dilated left and right atria*, *spared outflow tracts*.
- **Stages of endomyocardial (eosinophilic) disease** — a 3-box flow: *Acute necrotic (eosinophil infiltration & myocardial necrosis) → Intermediate/thrombotic (mural thrombus, embolism) → Fibrotic (endocardial scarring → restrictive cardiomyopathy)*.

Clinical / Diagnostic significance

- EMF is a **leading cause of restrictive cardiomyopathy and heart failure in the tropics**, and an important Indian cause (Kerala) — high-yield for an Indian postgraduate exam.
- The **eosinophil link** unifies tropical EMF with Löffler endocarditis; recognising an active eosinophilic phase allows **disease-modifying therapy** (treat parasitosis, corticosteroids, TKIs for myeloproliferative HES) *before* irreversible fibrosis.
- **Echocardiographic apical obliteration with AV-valve regurgitation and biatrial enlargement** is virtually diagnostic in an endemic setting.
- Distinguishing EMF from **constrictive pericarditis** is decisive because constriction is **surgically curable by pericardiectomy**, whereas EMF requires endocardial decortication/valve surgery.
- Mural thrombus mandates attention to **thromboembolic risk**.

Management

- **Medical (supportive):** the cornerstone is **euvolaemia** — judicious **diuretics** (loop ± thiazide ± aldosterone antagonist) balancing decongestion against the need for adequate filling. Rate control and anticoagulation for AF; anticoagulation for mural thrombus/embolism. **Beta-blockers** can prolong diastolic filling but may be poorly tolerated by lowering an already fixed stroke volume; **vasodilators are often poorly tolerated**. Standard HFrEF therapies are **not routinely indicated** in RCM.

- **Disease-specific (active eosinophilic phase):** treat the underlying cause; **corticosteroids and cytotoxic/cytolytic agents** (e.g. hydroxyurea), and **tyrosine-kinase inhibitors** for FIP1L1-PDGFRA / myeloproliferative HES.
- **Surgical (fibrotic stage): endocardectomy (decortication/resection of fibrous tissue) with mitral/tricuspid valve repair or replacement** can produce dramatic symptomatic and survival benefit, *but* carries **significant perioperative morbidity and mortality**.
- **Prognosis:** advanced fibrotic EMF with heart failure carries a poor prognosis; outcome depends on ventricular involvement, AV-valve regurgitation and operability.

High-yield exam pointers

- EMF = **fibrous obliteration of ventricular apices + subvalvular apparatus → restrictive cardiomyopathy**; eponym *Davies' disease*; first described in **Uganda, 1948**.
- One of the **commonest causes of RCM worldwide**; tropical Africa, India (Kerala), Brazil; **male predominance**, **bimodal age**, family clustering; ~20% prevalence reported in rural Mozambique.
- **Three histological stages:** acute necrotic → thrombotic → **fibrotic**.
- **Löffler endocarditis = temperate analogue with hypereosinophilia** (AEC >1500/μL); EMF usually has **no demonstrable eosinophilia**.
- Clues: **ascites out of proportion**, **raised JVP with steep Y descent + Kussmaul sign**, **S4 > S3**, MR/TR murmurs, AF.
- Echo: **apical obliteration + biatrial enlargement + AV regurgitation**; CMR: **subendocardial LGE**; cath: **square-root (dip-and-plateau) sign**.
- Distinguish from **constrictive pericarditis**: RCM has **no respiratory ventricular interaction, raised PA pressure, high BNP**.
- Treatment: **diuretic-based supportive care**; steroids/cytotoxics/TKI in the eosinophilic phase; **endocardectomy + valve surgery** in the fibrotic stage.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Amyloidosis and Other Restrictive Cardiomyopathies"* (restrictive physiology, Table of causes of RCM listing tropical endomyocardial fibrosis and Löffler's endocarditis) and *"Myocarditis"* (eosinophilic myocarditis → Loeffler endocarditis, hypereosinophilic syndrome).
- **Braunwald's Heart Disease, 13e** — *"The Dilated, Restrictive, and Infiltrative Cardiomyopathies"* (Endomyocardial disease; Löffler eosinophilic endocarditis with the acute/intermediate/fibrotic stages; Endomyocardial fibrosis — Uganda 1948, Mozambique prevalence, cerium, clinical and surgical management). *This dedicated cardiology text supplied the depth on staging, epidemiology and pathology.*
- **CMDT 2026** — *"Heart Failure & Cardiomyopathy"* (restrictive cardiomyopathy essentials; RCM vs constrictive pericarditis — ventricular interaction and PA pressure; diuretic/beta-blocker management principles).

Coverage note: The corpus covers the restrictive-cardiomyopathy framework, the eosinophilic (Löffler) spectrum and the core EMF epidemiology/pathology/management well, but **tropical-EMF-specific minutiae are relatively thin** — points such as the *Davies* eponym, the predominantly Kerala focus in India, calcific endocardial change and the dip-and-plateau/square-root sign are stated as universally accepted standard internal medicine, consistent with (but not all verbatim in) the corpus.

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Hypertrophic cardiomyopathy

Asked in: Paper II Jul 2020 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by **left ventricular hypertrophy (LVH) that develops in the absence of any abnormal loading condition** (hypertension, aortic stenosis) or systemic infiltrative/storage disease that could account for the wall thickening. It is the **commonest monogenic cardiovascular disease (prevalence ≈1:500)**, classically caused by autosomal-dominant pathogenic variants in genes encoding the **cardiac sarcomere**, and is histologically marked by myocyte hypertrophy, **myocyte disarray** and fibrosis. The preferred current term is *hypertrophic cardiomyopathy with or without obstruction* (replacing "HOCM"); it is a leading cause of **sudden cardiac death (SCD) in the young** and an important cause of heart failure.

Etiology and genetic basis

- **Sarcomeric HCM:** a pathogenic sarcomere-gene variant is found in ~**40–50%** of all patients — over **60%** of those with familial disease or childhood presentation, but ~30–40% of apparently sporadic cases. Inheritance is **autosomal dominant** with **age-dependent, incomplete penetrance** (~60%) and variable expressivity.
- **>1500 variants in ≥9 genes**; **~80% involve MYBPC3 or MYH7** (thick-filament proteins).

- **Mechanism:** most act as a **dominant-negative ("poison peptide")**; *MYBPC3* is the exception (~90% are truncating variants causing **haploinsufficiency**). At the myofilament level variants produce **increased force generation, increased Ca^{2+} sensitivity, impaired relaxation and abnormal energetics (increased ATP consumption)**.
- **Nonsarcomeric HCM:** polygenic, with **hypertension (esp. diastolic BP) and obesity** as the strongest environmental modifiers (Mendelian-randomisation data).

Sarcomere gene	Protein	Approx. share of genetic HCM
MYBPC3	Myosin-binding protein C	~45%
MYH7	β-myosin heavy chain	~35%
TNNT2	Cardiac troponin T	~5%
TNNI3	Cardiac troponin I	~3%
TPM1 / MYL2 / MYL3 / ACTC1 / TNNC1	Tropomyosin, light chains, actin, troponin C	<3% each

- **Genocopies / "pseudohypertrophy"** (mimic HCM, must be excluded — often a *short PR / pre-excitation* clue): **Fabry disease** (*GLA*, X-linked; angiokeratoma, renal failure, neuropathy), **Danon disease** (*LAMP2*, X-linked), **PRKAG2 cardiomyopathy** (pre-excitation/AV block), **Friedreich ataxia** (*FXN*), **Noonan/RASopathy** (*PTPN11*), **cardiac amyloidosis** (*TTR* — carpal tunnel, biceps-tendon rupture), and mitochondrial disease.

Pathology and pathophysiology

- **Macroscopy:** non-uniform wall thickening; **asymmetric septal hypertrophy with reversed septal curvature** is classic and most predictive of a sarcomere variant. Other patterns: **concentric, mid-ventricular, and apical** (apical HCM is less often familial, sarcomere variant in only ~15%, more common in Japanese/Asian descent).
- **Microscopy:** characteristic **myocyte disarray** (swirling/branching instead of parallel fibres), **interstitial and replacement fibrosis**, and **small thick-walled intramural arterioles** → microvascular ischaemia and angina with normal epicardial coronaries. Endomyocardial biopsy is **not** used to diagnose HCM (changes are patchy/deep) but can exclude infiltrative disease.
- **LVOT obstruction (dynamic):** present at rest in ~30% and provoked by exercise in a further ~30%. The hypertrophied septum + an enlarged, anteriorly-displaced anterior mitral leaflet generate **drag forces → systolic anterior motion (SAM)** of the mitral valve contacting the septum → late-peaking outflow obstruction and a **posteriorly-directed jet of mitral regurgitation**.
- **Load dependence:** obstruction worsens with ↓**preload** (dehydration, Valsalva, standing, diuretics), ↓**afterload** (vasodilators) and ↑**contractility** (exercise, digoxin, inotropes); it improves with squatting, handgrip and volume.
- **Diastolic dysfunction** (stiff, hypertrophied ventricle with impaired relaxation) is near-universal; systolic function is usually preserved/supranormal — an **EF <50% is abnormal** in HCM and signifies systolic decline.

Clinical features and physical signs

- **Symptoms:** exertional **dyspnoea** (commonest), **angina**, and **post-exertional syncope/pre-syncope** (volume loss + tachycardia worsen obstruction); palpitations; may be asymptomatic and detected on family screening or murmur. SCD may be the first presentation.
- **Pulse:** sharp, rapidly rising **bisferiens (spike-and-dome) carotid pulse** (contrast with the slow-rising *pulsus parvus et tardus* of aortic stenosis).
- **Apex: triple apical impulse**, prominent **a-wave** in JVP, **loud S4**.
- **Murmur:** harsh, **late-peaking systolic ejection murmur** at the left sternal border ± apical pansystolic murmur of MR. **Dynamic auscultation is the key bedside test:** murmur **increases** with Valsalva strain and standing from squatting (↓preload); **decreases** with squatting and sustained handgrip (↑afterload/preload) — the opposite of valvular AS.
- *Brockenbrough–Braunwald–Morrow sign:* a paradoxical **fall in aortic pulse pressure in the post-extrasystolic beat** (augmented contractility increases obstruction) — a classic confirmatory sign of dynamic LVOT obstruction.

Diagnosis and investigations

- **Echocardiography (diagnostic, first-line):** maximal LV wall thickness **≥15 mm** in adults (or **≥13 mm** with a family history or proven pathogenic variant; z-score ≥2.5 in children) with a non-dilated, hypercontractile, **small LV cavity**, **SAM**, dynamic LVOT gradient, and diastolic dysfunction. **Obstruction = peak instantaneous gradient ≥30 mmHg**; **≥50 mmHg** (rest or provoked) is the threshold for limiting symptoms/intervention. Use **provocation** (Valsalva, squat-to-stand, exercise echo) if resting gradient <30 mmHg but symptomatic.
- **ECG** (abnormal but non-specific; insensitive): LVH, deep **inferolateral/septal Q waves**, ST-T changes; **giant T-wave inversions** suggest apical HCM. May be normal in ~25%.
- **Cardiac MRI:** quantifies hypertrophy in areas missed by echo, and **late gadolinium enhancement (LGE)** identifies fibrosis (arrhythmic substrate and emerging SCD risk marker).
- **Genetic testing:** multigene panel in the proband chiefly to **enable cascade (predictive) testing of relatives** and to distinguish genocopies; phenotype, not genotype, guides therapy.
- **Athlete's heart vs HCM:** physiological hypertrophy shows mild LV **dilation**, **normal diastolic function**, supranormal **VO_2max (>50 mL/kg/min)**, no LGE, and **regression with detraining** — features absent in HCM.

Management

Three pillars: **symptom control, SCD-risk/arrhythmia management, and family screening + lifestyle counselling.** No therapy yet proven to alter mortality; treat the symptomatic patient.

Setting	Approach
Obstructive, symptomatic	First-line **β-blocker** OR non-dihydropyridine CCB (**verapamil/diltiazem**); optimise volume; **stop vasodilators**. Add **disopyramide** (negative inotrope, give with AV-nodal blocker) or a **cardiac myosin inhibitor (mavacamten)** for persistent symptoms

Setting	Approach
Refractory + gradient ≥50 mmHg	**Septal reduction therapy** — surgical **septal myectomy** (gold standard; experienced-centre 30-day mortality <1%, 90–95% success) or **alcohol septal ablation** (for non-surgical candidates / suitable septal-perforator anatomy)
Nonobstructive, symptomatic	β-blocker / verapamil, cautious **diuretics** for congestion; trials of myosin inhibitors and SGLT2 inhibitors ongoing; transplant for refractory/end-stage disease
Avoid	Arterial **vasodilators** (ACE-I/ARB, nitrates, dihydropyridine CCB, PDE5 inhibitors) and **digoxin** (↑contractility worsens obstruction)

- **Cardiac myosin inhibitors (disease-specific): mavacamten** allosterically inhibits myosin ATPase, favouring the super-relaxed "off" state → fewer cross-bridges → ↓contractility and ↓LVOT gradient. **FDA-approved April 2022** for symptomatic obstructive HCM; trials **EXPLORER-HCM** and **VALOR-HCM** showed improved exercise capacity, symptoms and reduced need for SRT. Chief risk: **reversible fall in LVEF** → mandatory echo monitoring/REMS. **Aficamten** (SEQUOIA-HCM) is the second-in-class agent.
- **Atrial fibrillation:** common, poorly tolerated (loss of atrial kick worsens filling/obstruction). Rate-control with β-blocker/verapamil, restore sinus rhythm; **disopyramide/amiodarone** preferred antiarrhythmics; ablation for refractory cases. **Anticoagulate regardless of CHA_2DS_2-VASc score**, DOAC preferred over warfarin.
- **Septal-reduction complication: complete heart block needing permanent pacing** (commoner after ablation). Pacing alone is **not** effective primary therapy.
- **Lifestyle:** recent data show low arrhythmic risk with recreational/competitive sport; blanket restriction is no longer mandated — **shared decision-making**.

Risk stratification for sudden cardiac death

- Baseline SCD risk **~0.5–1% per year**; SCD is not reduced by drugs/septal reduction, so prevention rests on the **ICD**.
- **Secondary prevention (Class I ICD):** prior cardiac arrest / sustained VT/VF.
- **Primary prevention major risk factors** (each weighed for shared decision-making): **family history of SCD**, **unexplained (non-vagal) syncope**, **massive LVH ≥30 mm**, **LV apical aneurysm**, **LV systolic dysfunction (EF <50%)**, and **non-sustained VT** on monitoring. Extensive **LGE on CMR** is a modifying marker.
- The **ESC HCM Risk-SCD calculator** estimates **5-year risk** from age, max wall thickness, LA diameter, LVOT gradient, FH of SCD, NSVT and syncope: **≥6% → ICD advised; 4–6% → consider; <4% → not advised.**
- **Prognosis:** generally better than older referral series suggested; **~1 in 20 (5–8%) progress to systolic dysfunction / "burnt-out" end-stage HCM (EF <50%)** needing HFrEF therapy or transplant.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Parasternal long-axis echo of obstructive HCM** — label: *hypertrophied interventricular septum, asymmetric LVH, small LV cavity, systolic anterior motion (SAM) of anterior mitral leaflet contacting septum, narrowed LVOT, posteriorly-directed mitral regurgitation jet, enlarged left atrium, aorta.*
- **Cardiac sarcomere schematic** — label: *thick filament (β-myosin heavy chain MYH7, myosin-binding protein C MYBPC3, myosin light chains), thin filament (actin ACTC1, tropomyosin TPM1, troponin T/I/C complex), Z-disc* — marking the genes mutated in HCM.

Clinical / Diagnostic significance

- HCM is the **leading cause of sudden death in young athletes**; pre-participation evaluation and family cascade screening (ECG + echo, beginning in adolescence and continued lifelong) are critical.
- **Dynamic auscultation** distinguishing HCM from aortic stenosis is a high-yield clinical and viva skill.
- Always **exclude genocopies** (Fabry, amyloid, Danon, PRKAG2) — several are specifically treatable (enzyme replacement / migalastat for Fabry; tafamidis/acoramidis for ATTR amyloid).
- **Mavacamten** is a landmark first disease-specific therapy reshaping management of symptomatic obstructive HCM.

High-yield exam pointers

- Commonest **monogenic** CVS disease; **AD inheritance, prevalence 1:500**; **MYBPC3/MYH7 ≈80%** of sarcomeric cases.
- Diagnostic wall thickness **≥15 mm** (≥13 mm with FH/variant); **obstruction = gradient ≥30 mmHg**, intervene at **≥50 mmHg**.
- **SAM of mitral valve** → LVOT obstruction + **posteriorly-directed MR**; **myocyte disarray** is the histological hallmark.
- Murmur ↑ **with Valsalva/standing, ↓ with squatting/handgrip**; **Brockenbrough sign**; bisferiens pulse.
- **Avoid digoxin, nitrates and vasodilators**; first-line = **β-blocker / verapamil**; add **disopyramide** or **mavacamten**.
- Refractory obstruction → **septal myectomy** (gold standard) or **alcohol septal ablation**; main complication = **complete heart block**.
- SCD prevention = **ICD**; major risks = **FH SCD, syncope, LVH ≥30 mm, apical aneurysm, EF <50%, NSVT**; use the **ESC HCM Risk-SCD** score.
- **AF:** anticoagulate **irrespective of CHA_2DS_2-VASc**; **~5–8%** evolve to end-stage ("burnt-out") HCM.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Genetic Cardiomyopathies" (HCM section: epidemiology, genetics, pathophysiology, treatment algorithm, SCD risk table) and "Classification of Cardiomyopathy."
- **Braunwald's Heart Disease, 13e** — "Hypertrophic Cardiomyopathy" (Ho & Day): diagnosis/morphology, sarcomere genetics and genocopy table, SAM/LVOT pathophysiology, EXPLORER/VALOR/SEQUOIA trials, septal reduction, SCD risk algorithm.
- **CMDT 2026** — "Heart Failure & Cardiomyopathy" (HCM): physical signs, investigations, current drug/ICD management and 2020 AHA/ACC guideline risk factors.

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Left ventricular remodelling

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Left ventricular (LV) remodeling is the process by which the ventricle undergoes progressive changes in **shape, size, mass, wall thickness and geometry** in response to an *index injury* or chronic haemodynamic overload, occurring at the molecular, cellular and chamber levels. It is the structural substrate of heart failure with reduced ejection fraction (**HFrEF**): an index event (e.g., acute myocardial infarction, or chronic pressure/volume overload) is followed by **months to years of structural and functional cardiovascular remodeling**, during which compensatory mechanisms ultimately become maladaptive and drive disease progression. Initially adaptive, remodeling sets up a **self-perpetuating vicious cycle** of rising wall stress and falling pump function that culminates in clinical heart failure.

Pathophysiology — the remodeling cascade

- HFrEF is a **progressive disease** that begins with an *index event* — **sudden** (acute MI), **gradual** (chronic pressure or volume overload, e.g., valvular disease), **inherited** (genetic cardiomyopathy), or **congenital** in origin. Despite an early fall in cardiac performance, patients stay asymptomatic for prolonged periods because of **compensatory mechanisms** that later promote progression.
- The central driver is **increased myocardial wall stress**. By the **Law of Laplace**, wall stress ∝ (intracavitary pressure × chamber radius) ÷ (2 × wall thickness) — so chamber dilatation and pressure loading both raise wall stress, while wall thickening lowers it. *(Laplace formula is standard cardiac physiology — see Coverage note.)*
- **Remodeling stimuli** (Fig. 264-6) acting on the myocardium are: increased **wall stress**, inflammatory **cytokines**, **neurohormonal** signals, and **oxidative stress**.
- The myocardium responds with **adaptive and maladaptive** changes — myocyte hypertrophy, altered interstitial matrix, fetal-gene re-expression, altered calcium-handling proteins, and myocyte death — producing **ventricular enlargement** and **systolic and/or diastolic dysfunction**.

- Myocytes unable to adapt to remodeling stimuli are triggered to undergo **apoptosis (programmed cell death)**. Continued pump impairment plus systemic vasoconstriction and loss of neurohormonal adaptation produce **afterload mismatch**; these events **feed back on remodeling stimuli**, completing a **vicious cycle** that drives clinical HF.

Patterns of remodeling — concentric vs eccentric hypertrophy

- Different geometric patterns occur in response to **excess cardiac workload**, governed by the type of overload.

Feature	Concentric hypertrophy	Eccentric hypertrophy
Loading stimulus	**Pressure overload**	**Volume overload**
Typical causes	Hypertension, aortic stenosis	Aortic regurgitation, mitral regurgitation
Geometry	Increased mass **out of proportion** to chamber volume	Increased **cavity size/volume**, wall thinning
Effect on wall stress	**Reduces** wall stress (adaptive, initially)	Raised wall stress with progressive dilatation
Sarcomere change (standard)	Sarcomeres added **in parallel** → thicker wall	Sarcomeres added **in series** → elongated myocytes

- In **both** forms, increased ventricular mass is accompanied by tissue- and protein-level changes: **myocyte hypertrophy and interstitial fibrosis**; altered **calcium-handling and cytoskeletal protein** abundance/function; and **re-expression of fetal genes**.

Mechanisms of ventricular remodeling (Table 264-3)

- Remodeling is organised at three levels — **myocyte biology, myocardial composition, and ventricular geometry**:

Level	Mechanisms
Changes in myocyte biology	Abnormal **excitation–contraction coupling** and crossbridge interaction; **fetal gene expression** (e.g., **β-myosin heavy chain**); **β-adrenergic receptor desensitisation**; myocyte hypertrophy; impaired cytoskeletal proteins
Changes in myocardial composition	Myocyte **necrosis, apoptosis and autophagy**; **interstitial and perivascular fibrosis**; **matrix degradation**
Changes in ventricular geometry	**Ventricular dilation and wall thinning**; increased **sphericity** and **displacement of papillary muscles**; **atrioventricular valve regurgitation**

- **Neurohormonal activation** is pivotal: activation of the **sympathetic nervous system (SNS)** and the **renin–angiotensin–aldosterone system (RAAS)** initially supports heart rate, BP, contractility and Na^+/water retention, but unchecked promotes **myocyte hypertrophy, cell death and myocardial fibrosis** — remodeling the heart, vessels and kidneys.
- **Endothelin** (a potent vasoconstrictor with growth-promoting effects) drives **myocyte hypertrophy and interstitial fibrosis**; **inflammatory cytokines** (**TNF-α, IL-1β**) and **reactive oxygen species** (superoxide, peroxynitrite) also contribute to remodeling.

- **Counter-regulatory** vasodilatory hormones oppose remodeling — the **natriuretic peptides (ANP, BNP)** cause vasodilation, natriuresis and RAAS inhibition; they are degraded by **neprilysin** (the rationale for **angiotensin receptor–neprilysin inhibition, ARNI**).
- **Electrical dyssynchrony** (QRS prolongation/**LBBB** in up to one-third of HF patients) worsens remodeling; **secondary (functional) mitral regurgitation** arises from the **spherical ventricle**, papillary-muscle displacement and **mitral annular dilation**, feeding the vicious cycle.

Post-myocardial-infarction remodeling

- After STEMI the LV undergoes a series of changes in **shape, size and thickness in both infarcted and non-infarcted segments** — this is **ventricular remodeling**, and it generally **precedes clinically evident heart failure** by months to years.
- **Acute phase — infarct expansion**: soon after STEMI the LV begins to **dilate** due to **slippage of muscle bundles, disruption of myocardial cells and tissue loss** within the necrotic zone, causing **disproportionate thinning and elongation of the infarct zone**.
- **Later phase**: **lengthening of the non-infarcted segments** occurs, producing global chamber enlargement.
- **Determinants of severity**: overall chamber enlargement relates to **infarct size and location** — **anterior wall and apical** infarcts cause greater dilatation, more marked haemodynamic impairment, more frequent HF and a **poorer prognosis**.
- **Infarct healing** (Fig. 286-3): reparative monocytes and monocyte-derived fibroblasts synthesise **interstitial collagen** that reinforces the myocardial skeleton, **mitigating expansive remodeling** of the infarct and reducing the risk of chronic HF.
- **LV aneurysm**: defined as **dyskinesis or local expansile paradoxical wall motion**; a **true aneurysm** is composed of **scar tissue** and **neither predisposes to nor is associated with cardiac rupture**. Apical aneurysms are commonest; complications (HF, arterial embolism, ventricular arrhythmias) appear weeks–months later; a **double/diffuse/displaced apical impulse** is the key sign and **2-D echocardiography** detects the aneurysm and any **mural thrombus**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Remodeling stimuli in heart failure" (vicious cycle, after Fig. 264-6).** Boxes/arrows with EXACT labels: **Increased wall stress** → stimuli (**Wall stress, Cytokines, Neurohormonal, Oxidative stress**) → myocardial responses (**Myocyte hypertrophy, Altered interstitial matrix, Fetal gene expression, Altered calcium-handling proteins, Myocyte death**) → **Ventricular enlargement** → **Systolic or diastolic dysfunction** → feedback arrow returning to **Increased wall stress** (vicious cycle).
- **Diagram 2 — Concentric vs eccentric remodeling.** Three LV cross-sections labelled **Normal LV**, **Concentric hypertrophy (pressure overload — thick wall, small cavity)**, **Eccentric hypertrophy (volume overload — dilated cavity, thin wall)**; annotate **Laplace: wall stress = (P × r)/(2h)**.

Clinical / Diagnostic significance

- **Reverse remodeling is the therapeutic goal.** Antagonism of the **RAAS and SNS** with **RAS inhibitors (ACEi/ARB), mineralocorticoid-receptor antagonists, and beta-blockers attenuates or reverses ventricular and vascular remodeling and reduces morbidity and mortality**; **ARNI (sacubitril/valsartan)** and **SGLT-2 inhibitors** (effects on cardiac/vascular remodeling) extend this benefit in HFrEF.
- **Post-MI: ACE inhibitors reduce mortality after STEMI** via **reduction in ventricular remodeling**, with maximum benefit in high-risk patients (**anterior infarction, prior infarction, globally depressed LV function**); prescribe **ACEi/ARB ± beta-blocker** when **EF <40%**. Add an **MRA (spironolactone/eplerenone)** if EF ≤40% with symptomatic HF or diabetes (no significant renal dysfunction/hyperkalaemia). Note: **sacubitril/valsartan was NOT superior to an ACE inhibitor in preventing incident HF early post-MI**.
- **Cardiac resynchronisation therapy** (biventricular/LBBB pacing) for symptomatic HFrEF with LBBB **reverses ventricular remodeling**, improves contractile function and reduces mitral regurgitation.
- **Imaging:** chronic HF with remodeling is accompanied by **cardiac enlargement** with a **downward and leftward-displaced apical impulse**; **echocardiography** and serial **cardiac MRI** (quantifies LV mass, volumes and function) are used to **assess remodeling in response to therapy**.
- **Reverse remodeling** may also follow **weight loss** in obese HF patients.

High-yield exam pointers

- Remodeling = change in **shape, size, mass, wall thickness, geometry**; structural basis of **HFrEF**; the **index event → months–years of remodeling** concept is key.
- **Pressure overload → concentric** (parallel sarcomeres, reduces wall stress); **volume overload → eccentric** (series sarcomeres, dilatation).
- Three levels of remodeling (**Table 264-3**): **myocyte biology, myocardial composition, ventricular geometry**.
- **Fetal gene re-expression** classically = **β-myosin heavy chain**; **β-adrenergic receptor desensitisation** occurs.

- Maladaptive geometry → **increased sphericity, papillary-muscle displacement → functional mitral regurgitation**.
- Post-STEMI: **infarct expansion** (muscle slippage, thinning/elongation) → later non-infarct segment lengthening; **anterior/apical** infarcts remodel worst.
- **Drugs that reverse remodeling**: ACEi/ARB, **ARNI**, **MRA**, **beta-blockers**, **SGLT-2 inhibitors**, **CRT**.
- **True LV aneurysm = scar tissue**, does **NOT** cause rupture (contrast with pseudoaneurysm/free-wall rupture).
- **Endothelin blockade does NOT slow LV-failure HF** but helps PAH/right HF.

SOURCE & COVERAGE

Harrison 22e — Ch 264 "Heart Failure: Pathophysiology and Diagnosis" (Fig. 264-6, Table 264-3, neurohormonal mechanisms, reverse remodeling, imaging) + Ch 286 "ST-Segment Elevation Myocardial Infarction" (post-MI ventricular remodeling/dysfunction, infarct expansion, RAAS inhibition, LV aneurysm, Fig. 286-3). **Coverage note:** The provided chapters fully cover remodeling triggers, patterns, mechanisms, post-MI remodeling and reverse-remodeling therapy. Two adjuncts are *standard physiology/medicine not stated verbatim in the supplied text* — the explicit **Laplace formula** (wall stress = P·r/2h) and the **parallel- vs series-sarcomere** correlate of concentric vs eccentric hypertrophy — included as universally accepted cardiac physiology to complete the answer.

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Supraventricular tachycardia

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Supraventricular tachycardia (SVT) is a tachyarrhythmia arising from atrial tissue or from circuits using the AV node/accessory pathway, i.e. above or involving the His bundle. In exam practice, "SVT" usually refers to **regular paroxysmal narrow-complex tachycardia**, chiefly **AV nodal re-entrant tachycardia (AVNRT)** and **atrioventricular re-entrant tachycardia (AVRT)**, but focal atrial tachycardia and atrial flutter must be recognized. Management is algorithmic: assess stability, record the rhythm, terminate the episode safely, prevent recurrence, and offer curative ablation when appropriate.

Classification and mechanisms

- **AVNRT**: commonest paroxysmal SVT; re-entry within dual AV nodal physiology. Typical slow-fast AVNRT has a regular narrow QRS tachycardia with hidden/retrograde P waves, pseudo-r' in V1, or pseudo-S waves in inferior leads.
- **Orthodromic AVRT**: antegrade conduction through AV node and retrograde conduction through an accessory pathway; narrow QRS unless baseline bundle branch block/aberrancy. It is the usual tachycardia in Wolff-Parkinson-White (WPW) syndrome.

- **Antidromic AVRT**: antegrade conduction down the accessory pathway and retrograde conduction through AV node/another pathway; produces a regular broad-complex tachycardia and may mimic VT.
- **Focal atrial tachycardia**: automatic, triggered, or micro-re-entrant atrial focus; P-wave morphology differs from sinus rhythm and AV block may occur without terminating the atrial rhythm.
- **Atrial flutter / macro-re-entrant atrial tachycardia**: atrial rate often around 250-350/min; ventricular response depends on AV conduction, commonly 2:1 with a rate near 150/min.
- **Multifocal atrial tachycardia**: irregular atrial tachycardia with at least three P-wave morphologies, often in COPD, hypoxia, pulmonary disease, sepsis, or electrolyte disturbance; do not manage as AVNRT.

Immediate assessment and diagnosis

- First decide **unstable versus stable**. Instability includes hypotension/shock, acute pulmonary edema, ischemic chest pain, altered sensorium, severe dyspnea, or syncope attributable to tachycardia.
- Obtain a **12-lead ECG during tachycardia** before treatment if this does not delay emergency care; also record a post-conversion ECG to look for pre-excitation, ischemia, QT interval, and baseline conduction disease.
- Define the rhythm by **QRS width** and **regularity**:

ECG pattern	Likely diagnosis	Immediate implication
Regular narrow-complex	AVNRT, orthodromic AVRT, atrial tachycardia, flutter with fixed block	Vagal maneuvers and adenosine are useful
Irregular narrow-complex	AF, atrial flutter with variable block, MAT	Avoid reflex “SVT bolus” treatment; identify atrial rhythm
Regular broad-complex	VT, SVT with aberrancy, antidromic AVRT	Treat as VT if uncertain
Irregular broad-complex	AF with pre-excitation, polymorphic VT	Avoid AV nodal blockers; urgent specialist/emergency treatment

- Look for reversible precipitants: fever, pain, anemia, hypovolemia, hypoxia, pulmonary embolism, myocardial ischemia, thyrotoxicosis, alcohol/stimulants, sympathomimetics, digoxin toxicity, hypokalemia, and hypomagnesemia.
- Basic work-up after stabilization: electrolytes including Mg/Ca, renal function, glucose, thyroid testing when indicated, troponin only if ischemia is suspected, echocardiography for structural heart disease, ambulatory monitoring for undocumented episodes, and EP study for recurrent/uncertain SVT.

Acute management of regular narrow-complex SVT

- **Stable patient**: monitor ECG and blood pressure, establish IV access, give oxygen only if hypoxemic, prepare defibrillator, and explain that transient AV block or flushing may occur with adenosine.

- **Vagal maneuvers** are first-line: modified Valsalva is preferred where feasible; carotid sinus massage may be used with continuous monitoring after excluding carotid bruit, recent stroke/TIA, and significant carotid disease. Do not use ocular pressure.
- **Adenosine** is the drug of choice for AV node-dependent PSVT:

Step	Dose and method	Key point
First bolus	**6 mg rapid IV push** followed immediately by saline flush	Use a large proximal vein; record rhythm strip
If no conversion	**12 mg rapid IV push**	May repeat 12 mg once if needed
Modified dosing	Consider lower initial dose, e.g. 3 mg, with central line, heart transplant, or dipyridamole	Methylxanthines antagonize effect

- Adenosine terminates most **AVNRT/orthodromic AVRT** and may only transiently slow atrial tachycardia/flutter, thereby revealing flutter waves or atrial P waves.
- If adenosine is ineffective/contraindicated and the rhythm is definitely narrow-complex without pre-excitation, use **IV diltiazem or verapamil** or an **IV beta-blocker** with BP monitoring.
- Avoid combining IV beta-blockers with verapamil/diltiazem because of hypotension, bradycardia, or AV block risk. Avoid nondihydropyridine calcium channel blockers in significant LV systolic dysfunction or decompensated heart failure.
- If drug therapy fails or the patient deteriorates at any step, proceed to **synchronized DC cardioversion**.

Management of unstable SVT and broad-complex presentations

- **Unstable SVT**: perform immediate **synchronized electrical cardioversion**; give sedation/analgesia if time permits, but do not delay cardioversion for shock, ischemia, pulmonary edema, or altered sensorium.
- For regular narrow-complex SVT, start with **50-100 J biphasic synchronized shock** and escalate if required. Reassess airway, BP, rhythm, and precipitating cause after conversion.
- **Regular wide-complex tachycardia** should be treated as VT unless SVT with aberrancy is certain. Adenosine may be diagnostic/therapeutic only in a regular monomorphic rhythm with no evidence of pre-excited AF or polymorphic VT.
- **Pre-excited AF** is an emergency clue: irregular wide QRS, very rapid ventricular rates, beat-to-beat QRS variation, and WPW features. Avoid adenosine, digoxin, beta-blockers, verapamil, and diltiazem because AV nodal block may accelerate accessory pathway conduction.
- For stable pre-excited AF or antidromic AVRT, specialist-directed rhythm control with **procainamide or ibutilide** may be used; if unstable, use synchronized cardioversion.
- Treat electrolyte abnormalities aggressively: correct hypokalemia and hypomagnesemia, stop pro-arrhythmic drugs, and manage ischemia, hypoxia, sepsis, or stimulant/drug toxicity.

Drug choices: indications and cautions

- **Adenosine**: very short acting; adverse effects are flushing, chest tightness, dyspnea, sense of doom, transient AV block, and rarely bronchospasm or AF. Use caution in asthma/COPD with active bronchospasm.

- **Verapamil/diltiazem**: useful for AV node-dependent SVT and rate control in atrial tachyarrhythmias without pre-excitation; avoid in hypotension, HFrEF/decompensated HF, wide-complex undiagnosed tachycardia, and pre-excited AF.
- **Beta-blockers**: useful acutely and chronically for AVNRT/AVRT suppression and adrenergic atrial tachycardia; avoid or use cautiously in severe bronchospasm, acute decompensated HF, marked bradycardia, and advanced AV block.
- **Class IC drugs** such as flecainide/propafenone may prevent recurrent SVT or AVRT in patients without structural or ischemic heart disease; they require specialist selection and usually AV nodal protection when atrial flutter risk exists.
- **Amiodarone, sotalol, dofetilide** are not routine first-line drugs for uncomplicated AVNRT; reserve for selected patients with structural heart disease, refractory arrhythmia, or when ablation is not possible, considering QT, renal, pulmonary, thyroid, hepatic, and drug-interaction risks.
- **Digoxin** has limited contemporary use for PSVT prevention and must be avoided in pre-excited AF; toxicity can itself cause atrial tachycardia with block.

Long-term and definitive management

- Explain benign prognosis in structurally normal hearts, teach **self-administered vagal maneuvers**, identify triggers, and advise documentation of future episodes by ECG/wearable strip when feasible.
- **Catheter ablation** is the definitive treatment for recurrent symptomatic AVNRT, AVRT/accessory pathway-mediated tachycardia, recurrent focal atrial tachycardia, incessant SVT, tachycardia-induced cardiomyopathy, high-risk occupation, or patient preference to avoid lifelong drugs.
- For **AVNRT**, slow-pathway modification is standard; success is high and recurrence is low, with a small but important risk of AV block requiring pacing.
- For **AVRT/WPW**, ablate the accessory pathway, especially with syncope, documented AVRT, pre-excited AF, high-risk pathway properties, multiple pathways, or competitive athletics/high-risk work.
- If ablation is deferred: use oral beta-blocker, verapamil, or diltiazem for recurrent AVNRT/orthodromic AVRT without pre-excitation during AF; consider class IC drugs only in carefully selected patients without structural heart disease.
- **Pregnancy**: vagal maneuvers and adenosine are preferred acutely; synchronized cardioversion is safe when unstable. Use beta-blockers or verapamil selectively for prevention; consider low/zero-fluoroscopy ablation only for refractory, poorly tolerated SVT.
- **MAT** management is treatment of the underlying illness: oxygenation, bronchodilator optimization without excess beta-agonist exposure, correction of K/Mg, treatment of infection or pulmonary disease; cardioversion and adenosine usually do not cure MAT.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Acute SVT algorithm flowchart**: stable/unstable split; unstable -> synchronized cardioversion; stable regular narrow QRS -> vagal maneuver -> adenosine 6 mg -> 12 mg -> calcium channel blocker/beta-blocker -> cardioversion/EP referral; side box: "avoid AV nodal blockers in pre-excited AF."
- **Re-entry mechanism sketch**: AVNRT slow and fast AV nodal pathways with retrograde P wave; orthodromic AVRT circuit showing AV node antegrade limb and accessory pathway retrograde limb; label atrium, AV node, His-Purkinje system, ventricle, accessory pathway.

Clinical / Diagnostic significance

- A narrow regular tachycardia that terminates abruptly with adenosine strongly suggests **AV node-dependent re-entry**; transient slowing without termination suggests atrial tachycardia or flutter.
- P-wave position is diagnostically useful: short RP tachycardia suggests typical AVNRT/orthodromic AVRT; long RP tachycardia suggests atrial tachycardia, atypical AVNRT, or permanent junctional reciprocating tachycardia.
- Always obtain a sinus-rhythm ECG after conversion: delta wave and short PR identify WPW; QT prolongation, bundle branch block, ischemic changes, or Brugada pattern alter management.
- Recurrent incessant SVT may cause **tachycardia-induced cardiomyopathy**, which can improve after rhythm control or ablation.
- In older patients, SVT may present as falls, presyncope, angina, heart failure, or hypotension rather than palpitations.
- Troponin elevation can occur after prolonged tachycardia without plaque rupture; interpret in clinical context rather than labelling all cases acute coronary syndrome.

High-yield exam pointers

- Write the first line of management as **ABC, monitor, IV access, 12-lead ECG, assess hemodynamic stability**.
- **Unstable SVT = synchronized cardioversion**, not a prolonged drug trial.
- **Stable regular narrow SVT = vagal maneuver -> adenosine -> AV nodal blocker/cardioversion**.
- Adenosine dose: **6 mg rapid IV bolus, then 12 mg, then 12 mg** with immediate flush and rhythm strip.
- **Do not give AV nodal blockers in pre-excited AF**: avoid adenosine, digoxin, beta-blocker, verapamil, and diltiazem.
- Treat broad-complex tachycardia as **VT until proved otherwise**.
- Definitive therapy for recurrent symptomatic AVNRT/AVRT is **radiofrequency catheter ablation**.
- Look for reversible triggers: hypoxia, ischemia, thyrotoxicosis, stimulants, alcohol, sepsis, hypokalemia, and hypomagnesemia.

- Draw the acute algorithm and the AVNRT/AVRT re-entry circuit; these diagrams score quickly in a 10-mark answer.

SOURCE & COVERAGE

Harrison 22e — "Approach to Supraventricular Arrhythmias"; "Paroxysmal Supraventricular Tachycardias"; Braunwald's Heart Disease 13e — "Supraventricular Tachycardias"; CMDT 2026.

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Narrow QRS tachycardia

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — A **narrow QRS (narrow-complex) tachycardia** is a heart rate >100 beats/min with a **QRS duration <120 ms**, reflecting normal ventricular activation over the His–Purkinje system. Because the impulse originates from, or is dependent on conduction through, the atrium or AV node, these are essentially **supraventricular tachycardias (SVTs)**, and the QRS morphology is usually identical to that in sinus rhythm. Their importance lies in correct mechanistic identification at the bedside from a 12-lead ECG, as prognosis and treatment vary widely by mechanism.

Mechanistic Classification of Supraventricular Tachycardia (Table 253-1)

Group	Arrhythmia	Defining feature
Physiologic	Sinus tachycardia	Normal sinus mechanism driven by exertion, stress, stimulants, illness
Atrial origin	Inappropriate sinus tachycardia	Sinus-node-area tachycardia with no precipitant (dysfunctional autonomic regulation)
	Focal atrial tachycardia (AT)	Regular, defined P wave; foci at valve annuli, pulmonary veins, coronary sinus, SVC
	Atrial flutter / macroreentrant AT	Macroreentry; sawtooth flutter waves, atrial rate typically >200/min
	Atrial fibrillation (AF)	Chaotic atrial activity, variable ventricular rate; commonest sustained arrhythmia in older adults
	Multifocal atrial tachycardia (MAT)	Multiple discrete P-wave morphologies; pulmonary disease exacerbations
AV node	AV nodal reentry tachycardia (**AVNRT**)	Paroxysmal regular; P at end of QRS or invisible; commonest PSVT in healthy young adults, women
Accessory pathway	Orthodromic AVRT	Paroxysmal regular; preexcitation (WPW) or concealed pathway
	Preexcited (antidromic AVRT, preexcited AF/flutter)	**Wide** QRS — exception to the narrow-QRS rule

- A useful three-way split by mechanism: **AV-nodal-dependent reentry** (AVNRT, AVRT), **macroreentry within atrium** (atrial flutter), and **focal AT** (automaticity or microreentry).

- Other supraventricular rhythms: premature atrial contractions (PACs), sinus arrhythmia, accelerated junctional rhythm, ectopic atrial rhythm.

Bedside Differential by ECG Pattern (Fig 253-1)

Obtain a **full 12-lead ECG with a long rhythm strip** and decide first whether the rhythm is **regular or irregular**.

ECG appearance	Likely diagnoses
Regular, **1:1 AV** response	AVNRT, orthodromic AVRT, atrial tachycardia, rarely atrial flutter
Regular, **AV block (more A's than V's)**	Atrial flutter, atrial tachycardia, rarely AVNRT with 2:1 block below the His
Regular, **VA block (more V's than A's)**	Junctional tachycardia
Irregular	Atrial fibrillation, multifocal atrial tachycardia

Characteristic Features of Individual Narrow-QRS Tachycardias

- **AVNRT** — the most common PSVT (~60% of cases referred for ablation); manifests in the 2nd–4th decades, more often in women, usually with structurally normal hearts. Reentry uses dual AV nodal pathways within the **triangle of Koch** — a **slow pathway** (right inferior nodal extension) and a **fast pathway**. Near-simultaneous atrial and ventricular activation places the P wave **at the end of the QRS**, producing a *pseudo-r'* in V1 and *pseudo-S waves* in II, III, aVF. Simultaneous atrial contraction against a closed tricuspid valve gives **cannon A waves** ("frog sign," fluttering in the neck) and post-tachycardia diuresis via natriuretic peptide release.
- **Orthodromic AVRT** — the commonest tachycardia caused by an accessory pathway (AP); the wavefront travels **antegrade down the AV node/His–Purkinje system and retrograde up the AP**, so the QRS is **narrow** (or has fixed BBB). The P wave **always follows the QRS** (R-P shorter than P-R), inscribed in the ST segment. AV or VA block terminates it. The AP may be manifest (**WPW**: short PR <0.12 s, delta wave, wide QRS in sinus rhythm) or **concealed** (retrograde-only, normal sinus ECG).
- **Focal atrial tachycardia** — regular, with **discrete P waves separated by an isoelectric baseline**, distinct from sinus P; tachycardia can continue despite AV block (AV node not in the circuit).
- **Atrial flutter** — macroreentry giving **sawtooth flutter waves** (atrial rate typically >200/min, classically ~300/min); commonly conducts **2:1**, yielding a regular ventricular rate near 150/min.
- **Atrial fibrillation** — **irregularly irregular**, no discrete P waves; the commonest sustained arrhythmia in older adults.
- **Multifocal atrial tachycardia** — irregular with **multiple (≥3) discrete P-wave morphologies**, seen in acute pulmonary insufficiency exacerbations.
- **Junctional (ectopic) tachycardia (JET)** — automaticity within the AV node; **narrow QRS often with VA block / AV dissociation**; rare in adults, more often incessant in children after congenital heart surgery. *Accelerated junctional rhythm* is a junctional automatic rhythm of 50–100/min.

Diagnostic and Therapeutic Effect of AV Nodal Blockade (Fig 253-2)

Vagal maneuvers, carotid sinus massage (CSM), or **adenosine** both **treat and diagnose** by transiently blocking the AV node while the ECG runs continuously.

Response to AV nodal blockade	Inference
No effect	Fascicular VT, or inadequate dose/effect
Tachycardia slows then resumes	Sinus tachycardia, junctional tachycardia
Tachycardia terminates	AVNRT, AVRT, adenosine-sensitive focal AT
Atrial activity continues with transient AV block	Atrial flutter, atrial tachycardia

- **Vagal maneuvers**: Valsalva (bearing down), modified Valsalva with leg-raise, diver's reflex (cold-water face immersion), and CSM. CSM should be used cautiously or avoided if carotid bruits, prior stroke, or atherosclerosis risk (embolization).
- **Adenosine 6 mg, then 12 mg** IV rapid push causes transient AV block; it terminates AV-nodal-dependent SVT and unmasks AT/flutter. Note some focal ATs are adenosine-sensitive, so termination does not exclude AT.

Acute and Long-Term Management

- **Unstable** (hypotension with altered consciousness or respiratory distress): immediate **QRS-synchronous DC cardioversion** — rarely needed, as adenosine usually works promptly.
- **Stable PSVT (AVNRT / orthodromic AVRT)**: vagal maneuvers/CSM → IV adenosine → AV nodal blocking drugs (**beta blockers, verapamil or diltiazem**). Chronic options for recurrent episodes include these agents or **flecainide**; a single oral dose at onset ("pill-in-the-pocket") can abort episodes.
- **Curative catheter ablation**: slow-pathway ablation for AVNRT is curative in **>95%**, with **<1%** risk of AV block needing a pacemaker; AP ablation efficacy ~95%, serious complications <3%, mortality <1 in 1000.
- **Focal AT**: correct precipitants; rate control with beta/calcium channel blockers; antiarrhythmics (flecainide, propafenone, sotalol, amiodarone) or ablation (>80% success) if recurrent/incessant (risk of tachycardia-induced cardiomyopathy).
- **Preexcited AF (CRITICAL)**: **AV nodal blockers — adenosine, verapamil, diltiazem, beta blockers, IV amiodarone — are CONTRAINDICATED**, as they can accelerate AP conduction and precipitate VF. Treat with **DC cardioversion** or **IV procainamide / ibutilide**. Shortest preexcited R-R <250 ms during AF signals high sudden-death risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic flow-chart (Fig 253-1):** Top box "Narrow-complex tachycardia → 12-lead ECG + long rhythm strip"; branch into **Regular** vs **Irregular**. Under Regular: **1:1 AV response** (AVNRT, ORT/AVRT, AT, rarely atrial flutter); **AV block, more A's than V's** (atrial flutter, atrial tachycardia, rarely AVNRT with 2:1 block); **VA block, more V's than A's** (junctional tachycardia). Under Irregular: **atrial fibrillation, multifocal atrial tachycardia**.
- **AVNRT circuit in the triangle of Koch:** label **compact AV node (fast pathway)**, **inferior nodal extension (slow pathway)**, **His bundle**, **tricuspid valve**, **coronary sinus (CS)**, and arrows showing slow-pathway antegrade / fast-pathway retrograde reentry, with **retrograde P wave at end of QRS (pseudo-r′ in V1)**.

Clinical / Diagnostic significance

- Symptoms: palpitations, chest pain, dyspnea, reduced exertional capacity, occasionally syncope; rarely cardiac arrest in WPW or hypertrophic cardiomyopathy.
- **Ventricular preexcitation on the resting ECG** points to AVRT via an accessory pathway; the diagnosis of SVT requires capturing an ECG during symptoms — increasingly via wearables/smartphone single-lead ECG.
- Accessory pathways occur in **1 in 1500–2000** people and associate with **Ebstein's anomaly**, hypertrophic cardiomyopathy (**PRKAG2**), **Danon's disease**, and **Fabry's disease**. *Mahaim (atriofascicular) fibers* cause an LBBB-pattern wide-complex tachycardia.
- Most paroxysmal SVT occurs in structurally normal hearts; AF is the entity most often linked to structural/systemic heart disease, so initial evaluation should screen for it.

High-yield exam pointers

- **Narrow QRS = QRS <120 ms** = supraventricular origin; morphology usually identical to sinus rhythm.
- First branch point on the ECG is **regular vs irregular** — irregular narrow QRS = **AF or MAT**.
- **AVNRT** is the commonest PSVT; P at end of QRS → **pseudo-r′ in V1, pseudo-S in II/III/aVF**; **cannon A waves / frog sign**.
- **Orthodromic AVRT**: narrow QRS, **P always follows QRS, R-P < P-R**.
- **Adenosine 6 then 12 mg** — both diagnostic and therapeutic; terminates AVNRT/AVRT, unmasks flutter/AT.
- **Atrial flutter**: sawtooth waves, 2:1 conduction → ventricular rate ~150/min.
- **Preexcited AF: never give AV-nodal blockers** — use procainamide/ibutilide or DC shock.
- **Slow-pathway ablation cures AVNRT in >95%**, AV block needing pacemaker <1%.
- Unstable narrow-QRS tachycardia → **synchronized DC cardioversion**.

SOURCE & COVERAGE

Harrison 22e — Ch 253 "Approach to Supraventricular Arrhythmias" and Ch 256 "Paroxysmal Supraventricular Tachycardias" (with focal-AT management from the adjoining Ch 255 figure carried in the Ch 256 text file). **Coverage note:** The provided Ch 256 text ends mid-"Treatment of PSVT," so the full acute drug algorithm beyond adenosine is truncated; specific IV doses of verapamil/diltiazem/beta blockers are not stated in the supplied text and are given here only as drug classes. The "~300/min" flutter rate and "≥3 P-wave morphologies" for MAT are universally accepted textbook standards added to the source's "rate >200/min" and "multiple discrete P waves."

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Neurally mediated syncope

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Syncope is a transient, self-limited loss of consciousness (TLOC) due to acute *global* impairment of cerebral blood flow, with rapid onset, brief duration and spontaneous, complete recovery. **Neurally mediated syncope** (synonyms: *reflex*, *vasovagal*, *neurocardiogenic* syncope) is the final common pathway of a complex central-and-peripheral reflex arc in which a transient change in autonomic efferent activity — increased parasympathetic (vagal) outflow plus sympathoinhibition — produces **bradycardia, vasodilatation and/or loss of vasoconstrictor tone**, leading to a fall in systemic blood pressure and cerebral hypoperfusion. It requires an *intact* autonomic nervous system (unlike syncope of autonomic failure) and is the single commonest cause of syncope in population-based studies.

Epidemiology and clinical importance

- Syncope accounts for **~3% of all emergency-department visits and ~1% of hospital admissions**; lifetime cumulative incidence is up to **40%** (CMDT: ~30% of adults faint at least once).
- **Bimodal age distribution** — first peak in the young (10–30 yr, median ~15 yr), where neurally mediated syncope dominates; a second sharp rise after age 70 (where orthostatic and cardiac causes climb). Incidence is higher in women; first-degree family history is common in young fainters.
- Prognosis of neurally mediated (and unexplained non-cardiac) syncope in the young is **excellent — life expectancy unaffected**; this contrasts sharply with cardiac syncope, which carries increased risk of sudden cardiac death.

Classification — placing neurally mediated syncope among the causes

Category	Mechanism	Key examples
A. Neurally mediated (reflex)	Transient reflex vasodilatation ± bradycardia; intact ANS	Vasovagal (common faint); situational; carotid sinus syndrome

Category	Mechanism	Key examples
B. Orthostatic hypotension	*Chronic* sympathetic vasoconstrictor (autonomic) failure	Synucleinopathies (PD, DLB, MSA/Shy–Drager, pure autonomic failure); diabetic/amyloid neuropathy; drug-induced; volume depletion
C. Cardiac	↓ Cardiac output from arrhythmia or structural disease	SND, AV block, VT/SVT, channelopathies; AS, HOCM, atrial myxoma, tamponade, PE

Sub-classification of neurally mediated syncope — by *afferent trigger* and by *efferent (haemodynamic) pattern*:

By afferent trigger	Provoking stimulus
Vasovagal syncope (common faint)	Fear, pain, intense emotion, sight of blood, prolonged motionless standing, heat, venepuncture
Situational reflex syncope	*Pulmonary* — cough, sneeze, wind-instrument/weight-lifter; *Urogenital* — post-micturition, instrumentation; *GI* — swallow, defecation, glossopharyngeal neuralgia; *Cardiac* — Bezold–Jarisch reflex; *Ocular* — ocular pressure
Carotid sinus syndrome	Carotid sinus stimulation (tight collar, head-turning, shaving)

By efferent pattern	Dominant mechanism
Vasodepressor	Sympathetic vasoconstrictor *withdrawal* → hypotension predominates
Cardioinhibitory	Excess vagal tone → bradycardia/asystole predominates
Mixed	Both vagal and sympathetic reflex changes (most common)

Pathophysiology — the reflex arc

- **The orthostatic stress:** standing pools **500–1000 mL** of blood in the legs, buttocks and splanchnic bed, reducing venous return, ventricular filling, cardiac output and BP. Normally the **baroreflex** corrects this: unloading of carotid-sinus and aortic-arch baroreceptors → afferents via *glossopharyngeal (IX)* and *vagus (X)* nerves to the **nucleus tractus solitarius (NTS)** in the dorsomedial medulla → reduced vagal output to the sinus node (via *nucleus ambiguus*) and increased sympathetic outflow (via CVLM→RVLM disinhibition), restoring peripheral resistance and cardiac output.
- **In neurally mediated syncope this reflex paradoxically reverses.** The favoured model: reduced preload from venous pooling → vigorous contraction of a relatively *empty, catecholamine-stimulated* ventricle → activation of *unmyelinated ventricular mechanoreceptors (C-fibres)* in the atria, ventricles and pulmonary artery → afferents to the dorsal vagal nucleus → **"paradoxical" sympathetic withdrawal + surge in vagal tone** → vasodilatation and bradycardia (the **Bezold–Jarisch reflex**). The result mimics a "fictitious haemorrhage" to which the brainstem responds, paradoxically, by slowing/stopping the heart.

- Higher cortical centres also participate — emotion and the sight of blood can trigger fainting without preload reduction. Many situational faints additionally involve **hyperventilation (hypocarbia → cerebral vasoconstriction)** and **raised intrathoracic pressure (↓ venous return)**.
- **Critical thresholds:** cessation of cerebral flow for **6–8 s**, a fall in systolic BP to **~50 mmHg**, or cerebral flow <25 mL/min/100 g causes loss of consciousness. Cerebral autoregulation normally holds flow constant over a perfusion pressure of **50–150 mmHg**.

Clinical features and recognition

- **Triphasic episode:** (1) *Prodrome (presyncope)* of autonomic activation — light-headedness, nausea, diaphoresis, pallor, warmth, palpitations, yawning, blurred/tunnel vision; (2) *transient LOC* with loss of postural tone; (3) *rapid, complete recovery* (no true post-ictal confusion).
- During the faint: eyes typically remain **open and deviate upward**, pupils dilated; brief **arrhythmic, multifocal myoclonic jerks (<30 s)** may simulate a seizure ("convulsive syncope"); urinary incontinence can occur but **faecal incontinence is very rare**.
- **Provocative/predisposing factors:** motionless upright posture, warm environment, volume depletion, alcohol, anaemia, hypoxaemia, pain, venepuncture, emotion.

Differentiating reflex syncope from its mimics

Feature	Neurally mediated syncope	Generalised seizure	Cardiac (arrhythmic) syncope
Posture/ trigger	Usually upright; emotion, pain, heat	Any position; aura	Often exertional or supine; no trigger
Prodrome	Long autonomic prodrome (nausea, sweat, pallor)	Aura (e.g. unpleasant smell)	Brief/none (<5 s), sometimes palpitations
Movements	Brief, arrhythmic, multifocal myoclonus	Rhythmic tonic–clonic; tongue-biting	None typical
Recovery	Immediate re-orientation	Prolonged post-ictal confusion (>5 min)	Prompt but injury common
Colour	Pale	Cyanosed/flushed	Pale

Other mimics: **hypoglycaemia** (hunger, tremor, sweating — not features of syncope), **cataplexy** (consciousness preserved), **vertebrobasilar ischaemia**, and **psychogenic pseudosyncope** (frequent falls without haemodynamic change or injury).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **The baroreflex / reflex arc (Fig. 23-1):** label — *carotid sinus & aortic-arch baroreceptors → glossopharyngeal (IX) and vagus (X) afferents → Nucleus Tractus Solitarius (NTS) → Nucleus Ambiguus (→ vagal/parasympathetic to sinus node)* and *CVLM → RVLM (→ sympathetic efferent to heart & vessels)*; mark *ventricular C-fibre mechanoreceptors → dorsal vagal nucleus (Bezold–Jarisch limb)*. Annotate the efferent result: *vasodilatation + bradycardia → ↓BP → cerebral hypoperfusion*.
- **Tilt-table tracing (Fig. 23-2):** two stacked curves over time on 70° head-up tilt — upper = *Heart Rate (bpm)*, lower = *Blood Pressure (mmHg)* — showing the **paroxysmal hypotensive–bradycardic response** of neurally mediated syncope; contrast with the *gradual BP fall without HR rise* of orthostatic hypotension.

Clinical / Diagnostic significance

- **Initial evaluation (the cornerstone, diagnostic in ~50%):** detailed history, eyewitness account (± phone video), full cardiac/neurological exam, **supine and 3-min standing BP/HR**, and a **12-lead ECG**. Screen for high-risk features mandating admission (Table 23-1): exertional/supine syncope, palpitations preceding syncope, structural/ischaemic heart disease, **QTc >500 ms**, bifascicular block/QRS ≥120 ms, *Brugada* pattern, persistent bradycardia, family history of sudden death.
- **Tilt-table test:** confirms susceptibility to neurally mediated syncope when the diagnosis is unclear (ACC/AHA/HRS **Class IIa**). Protocol — 20-min supine stabilisation, then head-up tilt at **60–80° (70° usual) for 30–45 min**; sensitised with **isoproterenol (1–3 µg/min to raise HR ~25%)** or **sublingual nitroglycerin 300–400 µg**. Unmedicated specificity ~90%; it also classifies the response as cardioinhibitory, vasodepressor or mixed (*VASIS* types) and exposes psychogenic pseudosyncope (LOC with normal BP/HR).
- **Carotid sinus massage:** for patients >40 yr with recurrent unexplained syncope. Apply 5–10 s pressure below the angle of the jaw, supine and upright, under continuous ECG/BP. **Positive (carotid sinus hypersensitivity):** *cardioinhibitory* = asystole **>3 s**, or *vasodepressor* = SBP fall **>50 mmHg**, with reproduction of symptoms. **Avoid** with carotid bruit, plaque/stenosis or recent TIA/stroke.
- **Cardiac work-up only if indicated:** echocardiography (if structural disease suspected), ambulatory/Holter monitoring for frequent spells, **external or implantable loop recorder** for infrequent spells (monitor ≥ twice the inter-spell interval), exercise testing for exertional syncope, EP study only with structural heart disease. Routine bloods are low-yield.

Management (stepped; ACC/AHA/HRS 2017 & ESC 2018)

- **Foundation (all patients): education and reassurance** about the benign nature, recognition of prodrome, avoidance of triggers (heat, dehydration, alcohol, prolonged standing), and prompt **supine positioning** at symptom onset. Liberalise **salt and fluid**; acute ingestion of ~500 mL water aborts orthostatic intolerance.

- **Physical counterpressure manoeuvres (Class IIa):** leg-crossing, squatting, handgrip/arm-tensing and **abdominal + leg-muscle tensing** (most effective) raise central blood volume — most useful in those with a long prodrome (RCT-supported). *Tilt/standing training* is of uncertain benefit.
- **Pharmacotherapy (refractory cases): Midodrine** (α1-agonist) is the *only* agent proven effective in multicentre RCTs (Class IIa; avoid in hypertension, HF, urinary retention). **Fludrocortisone** (volume expansion, Class IIb) and an **SSRI** may be tried; **β-blockers are generally ineffective** (no better than placebo in POST) except possibly age ≥42 yr (Class IIb). Withdraw offending hypotensive drugs.
- **Cardiac pacing — narrow indication:** *not* routinely beneficial (vasodepression dominates most faints). A **dual-chamber pacemaker with closed-loop stimulation** reduces recurrence only in selected patients **>40 yr with frequent syncope and a documented spontaneous/ tilt-induced cardioinhibitory (asystolic) response** (SPAIN, ISSUE-3-type data; ESC Class IIa, ACC/AHA IIb).
- **Carotid sinus syndrome:** dual-chamber pacing for recurrent syncope with a dominant cardioinhibitory/mixed response (Class IIa).
- **Emerging: cardioneuroablation** (radiofrequency/cryo ablation of vagal ganglionated plexi) shows high freedom from syncope in cardioinhibitory VVS in small RCTs — still investigational.

High-yield exam pointers

- Triad of neurally mediated syncope mechanism: **vasodilatation + bradycardia + loss of vasoconstrictor tone** via vagal surge and sympathetic withdrawal — *requires an intact ANS.*
- **Bezold–Jarisch reflex** (ventricular C-fibre mechanoreceptors) underlies the "empty-ventricle" paradoxical faint.
- Efferent patterns: **vasodepressor / cardioinhibitory / mixed** — mixed is commonest; pacing helps *only* cardioinhibitory.
- Carotid sinus hypersensitivity numbers: **asystole >3 s** (cardioinhibitory), **SBP drop >50 mmHg** (vasodepressor).
- Tilt-table: **70°, 30–45 min**; isoproterenol or SL-GTN sensitisation; specificity ~90% unmedicated.
- **Midodrine** = only drug with RCT-proven benefit; **β-blockers don't work** (POST).
- Critical thresholds: LOC after **6–8 s** of arrested flow or SBP **~50 mmHg**; cerebral autoregulation **50–150 mmHg**.
- Distinguish from seizure: brief arrhythmic myoclonus, *immediate* recovery, no tongue-biting, no true post-ictal phase.
- Convulsive syncope, upward eye deviation and urinary incontinence do **not** equal epilepsy; faecal incontinence is very rare in syncope.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Syncope" (Freeman & Raj): definition, classification, baroreflex/pathophysiology, neurally mediated subtypes, clinical features, evaluation and treatment.
- **Braunwald's Heart Disease, 13e** — "Hypotension and Syncope": Bezold–Jarisch/C-fibre mechanism, carotid sinus hypersensitivity criteria, tilt-table protocol and sensitisation, ACC/AHA/HRS treatment table, SPAIN trial, pacing and cardioneuroablation.
- **CMDT 2026** — "Disorders of Cardiac Rhythm" (Syncope): current diagnostic approach, counterpressure manoeuvres, midodrine/fludrocortisone/SSRI, pacing caveats, cardioneuroablation, driving restrictions.
- *Coverage note:* The named **VASIS** tilt-response typing is standard cardiology nomenclature; the corpus describes the underlying cardioinhibitory/vasodepressor/mixed responses but does not spell out the VASIS subtype letters.

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Congestive cardiac failure — pathogenesis and management

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Heart failure (HF) is a complex clinical syndrome of symptoms and signs (breathlessness, fatigue, ankle swelling) arising from any structural or functional impairment of ventricular filling or ejection, leading to elevated intracardiac filling pressures and/or inadequate cardiac output at rest or on exertion. Because many patients lack overt volume overload, the *universal definition* prefers the term "heart failure" over the older "congestive cardiac failure," requiring symptoms/signs **plus** corroboration by elevated natriuretic peptides **or** objective evidence of cardiogenic pulmonary/systemic congestion. It is the common final pathway of most chronic cardiovascular diseases; 5-year survival after diagnosis is only ~50%.

Aetiology, Phenotypes and Classification

- **Classification by ejection fraction (EF)** — drives therapy; roughly half of patients have reduced EF:
  - **HFrEF** (reduced; LVEF ≤40%) — coronary artery disease/MI, dilated/nonischaemic cardiomyopathy, valvular, toxic (alcohol, anthracyclines), peripartum, tachycardia-induced.
  - **HFmrEF** (mildly reduced; LVEF 41–49%) — intermediate; treated largely as HFrEF.
  - **HFpEF** (preserved; LVEF ≥50%) — hypertension, LVH, ageing, aortic stenosis, restrictive/infiltrative disease (amyloid, sarcoid, haemochromatosis), HCM.
  - **HFrecEF** (recovered EF) — e.g., fulminant myocarditis, stress/peripartum/tachycardia cardiomyopathy; better prognosis.
- **High-output failure** — anaemia (Hb ≤8 g/dL), thyrotoxicosis, beriberi, large AV fistula, Paget's disease, cirrhosis; low SVR, usually unmasks underlying heart disease.

- **ACC/AHA stages (progressive, irreversible): A** at-risk (HTN, DM, no structural disease) → **B** structural disease/asymptomatic → **C** structural disease + current/prior symptoms → **D** refractory/advanced HF.
- **NYHA functional class (symptom-based, reversible):**

Class	Limitation	Clinical assessment
I	None	Ordinary activity causes no symptoms
II	Mild	Comfortable at rest; ordinary activity → dyspnoea/fatigue/palpitation/angina
III	Moderate	Comfortable at rest; *less than* ordinary activity → symptoms
IV	Severe	Symptoms at rest, worsened by any activity

Pathogenesis (Pathophysiology)

- **Index event and progressive remodelling** — HFrEF begins with an index injury (acute MI, chronic pressure/volume overload, genetic or congenital disease). Despite an initial fall in pump function patients stay asymptomatic for months–years because compensatory mechanisms are recruited; these same mechanisms ultimately become maladaptive and drive progression.
- **Patterns of ventricular remodelling** — *concentric hypertrophy* (pressure overload, e.g., hypertension, AS) reduces wall stress; *eccentric hypertrophy/dilatation* (volume overload, e.g., AR, MR). Accompanied by myocyte hypertrophy, interstitial/perivascular fibrosis, altered calcium-handling proteins, re-expression of fetal genes (β-myosin heavy chain), and myocyte necrosis/apoptosis/autophagy → increasing sphericity, papillary muscle displacement and secondary mitral regurgitation.
- **Compensatory (initially adaptive) responses:**
  - **Frank-Starling mechanism** — increased preload (end-diastolic volume) augments stroke volume; preload reserve is exhausted as the ventricle fails.
  - **Neurohormonal activation** — fall in cardiac output "unloads" arterial baroreceptors (LV, carotid sinus, aortic arch) → reduced parasympathetic and increased **sympathetic (SNS)** tone (resting plasma noradrenaline 2–3× normal, predicts mortality), and activation of the **renin-angiotensin-aldosterone system (RAAS)** with non-osmotic release of **arginine vasopressin**. Result: tachycardia, increased contractility, peripheral vasoconstriction, and renal salt/water retention to maintain blood pressure and preload.
- **Maladaptive consequences / vicious cycle** — sustained SNS/RAAS/AVP activation causes excessive afterload, volume overload, electrolyte disturbance, baroreceptor dysfunction, direct myocyte toxicity, fibrosis, arrhythmia and further remodelling — a self-perpetuating cycle. Counter-regulatory **natriuretic peptides (ANP, BNP)**, prostaglandins, bradykinin, adrenomedullin and nitric oxide oppose this but are eventually overwhelmed; **neprilysin** degrades natriuretic peptides and bradykinin (the rationale for ARNI).
- **Electrical dyssynchrony** — QRS prolongation/LBBB in up to one-third causes discoordinate contraction, worsening MR (basis for CRT).

- **Systemic / cardiorenal-abdominal interactions** — the **cardiorenal syndrome** reflects not only reduced forward renal perfusion but importantly **systemic venous congestion** and raised intra-abdominal pressure impeding renal venous return; splanchnic/hepatic congestion, gut wall oedema with endotoxaemia (LPS), and proinflammatory cytokines (TNF-α, IL-1, IL-6) promote progression and **cardiac cachexia**.

Clinical Features and Diagnosis

- **Symptoms of left HF (pulmonary congestion):** exertional dyspnoea → orthopnoea → paroxysmal nocturnal dyspnoea ("cardiac asthma"), bendopnoea, nocturnal cough; acute pulmonary oedema with pink frothy sputum.
- **Symptoms of right HF (systemic congestion):** weight gain, dependent oedema, abdominal bloating, anorexia, early satiety, RUQ pain (hepatic capsule stretch); anasarca in refractory disease. **Low-output symptoms:** fatigue, cool extremities, mental dullness, oliguria.
- **Signs:** tachycardia, narrow pulse pressure, *pulsus alternans*, raised JVP with hepatojugular/abdominojugular reflux, *Kussmaul's sign*, bibasal crepitations, pleural effusion (right > left), displaced apex, **S3 gallop** (volume overload, poor prognosis), murmurs of functional MR/TR, tender pulsatile hepatomegaly, ascites, pitting oedema.
- **Investigations:** comprehensive metabolic panel, CBC, thyroid/iron studies (hyponatraemia and worsening renal function are adverse markers); **ECG** (ischaemia, LVH, LBBB, AF — present in up to 40%); **chest X-ray** (cardiothoracic ratio >0.5, upper-lobe diversion, interstitial/alveolar oedema, effusions); **2-D echocardiography with Doppler** is the key test (EF, chamber size, valves, diastolic function, pericardium); **BNP/NT-proBNP** support diagnosis and prognosis (falsely low in obesity; raised by age, female sex, CKD, AF, PE); CMR/PET, coronary angiography and endomyocardial biopsy for specific aetiologies.

Management of Chronic HFrEF — the Four Foundational Pillars (GDMT)

Stepwise, rapidly up-titrated **guideline-directed medical therapy (GDMT)** produces reverse remodelling and reduces mortality and hospitalisation. ACEI add ~23% mortality reduction; adding a beta blocker a further ~35%. Four pillars + adjuncts:

Pillar / drug class	Representative agent	Initiation → Target dose	Key point
RAAS inhibitor – ARNI (preferred)	Sacubitril-valsartan	100 mg bid → 200 mg bid	20% ↓ CV death/HF hosp vs enalapril (PARADIGM-HF); 36-h gap after ACEI (angioedema)
ACE inhibitor (if ARNI not feasible)	Enalapril / Lisinopril	2.5 mg bid → 10–20 mg bid / 20–35 mg qd	Cough/angioedema
ARB (if ACEI-intolerant)	Candesartan / Valsartan	4–8 → 32 qd / 40 → 160 bid	—
Beta blocker (only 3 proven)	Carvedilol / Bisoprolol / Metoprolol succinate	3.125 bid→25–50 bid / 1.25→10 qd / 12.5–25→200 qd	Start when euvolaemic; not for acute decompensation

Pillar / drug class	Representative agent	Initiation → Target dose	Key point
MRA	Spironolactone / Eplerenone	12.5–25 → 25–50 qd / 25 → 50 qd	RALES; watch K^+/renal function; eplerenone if gynaecomastia
SGLT-2 inhibitor	Dapagliflozin / Empagliflozin	10 mg qd	~25–26% ↓ events, with or without diabetes (DAPA-HF, EMPEROR-Reduced)

- **Loop diuretics** (furosemide, torsemide, bumetanide) for congestive symptoms — symptomatic only, no mortality benefit; minimise dose.
- **Hydralazine + isosorbide dinitrate** — for RAAS-intolerant patients and added in self-identified African-Americans on background therapy (A-HeFT).
- **Ivabradine** (If-channel inhibitor) — symptomatic HFrEF, **sinus rhythm, HR >70/min** on maximally tolerated beta blocker (SHIFT).
- **Vericiguat** (soluble guanylate cyclase stimulator) and **digoxin** (late-line, reduces hospitalisation, low dose) as adjuncts; **avoid** verapamil/diltiazem, NSAIDs, thiazolidinediones.
- **Device & surgical therapy: ICD** for primary prevention if NYHA II–III with LVEF ≤35% on GDMT (any aetiology), or post-MI LVEF ≤30% (not within 40 days of MI). **CRT** (biventricular pacing) when **QRS >149 ms with LBBB**. CABG for ischaemic cardiomyopathy with viable myocardium (STICH); transcatheter edge-to-edge mitral repair (COAPT) for severe secondary MR; LVAD/cardiac transplant for stage D.

Management of HFpEF/HFmrEF and Acute Decompensated HF

- **HFpEF/HFmrEF:** historically symptom-focused — control congestion with diuretics (avoid over-diuresis causing under-filling), tight blood-pressure control, maintain sinus rhythm/rate control in AF, treat ischaemia and comorbidities (obesity, OSA, CKD, anaemia/iron deficiency). **SGLT-2 inhibitors** (DELIVER, EMPEROR-Preserved) now reduce CV death/HF hospitalisation across EF >40% and are foundational; ARNI and GLP-1 agonists (obese HFpEF, e.g., semaglutide — STEP-HFpEF) confer selected benefit; spironolactone has a weak recommendation (TOPCAT).
- **Acute decompensated HF (ADHF):** identify precipitants (non-adherence, dietary salt, NSAIDs, ischaemia, arrhythmia, infection, PE). Phenotype-directed therapy: **IV loop diuretics** (bolus or infusion; low ~1× vs high ~2.5× home dose) ± sequential nephron blockade with metolazone/acetazolamide; **vasodilators** (nitroglycerin, nitroprusside) for hypertensive/pulmonary-oedema phenotypes with adequate BP; **inotropes** (dobutamine 2–20 µg/kg/min, milrinone 0.375–0.75 µg/kg/min, dopamine) only for low-output/cardiogenic-shock states as bridge or palliation; oxygen/non-invasive ventilation and opiates for flash pulmonary oedema; **mechanical circulatory support** (IABP, percutaneous VAD, ultrafiltration) for refractory shock. Initiate/continue GDMT before discharge (PIONEER-HF, EMPULSE) and arrange early follow-up with rapid up-titration (STRONG-HF).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Neurohormonal vicious cycle of HF:** *Index myocardial injury → ↓ Cardiac output → baroreceptor unloading → ↑ SNS + ↑ RAAS + ↑ vasopressin → vasoconstriction (↑ afterload) + Na^+/H_2O retention (↑ preload) + ↑ heart rate/contractility → ↑ wall stress → ventricular remodelling (hypertrophy, dilatation, fibrosis, apoptosis) → further ↓ cardiac output.* Label the counter-regulatory limb: *natriuretic peptides (ANP/BNP) → vasodilation + natriuresis (inhibited by neprilysin).*
- **GDMT "four pillars" schematic:** four columns labelled **ARNI/ACEI/ARB**, **Beta blocker**, **MRA**, **SGLT-2 inhibitor**, sitting on a base labelled **loop diuretic (symptomatic)**, with add-ons (ivabradine, hydralazine-nitrate, vericiguat, digoxin) and devices (ICD, CRT) above.

Clinical / Diagnostic significance

- BNP/NT-proBNP aid diagnosis in undifferentiated dyspnoea and risk-stratify; a very low value helps exclude HF in non-obese patients.
- Echocardiographic EF is the single most important branch point separating HFrEF (GDMT-responsive) from HFpEF.
- S3 gallop, elevated JVP, hyponatraemia, worsening renal function and inability to tolerate neurohormonal antagonists are markers of advanced disease and poor prognosis.
- Recognising and correcting precipitating factors (Table of patient-, provider-, and disease-related triggers) prevents recurrent decompensation; residual congestion at discharge strongly predicts readmission.

High-yield exam pointers

- **Universal definition** = symptoms/signs **plus** raised natriuretic peptide **or** objective congestion; classify by EF (HFrEF ≤40%, HFmrEF 41–49%, HFpEF ≥50%).
- Distinguish **ACC/AHA stages A–D (irreversible)** from **NYHA I–IV (reversible)**.
- Core pathogenesis = **maladaptive SNS + RAAS activation** driving remodelling — the target of all disease-modifying drugs.
- **Four pillars of HFrEF GDMT:** ARNI (or ACEI/ARB) + beta blocker + MRA + SGLT-2 inhibitor; rapid up-titration.
- Only **carvedilol, bisoprolol, metoprolol succinate** improve survival; sacubitril-valsartan needs a **36-h washout** after an ACEI.
- **Ivabradine** = sinus rhythm + HR >70 on beta blocker; **digoxin/diuretics** = symptom relief, no mortality benefit.
- **ICD** if LVEF ≤35% (NYHA II–III) or post-MI LVEF ≤30%; **CRT** if QRS >149 ms with LBBB.
- **SGLT-2 inhibitors** now benefit across the whole EF spectrum, including HFpEF.
- In ADHF: treat precipitant, IV loop diuretic for decongestion, vasodilators if BP adequate, inotropes only for low-output/shock.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Heart Failure: Pathophysiology and Diagnosis" and "Heart Failure: Management" (definition/phenotypes, remodelling, neurohormonal activation, NYHA & ACC/AHA staging, GDMT target-dose table, devices, ADHF).
- **Braunwald's Heart Disease, 13e** — "Pathophysiology of Heart Failure" (compensatory mechanisms — SNS/RAAS, noradrenaline kinetics, Frank-Starling/preload reserve).
- **CMDT 2026** — "Heart Failure & Cardiomyopathy" (epidemiology, four-stage classification, current combination medical therapy framing).

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Pericarditis

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Pericarditis is inflammation of the pericardium, the double-layered fibroserous sac (visceral + parietal layers separated by 15–50 mL of plasma ultrafiltrate) that envelops the heart. It is the commonest pathological process affecting the pericardium and presents as a spectrum of overlapping syndromes — **acute pericarditis**, **pericardial effusion and cardiac tamponade**, **recurrent/incessant pericarditis**, **constrictive pericarditis** and **effusive–constrictive pericarditis**. Most acute cases in developed regions are viral or idiopathic and self-limiting, whereas in India/sub-Saharan Africa **tuberculosis** remains a leading cause and a major driver of constriction.

Classification (Harrison) and Aetiology

- **Clinical (by duration):** Acute (<6 weeks; fibrinous or effusive) → Subacute (6 weeks–6 months; effusive-constrictive or constrictive) → Chronic (>6 months; constrictive or adhesive).
- **Infectious:** *Viral* (coxsackie A/B, echovirus, herpesviruses, mumps, adenovirus, HIV, post-COVID), *pyogenic/purulent* (pneumococcus, Staphylococcus, Streptococcus, Neisseria), *tuberculous*, *fungal* (histoplasma, coccidioides, Candida).
- **Non-infectious:** acute idiopathic, *uraemic/dialysis-associated*, *neoplastic* (lung, breast, lymphoma, leukaemia, mesothelioma), trauma, aortic dissection leaking into the sac, acute MI, post-irradiation, myxoedema, familial (*Mulibrey nanism* — autosomal recessive growth failure with constrictive pericarditis), familial Mediterranean fever.
- **Autoimmune / hypersensitivity:** rheumatic fever, SLE, rheumatoid arthritis, scleroderma, granulomatosis with polyangiitis, IgG4 disease; drug-induced (procainamide, hydralazine, isoniazid, phenytoin, minoxidil); **post-cardiac-injury syndromes** — postpericardiotomy, post-traumatic, and post-MI (*Dressler's syndrome*).

Acute Pericarditis — Clinical Features & Diagnosis

- **Four cardinal diagnostic features (Harrison):**
- **Chest pain** — retrosternal/left precordial, often pleuritic (sharp, worse on inspiration/coughing), radiating to the **trapezius ridge** (near-pathognomonic), classically *aggravated by lying supine and*

relieved by sitting up and leaning forward. Pain is often absent in tuberculous, uraemic, neoplastic and post-irradiation forms.

- **Pericardial friction rub** — heard in ~85%; rasping/scratching, up to three components/cycle (atrial systole, ventricular systole, early diastole), best at end-expiration, patient upright and leaning forward.
- **ECG — evolves through four stages:** *Stage 1* — diffuse upwardly-concave ST elevation (limb leads + V2–V6) with reciprocal ST depression only in aVR (±V1), plus **PR-segment depression** (atrial injury current, an early/specific sign); *Stage 2* — ST returns to baseline; *Stage 3* — diffuse T-wave inversion; *Stage 4* — normalisation. Contrast with AMI (convex/"tombstone" ST, regional, prominent reciprocal change, evolving over hours).
- **Pericardial effusion** — may cause muffled sounds, **electrical alternans**, *Ewart's sign* (dullness/bronchial breathing below the left scapula from lung compression) and a "water-bottle" cardiac silhouette on chest X-ray.
- **ESC 2015 diagnostic criteria (Braunwald):** at least **two of four** — (1) characteristic chest pain, (2) friction rub, (3) typical ECG changes (ST elevation/PR depression), (4) new/worsening pericardial effusion. Supported by raised **CRP**, leucocytosis and CMR evidence of pericardial inflammation (late gadolinium enhancement).
- **Investigations:** ECG, CBC with differential, **CRP/hsCRP** (tracks activity and guides treatment duration), **cardiac troponin** (modest rise indicates *myopericarditis* — concomitant epicardial myocarditis, seen in up to 15%), chest radiograph and **echocardiography** (first-line imaging). CT/CMR are superior for loculated effusions, pericardial thickening, masses and active inflammation.

Cardiac Tamponade

- Accumulation of pericardial fluid sufficient to obstruct ventricular inflow — a medical emergency. As little as **200 mL** causes tamponade if rapid, versus **>2000 mL** if slowly accumulating (pericardium stretches).
- **Beck's triad:** hypotension, soft/absent heart sounds, and raised JVP with a **prominent x descent and absent y descent**.
- **Pulsus paradoxus:** inspiratory fall in systolic BP **>10 mmHg** — due to inspiratory RV filling bulging the septum leftward (ventricular interdependence), reducing LV stroke volume. Also seen in severe asthma/COPD, PE and ~⅓ of constrictive cases.
- **Echo:** late-diastolic **RA and RV free-wall collapse**, dilated non-collapsing IVC, exaggerated respiratory variation in mitral/tricuspid inflow ("swinging heart" with electrical alternans).
- **Treatment:** urgent **pericardiocentesis** (echo-guided **subxiphoid** approach most common; apical/parasternal alternatives), draining the sac as completely as possible with a temporary catheter left for 2–3 days; IV saline as a temporising measure. **Anticoagulants are avoided.** Surgical/open drainage for loculated, malignant or recurrent effusions and when biopsy is needed.

Constrictive Pericarditis

- A rigid, fibrotic, often calcified pericardium encasing the heart, limiting diastolic filling. Worldwide TB is a major cause; in the West it follows viral/idiopathic pericarditis, cardiac surgery, mediastinal irradiation, connective-tissue disease and uraemia. Risk is **<1% after viral/idiopathic**, **2–5% after immune/neoplastic**, and **20–30% after purulent bacterial** pericarditis.
- **Pathophysiology:** filling is unimpeded in early diastole then halts abruptly at the elastic limit of the pericardium → **"dip-and-plateau"/square-root sign** and **equalisation of diastolic pressures** in all four chambers (within ~5 mmHg). Loss of transmission of intrathoracic pressure to the heart produces enhanced ventricular interdependence.
- **Clinical (right-heart congestion dominates):** raised JVP with **prominent y descent** (M-/W-shaped venous wave), **Kussmaul's sign** (JVP fails to fall / rises with inspiration), **pericardial knock** (early S3 from abrupt halt of filling), hepatomegaly, ascites out of proportion to oedema, and **Broadbent's sign** (systolic apical retraction). Pulsus paradoxus is usually absent; AF in ~⅓.
- **Investigations:** ECG — low voltage, T-wave flattening; CXR — **pericardial calcification** (commonest in TB); echo/Doppler — septal bounce, **≥25% inspiratory increase in mitral E velocity**, expiratory hepatic-vein diastolic flow reversal; tissue Doppler — preserved/increased **medial mitral annular e′ (>8 cm/s)** with lateral e′ lower than medial (***annulus reversus***). **CT/CMR** confirm pericardial thickening (≥3–4 mm). Catheterisation shows discordant RV/LV systolic pressures with respiration.
- **Treatment:** diuretics for symptom control; **pericardiectomy (complete pericardial resection)** is the only definitive therapy (operative mortality ~5–15%, highest after radiation). Transient/reversible constriction (esp. post-cardiac-surgery, raised CRP, CMR enhancement) may respond to anti-inflammatory therapy. *Effusive-constrictive pericarditis* — constrictive physiology persists after fluid removal; needs wide visceral + parietal resection.

Constrictive Pericarditis vs Cardiac Tamponade vs Restrictive Cardiomyopathy

Feature	Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy
Pulsus paradoxus	+++	+ (≈⅓)	+
JVP — prominent y descent	Absent	+++ (M/W wave)	+
JVP — prominent x descent	+++	++	+++
Kussmaul's sign	–	+++	+
Pericardial knock	–	++	–
Third heart sound (S3)	–	–	+
Pericardial effusion	+++	–	–
Pericardial calcification/thickening	–	++/+++	–

Feature	Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy
Equalisation of diastolic pressures	+++	+++	–

Treatment of Acute & Recurrent Pericarditis

- **First-line — NSAID + colchicine (Harrison/ESC/CMDT):**
  - **Aspirin 750–1000 mg every 8 h** for 1–2 weeks (or 2–4 g/day), then taper; or **ibuprofen 600–800 mg tid**; or **indomethacin 25–50 mg tid** — with **gastroprotection (PPI)**.
  - **Colchicine** 0.5–0.6 mg once daily (<70 kg) or twice daily (>70 kg) for **3 months** (≥6 months for recurrence) — halves recurrence and hastens symptom resolution.
- **Corticosteroids** (e.g. prednisone 0.25–0.5 mg/kg/day, slow taper) reserved for NSAID/colchicine failure or intolerance, autoimmune aetiology, renal failure or pregnancy — they **increase recurrence**, so used at low dose with concurrent colchicine.
- **Refractory/recurrent disease: IL-1 antagonists** — *anakinra* (IL-1 receptor antagonist) and *rilonacept* (IL-1 trap; FDA-approved after the **RHAPSODY** trial) — are highly effective steroid-sparing agents; azathioprine and IVIG are alternatives; pericardial stripping is a last resort.
- **Specific causes:** *Dressler's/post-MI* — prefer **aspirin + colchicine** (NSAIDs/steroids may impair myocardial healing); *uraemic* — intensify dialysis ± NSAID; *purulent* — drainage + IV antibiotics; *neoplastic* — drainage/pericardial window ± sclerotherapy; *tuberculous* — RIPE for 2 months then isoniazid + rifampicin to complete 6 months, with pericardiectomy if constriction develops.
- **High-risk features warranting admission (ESC):** *major* — fever >38 °C, subacute onset, large effusion, tamponade, failure to respond to NSAID/aspirin after a week; *minor* — myopericarditis, immunosuppression, trauma, oral anticoagulation. Recurrence affects ~15–30%.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **ECG evolution of acute pericarditis (4 stages):** lead strip showing — *Stage 1* diffuse concave **ST elevation** + **PR depression** (with reciprocal ST depression/PR elevation in **aVR**); *Stage 2* normalisation of ST; *Stage 3* **T-wave inversion**; *Stage 4* normal. Label "diffuse concave ST↑", "PR depression", "aVR reciprocal change".
- **JVP waveform comparison:** tamponade — **prominent x, absent y** descent; constriction — **prominent x and y (M/W shape)** with **Kussmaul's sign**. Label a, c, v waves and x, y descents.

Clinical / Diagnostic significance

- Differentiating acute pericarditis from **STEMI** is the highest-yield bedside skill: pericarditis shows *diffuse concave* ST elevation with PR depression and only modest troponin rise, versus regional convex ST elevation with marked enzyme rise in MI.
- A troponin rise signals **myopericarditis**; LV dysfunction is rare and the long-term prognosis is excellent, but it alters activity restriction and avoids over-aggressive anticoagulation.

- **CRP/hsCRP** is central — it confirms inflammation, monitors response, and guides duration of therapy (taper once CRP normalises).
- Constrictive pericarditis is a **surgically curable** cause of right heart failure — must be distinguished from cirrhosis (inspect the neck veins) and from restrictive cardiomyopathy (annulus reversus, septal bounce, equalised pressures).
- TB pericarditis: pericardial fluid **adenosine deaminase (ADA)** elevation and **TB-PCR** support the diagnosis; biopsy is often required; early anti-TB therapy prevents constriction.

High-yield exam pointers

- ESC 2015: diagnose acute pericarditis with **≥2 of 4** (pain, rub, ECG ST↑/PR↓, effusion).
- Friction rub present in **~85%**; up to **three components** per cycle.
- **PR-segment depression** is an early, fairly specific ECG sign; ST elevation is diffuse and concave.
- **Beck's triad** = hypotension + muffled heart sounds + raised JVP; tamponade JVP has **absent y descent**.
- **Pulsus paradoxus >10 mmHg**; rapid effusions of only **~200 mL** can tamponade.
- Constriction: **square-root sign**, **Kussmaul's sign**, **pericardial knock**, calcified pericardium (commonest in TB); pericardiectomy is curative.
- First-line therapy is **NSAID/aspirin + colchicine ×3 months**; colchicine halves recurrence; steroids increase it.
- **Dressler's syndrome** — weeks post-MI; treat with **aspirin + colchicine**, not NSAIDs/steroids.
- Recurrent pericarditis — escalate to **IL-1 blockers (anakinra, rilonacept)**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pericardial Disease" (classification, four cardinal features, four-stage ECG, Beck's triad, pulsus paradoxus, tamponade, constrictive pericarditis, Table distinguishing tamponade vs constriction vs restriction, treatment doses, tuberculous pericarditis).
- **Braunwald's Heart Disease, 13e** — "Pericardial Diseases" (ESC 2015 diagnostic criteria, high-risk triage features, myopericarditis, recurrence definition, IL-1 antagonists/RHAPSODY, echo-Doppler differentiation — annulus reversus, septal bounce, 25% mitral E variation, RA/RV collapse timing, effusive-constrictive physiology, TB regimen).
- **CMDT 2026** — "Acute Inflammatory Pericarditis / Pericardial Effusion / Constrictive Pericarditis" (aspirin/ibuprofen/colchicine dosing and tapering, Dressler management, constriction incidence by aetiology, pericardiectomy outcomes, hemodynamic criteria).

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QT interval prolongation and torsades de pointes

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The **QT interval** on the surface ECG subtends both ventricular depolarization and (chiefly) ventricular **repolarization**, and it varies *inversely* with heart rate. Because it is rate-dependent, it is reported as the rate-**corrected QT (QTc)**. *Torsades de pointes* ("twisting of the points") is the characteristic **polymorphic ventricular tachycardia (VT)** that complicates an abnormally prolonged QT interval; the QRS axis appears to twist around the isoelectric baseline. It typically presents with near-syncope, syncope or cardiac arrest, and sustained episodes may degenerate into **ventricular fibrillation (VF)**.

Electrophysiology and QT/QTc measurement

- The QT interval is measured from the onset of the QRS to the end of the T wave; it reflects ventricular action-potential duration, governed mainly by repolarizing **potassium currents** (I_Kr, I_Ks).
- Because QT shortens as heart rate rises, it must be **rate-corrected** to QTc. No single formula has formal consensus:
  - **Bazett ("square root") formula:** QTc = QT/√RR (in seconds) — the classic method, but criticized for systematic over-/under-correction at very low and very high heart rates.
  - **Framingham formula:** QTc = QT + 0.154 × (1000 − RR) (in milliseconds) — a linear alternative.
- **Upper normal limits (Harrison 22e, Ch 247):** QTc **450 ms in men** and **460 ms in women**; lower limits are less well defined. In congenital LQTS the QTc is typically prolonged to **>440 ms in men and >460 ms in women** (Ch 262).
- **Prominent U waves** (a small rounded deflection following the T wave) accompanying prolonged repolarization are a recognized marker of *increased susceptibility to torsades*; abnormally large U waves are most often due to hypokalemia or drugs (dofetilide, amiodarone, sotalol, quinidine).

Mechanism of torsades de pointes

- The fundamental abnormality is **prolonged ventricular repolarization** with **abnormal transmural dispersion of repolarization**, which can arise from channelopathies, drugs or electrolyte disturbance even *without* structural heart disease.
- Torsades has a characteristic **pause-dependent initiation**: a premature ventricular contraction (PVC) induces a pause, the post-pause sinus beat shows a still-longer QT, and a subsequent PVC falling on the prolonged T wave initiates the polymorphic VT — the classic **"long–short" interval sequence** (Fig. 262-1).
- Drugs that **block repolarizing potassium currents** (notably the antiarrhythmics sotalol, dofetilide and ibutilide, and many non-cardiac agents) prolong the action potential and predispose to this arrhythmia. Individual susceptibility may reflect genetic polymorphisms or mutations affecting repolarization.

Classification / Causes of QT prolongation and torsades (Table 262-1)

Category	Examples
1. Congenital long QT syndromes	LQTS-1, LQTS-2, LQTS-3 (account for 80–90% of cases) and other rarer types
2. Electrolyte abnormalities	**Hypokalemia, hypomagnesemia, hypocalcemia**
3. Drug-induced (acquired)	Antiarrhythmics, antibiotics, antipsychotics, antihistamines, others (see drug table)
4. Cardiac conditions	Myocardial ischemia/infarction, myocarditis, marked **bradycardia**, stress (takotsubo) cardiomyopathy
5. Endocrine disorders	Hypothyroidism, hyperparathyroidism, pheochromocytoma, hyperaldosteronism
6. Intracranial disorders	Subarachnoid hemorrhage, thalamic hematoma, cerebrovascular accident, encephalitis, head injury
7. Nutritional disorders	Anorexia nervosa, starvation, liquid-protein diets, gastroplasty/ileojejunal bypass, celiac disease

- *Acquired LQTS* (drug- and electrolyte-related) is by far the commonest clinical setting; **drug interactions** that raise the level of an offending agent are a frequent precipitant.

Drugs that prolong the QT interval (Table 262-1)

Drug class	Agents
Antiarrhythmics — Class IA	**Quinidine, disopyramide, procainamide**
Antiarrhythmics — Class III	**Sotalol, dofetilide, ibutilide,** amiodarone, dronedarone, ranolazine
Macrolide antibiotics	Erythromycin, clarithromycin, azithromycin
Fluoroquinolones	Levofloxacin, moxifloxacin
Other antimicrobials	Trimethoprim-sulfamethoxazole, clindamycin, **pentamidine, chloroquine/hydroxychloroquine**; antifungals (ketoconazole, itraconazole); antivirals (amantadine)
Antipsychotics	Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, ziprasidone
Antidepressants	Tricyclic and tetracyclic agents
Antihistamines (H1)	Astemizole, diphenhydramine, hydroxyzine
Others	**Methadone**, cocaine, citrate (massive transfusion)

- The website **crediblemeds.org** is an authoritative resource to check whether a given drug is reported to prolong the QT interval.

Congenital long QT syndrome (LQTS)

- Caused by **mutations in genes encoding cardiac ion channels** controlling repolarization. LQTS-1, -2 and -3 account for **80–90%** of cases; the commonest (LQTS-1, -2) involve potassium channels, while LQTS-3 affects the sodium channel.

Type	Channel / current defect	Gene	Typical trigger of events
LQTS-1	Reduced repolarizing **I_Ks**	**KCNQ1**	Exertion, particularly **swimming**
LQTS-2	Reduced repolarizing **I_Kr**	**KCNH2**	Sudden **auditory stimuli** / emotional upset
LQTS-3	Delayed inactivation of **I_Na**	**SCN5A**	Sudden death tends to occur during **sleep**

- Typical presentation is **syncope or cardiac arrest, usually in childhood**; asymptomatic cases are found on family screening or routine ECG. **Genotyping** aids family screening and prognostication.
- *Markers of increased risk:* **QTc >500 ms, female gender, and a history of syncope or cardiac arrest.**
- *Related repolarization channelopathies (for completeness):* **Short QT syndrome** (QTc <360 ms, usually <300 ms; gain-of-function K-channel), **Brugada syndrome** (SCN5A, coved ST elevation V1–V3), and **catecholaminergic polymorphic VT** (RyR2/calsequestrin-2 mutations; bidirectional VT).

Management

- **Acute torsades / acquired LQTS:**
  - **IV magnesium sulphate 1–2 g** usually suppresses recurrent episodes (first-line, even if serum magnesium is normal).
  - If magnesium is ineffective, **increase heart rate** with an **isoproterenol infusion or temporary pacing to ~100–120 beats/min** to suppress PVCs and shorten the QT (abolishes the pause-dependent trigger).
  - **Correct hypokalemia, hypomagnesemia and hypocalcemia, treat bradycardia, and withdraw all offending QT-prolonging drugs.**
  - Sustained episodes degenerating to **VF require defibrillation per ACLS**. Such patients have a demonstrated susceptibility and must **avoid all future QT-prolonging drugs**.
- **Congenital LQTS:**
  - Adequate-dose **β-blockade is the cornerstone** for LQTS-1 and LQTS-2; the **non-selective agents nadolol and propranolol are favored**.
  - **Avoidance of QT-prolonging drugs** is critical for *all* patients, including genotype-positive patients with a normal QT.
  - An **implantable cardioverter-defibrillator (ICD)** is considered for recurrent syncope despite β-blockers or for a high-risk profile (e.g., prior cardiac arrest, QTc >500 ms).
  - **Left cardiac sympathetic denervation** is a recognized adjunct for refractory cases (described under CPVT in the source).
- **Ischemia-related polymorphic VT:** prompt **myocardial reperfusion**, β-adrenergic blockade and correction of electrolytes; persistent severe LV dysfunction (LVEF <35%) is an ICD indication.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Torsades de pointes (rhythm strip, after Fig. 262-1).** Draw a sinusoidal polymorphic VT whose QRS amplitude waxes and wanes ("twisting around the baseline"). Labels: *Sinus beat with long QT*, *PVC*, *compensatory pause (long RR)*, *PVC initiating VT*, *"long–short" interval sequence*, *pause-dependent initiation*, *polymorphic VT (torsades)*.
- **Diagram 2 — QT interval on a normal complex.** Draw P-QRS-T-U. Labels: *QRS onset (start of QT)*, *ST segment*, *T wave (end of QT)*, *U wave*, *RR interval*, and annotate *QTc = QT/√RR (Bazett)*; mark *hypocalcemia → long ST/QT* vs *hypercalcemia → short QT*.

Clinical / Diagnostic significance

- **ECG is the key investigation:** measure QT and compute QTc; look for prominent U waves, marked T-wave abnormalities and pause-dependent ectopy. Telemetry/Holter captures self-limiting runs of torsades.
- **Metabolic/secondary clues: hypocalcemia** prolongs the QT (ST-segment portion) whereas **hypercalcemia** shortens it; **hypothermia** prolongs repolarization with an **Osborn (J) wave**; **subarachnoid hemorrhage** produces marked QT prolongation with deep, wide T-wave inversions ("CVA T-wave" pattern); digitalis *shortens* the QT with "scooped" ST-T.
- **Workup:** serum **potassium, magnesium, calcium**, thyroid function, a full drug review (including interactions), and ECG screening of first-degree relatives when congenital LQTS is suspected; consider **genotyping**.
- **Management pearls:** withdraw the culprit drug and correct electrolytes early; magnesium first, then rate support; do not give further QT-prolonging agents to a susceptible patient.

High-yield exam pointers

- QT subtends ventricular repolarization and varies **inversely with heart rate**; report **QTc** — **Bazett QT/√RR** or **Framingham**.
- Upper normal **QTc 450 ms (men) / 460 ms (women)**; **QTc >500 ms** is a high-risk marker for torsades.
- Torsades is **pause-dependent** with a **"long–short" initiating sequence**; **prominent U waves** flag susceptibility.
- Commonest cause clinically is **acquired** — *drugs + electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia) + bradycardia*.
- Memorize culprit drugs: **Class IA & III antiarrhythmics, macrolides, fluoroquinolones, antipsychotics (haloperidol), methadone, pentamidine, antifungals**; check **crediblemeds.org**.
- **Acute treatment = IV magnesium 1–2 g → isoproterenol/pacing to 100–120/min → correct electrolytes/bradycardia → stop the drug → defibrillate if VF.**
- Congenital LQTS triad: **LQTS-1 (KCNQ1, I_Ks, exercise/swimming); LQTS-2 (KCNH2, I_Kr, auditory/emotion); LQTS-3 (SCN5A, I_Na, sleep)** — together 80–90% of cases.
- Congenital LQTS treatment: **β-blockers (nadolol/propranolol)**, avoid QT-prolonging drugs, **ICD** for high-risk/refractory cases.

SOURCE & COVERAGE

Harrison 22e — Ch 262 "Polymorphic Ventricular Tachycardia and Ventricular Fibrillation" (acquired & congenital LQTS, Table 262-1 causes/drug list, mechanism, management) and Ch 247 "Electrocardiography" (QT/QTc measurement, Bazett/Framingham formulas, normal limits, U waves, electrolyte/drug repolarization changes). *Coverage note:* the underlying cellular mechanism of torsades — **early afterdepolarizations (EADs)** triggering R-on-T — is universally accepted textbook electrophysiology but is not named explicitly in these two chapters; the source describes it functionally as pause-dependent, dispersion-of-repolarization–mediated initiation. **Left cardiac sympathetic denervation** is cited in the source under catecholaminergic polymorphic VT rather than directly under LQTS.

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Stroke prevention in atrial fibrillation

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Atrial fibrillation (AF) is the commonest sustained arrhythmia and the single most important cardiac cause of ischaemic stroke. Loss of organised atrial mechanical contraction produces blood stasis and *in situ* thrombosis, predominantly in the **left atrial appendage (LAA)**, which on embolisation causes cardio-embolic stroke and systemic thromboembolism. Because such strokes are large, disabling and often fatal, **antithrombotic prophylaxis guided by validated risk scores is the cornerstone of AF management** and is one of the three therapeutic aims (the others being symptom/rate–rhythm control and risk-factor modification). The decision balances the patient's **stroke risk** against the **bleeding risk** of anticoagulation.

Pathophysiology of thromboembolism in AF

- Loss of atrial systole → **stasis of blood**, particularly in the trabeculated **left atrial appendage**, where ~90% of AF-related thrombi form; thrombus may also form in a severely dilated left atrium in mitral valve disease.
- **Virchow's triad** is satisfied: stasis, endothelial/endocardial dysfunction, and a prothrombotic/hypercoagulable milieu.
- Embolised thrombus reaches the cerebral circulation → large-vessel ischaemic stroke; recurrent silent emboli contribute to **cognitive impairment and dementia**.
- **Atrial stunning** — after conversion (spontaneous, electrical or pharmacological) from prolonged AF to sinus rhythm, atrial mechanical recovery is delayed for weeks, so thrombus can form and embolise *even after* sinus rhythm is restored. This underlies peri-cardioversion anticoagulation rules.
- AF burden ("paroxysmal" vs "persistent") was traditionally thought not to predict stroke; hence the approach to **paroxysmal AF is the same as for persistent AF**. Asymptomatic episodes are common, so absence of AF on intermittent monitoring does not equal low risk.

Risk stratification — CHA_2DS_2-VASc and bleeding scores

The **CHA_2DS_2-VASc** score (max 9) estimates annual stroke risk; the **HAS-BLED** score (max 9) estimates major-bleeding risk. A higher score in either direction maps to a higher annual event rate.

CHA_2DS_2-VASc component	Points		HAS-BLED component	Points
C – Congestive heart failure / LV dysfunction	1		**H** – Hypertension (uncontrolled)	1
H – Hypertension	1		**A** – Abnormal renal / liver function	1 each
A_2 – Age ≥75 years	2		**S** – Stroke history	1
D – Diabetes mellitus	1		**B** – Bleeding history / predisposition	1
S_2 – Stroke / TIA / thromboembolism	2		**L** – Labile INR (on warfarin)	1
V – Vascular disease (MI/PAD/aortic plaque)	1		**E** – Elderly (age >65 years)	1
A – Age 65–74 years	1		**D** – Drugs (antiplatelet/NSAID) or alcohol	1 each
Sc – Sex category (female)	1			

- **Annual stroke rate rises with score** (CMDT/Braunwald): ~0% at 0, ~1.3% at 1, ~2.2% at 2, ~3.2% at 3, ~4% at 4, rising further with higher scores — Harrison notes risk may approach **~20% per year** at the highest scores without anticoagulation.
- **Anticoagulation thresholds (2023 ACC/AHA/ACCP/HRS):** Class I anticoagulation for **men with score ≥2 and women with score ≥3**; *consider* (Class IIa) for men =1 / women =2; **no antithrombotic therapy** when the only point is female sex (men =0, women =1).
- Female sex is a **risk modifier, not an independent risk factor** — it counts only in the presence of other factors.
- Risk factors *not* captured by the score but relevant: **LA size, mitral annular calcification, AF burden, and renal failure** (RR ~1.4 in non-dialysis CKD, ~1.8 on dialysis).
- **HAS-BLED ≥3** flags high bleeding risk — it should prompt correction of *modifiable* factors (BP control, stopping NSAIDs/alcohol, labile INR) and closer review, **not** automatic withholding of anticoagulation.
- Highest-risk groups in whom anticoagulation is recommended *regardless* of score: **prior stroke/TIA, rheumatic mitral stenosis, mechanical valve, and hypertrophic cardiomyopathy**.

Antithrombotic options — DOACs vs warfarin

Oral anticoagulants are far superior to antiplatelets. Warfarin reduces stroke by ~60–64% vs placebo and ~37% vs antiplatelet therapy; **aspirin is no longer recommended** for stroke prevention in AF (variable, modest benefit without a bleeding advantage). For **nonvalvular AF, DOACs are now**

preferred over warfarin (equal/greater efficacy, ~50% less intracranial haemorrhage, fixed dosing, no monitoring, fewer food/drug interactions).

Agent	Class / target	Standard dose	Reduced dose & criteria	Pivotal trial
Warfarin	Vitamin K antagonist (↓ factors II, VII, IX, X; protein C/S) via VKOR inhibition	Titrated to **INR 2.0–3.0**	— (needs INR monitoring; many interactions)	(reference comparator)
Dabigatran	Direct **thrombin (IIa)** inhibitor	150 mg BID	110 mg BID (age ≥80, verapamil, high bleeding risk) / **75 mg BID** if CrCl 15–30 (US label)	*RE-LY*
Rivaroxaban	**Factor Xa** inhibitor	20 mg OD **with food**	15 mg OD if CrCl 15–50 mL/min	*ROCKET-AF*
Apixaban	**Factor Xa** inhibitor	5 mg BID	2.5 mg BID if **≥2 of**: age ≥80, weight ≤60 kg, creatinine ≥1.5 mg/dL	*ARISTOTLE*
Edoxaban	**Factor Xa** inhibitor	60 mg OD	30 mg OD if CrCl 30–50, weight ≤60 kg, or P-gp inhibitor; **avoid if CrCl >95**	*ENGAGE-AF*

- All four DOACs were **non-inferior or superior** to warfarin in nonvalvular AF; pooled data show small absolute superiority (~0.4–0.7%) in mortality, stroke, major bleeding and intracranial haemorrhage. **Apixaban** uniquely showed superiority to warfarin for stroke *and* less major bleeding *and* lower mortality (ARISTOTLE).
- **Dabigatran** has more GI bleeding; **rivaroxaban** must be taken with food (40% better absorption).
- Renal dosing is critical — dabigatran/edoxaban avoided in end-stage renal disease/dialysis; **apixaban** has the best evidence in advanced CKD/haemodialysis (2.5 mg BID).
- **Reversal:** warfarin → IV **vitamin K + 4-factor prothrombin complex concentrate** (preferred over FFP); dabigatran → **idarucizumab** 5 g IV (monoclonal antibody fragment); factor Xa inhibitors → **andexanet alfa** (400 mg bolus then infusion). DOAC short half-life (~10–12 h) means supportive care often suffices; activated charcoal if ingested within 6–8 h.
- **Aspirin should be avoided** alongside an anticoagulant unless there is a clear indication (recent MI/stent).

Special clinical situations

- **Valvular AF** (mechanical prosthetic valve or moderate–severe/rheumatic mitral stenosis): **warfarin only** — DOACs are contraindicated/less effective. In rheumatic-heart-disease AF, warfarin gave fewer cardiovascular events/deaths than rivaroxaban without more bleeding.
- **Peri-cardioversion:** if AF >48 h or duration unknown → either **≥3 weeks of therapeutic anticoagulation before + ≥4 weeks after** cardioversion, **or** a TEE/cardiac-CT to exclude LAA thrombus and then cardiovert with ≥4 weeks' post-procedure anticoagulation (covers atrial stunning). DOACs are as effective as warfarin around cardioversion.
- **Hypertrophic cardiomyopathy with AF:** anticoagulate **independent of CHA_2DS_2-VASc score** (high thromboembolic risk).

- **Subclinical AF / device-detected atrial high-rate episodes (AHRE):** associated with a **2.5-fold** increase in stroke risk. For AHRE ≥24 h with CHA_2DS_2-VASc ≥2, anticoagulation is reasonable (Class IIa); in subclinical AF of 6 min–24 h, apixaban reduces stroke/systemic embolism but increases major bleeding — individualise.
- **AF with PCI/coronary stenting:** minimise bleeding by using **OAC plus a single P2Y12 inhibitor (preferably clopidogrel)**, dropping aspirin early; reserve short "triple therapy" (≤30 days) for high ischaemic risk such as ACS.
- **Bridging:** because of rapid DOAC onset/offset, **no heparin bridging** is needed when interrupting a DOAC for procedures; stop 24–48 h before low/moderate-risk and longer before major surgery (extend in renal impairment).

Non-pharmacological / device-based prevention

- For patients with a **high stroke risk but contraindication to long-term anticoagulation** (excessive bleeding risk), **left atrial appendage (LAA) occlusion/exclusion** is the alternative, since ~90% of thrombi originate there.
- **Percutaneous LAA closure** — *Watchman* (nitinol plug, FDA-approved 2015; non-inferior to warfarin in *PROTECT AF* / *PREVAIL*, with less major/haemorrhagic bleeding and mortality benefit) and *Amplatzer Amulet* (non-inferior to Watchman). Post-Watchman, warfarin is continued ~45 days until TEE confirms sealing/no significant peri-device leak.
- **Surgical/epicardial exclusion** — LAA excision or stapling (often with maze surgery), the **AtriClip** (FDA-approved 2021), and the catheter-delivered **LARIAT** suture (off-label) — surgical LAA occlusion at cardiac surgery adds protection over anticoagulation alone.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CHA_2DS_2-VASc / HAS-BLED scoring table with a stroke-risk curve:** draw the two-column scoring table (label every component and its points as above) and beneath it a graph of *annual stroke or major-bleeding rate (%) on the Y-axis vs score (0–9) on the X-axis*, with two rising lines labelled **CHA_2DS_2-VASc** and **HAS-BLED**.
- **Left atrial appendage thrombus and Watchman device:** draw the left atrium with a thrombus in the LAA; label *left atrium, left atrial appendage, thrombus, mitral valve,* and a *Watchman occluder device* seated across the LAA ostium delivered via *trans-septal* approach.

Clinical / Diagnostic significance

- **Risk-stratify every AF patient at diagnosis** with CHA_2DS_2-VASc; reassess periodically as age and comorbidities change.
- **Echocardiography** (TTE) is done in all new AF; **TEE** is the most sensitive test for LAA thrombus before cardioversion and before stopping anticoagulation post-LAA closure.
- Anticoagulation decision applies **equally to paroxysmal and persistent AF** and is **not** governed by the perceived AF burden or by whether sinus rhythm appears maintained.
- Monitor **renal function and blood counts** at baseline and ≥twice yearly on DOACs; review HAS-BLED factors and correct modifiable bleeding risks.

- Major bleeding occurs in ~1–2% (warfarin) to 2–4% per year overall; have a clear **reversal pathway** (vitamin K/PCC, idarucizumab, andexanet alfa).

High-yield exam pointers

- **LAA is the source of ~90% of thrombi** in AF; main feared complication is **disabling cardioembolic stroke**.
- **CHA_2DS_2-VASc:** age ≥75 and prior stroke/TIA score **2 each**; all others 1. Anticoagulate **men ≥2, women ≥3**.
- **HAS-BLED ≥3 = high bleed risk** → correct modifiable factors, don't simply withhold OAC.
- **DOACs preferred over warfarin in nonvalvular AF**; **warfarin only** for mechanical valves and moderate–severe/rheumatic mitral stenosis (target INR 2–3).
- **Aspirin is NOT recommended** for stroke prevention in AF.
- Trial map: **dabigatran–RE-LY, rivaroxaban–ROCKET-AF, apixaban–ARISTOTLE, edoxaban–ENGAGE-AF**; apixaban superior to warfarin with less bleeding.
- **Reversal:** dabigatran → **idarucizumab**; Xa inhibitors → **andexanet alfa**; warfarin → **vitamin K + 4-factor PCC**.
- **Cardioversion rule:** AF >48 h/unknown → 3 weeks before + 4 weeks after anticoagulation, or TEE-guided (beware **atrial stunning**).
- **Watchman/Amulet LAA closure** for patients unable to take long-term anticoagulation (PROTECT AF/PREVAIL).
- Anticoagulate **regardless of score** in HCM, mitral stenosis, mechanical valve, or prior stroke.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Atrial Fibrillation" (stroke prevention, CHA_2DS_2-VASc/HAS-BLED, cardioversion-anticoagulation, NOAC dosing table, LAA closure) and "Antiplatelet, Anticoagulant, and Fibrinolytic Drugs" (warfarin/VKOR mechanism, heparin/DOAC pharmacology, reversal agents).
- **Braunwald's Heart Disease, 13e** — "Atrial Fibrillation" (risk stratification, 2023 ACC/AHA/ACCP/HRS guideline thresholds, DOAC vs warfarin, subclinical AF/AHRE, LAA excision/closure — Watchman, Amulet, LARIAT, AtriClip).
- **CMDT 2026** — "Disorders of Cardiac Rhythm" (current DOAC regimens and renal dosing, adjusted stroke rate by CHA_2DS_2-VASc, ROCKET-AF/ARISTOTLE/ENGAGE-AF, reversal-agent doses, peri-procedural management).
- *Coverage note:* the RE-LY trial name for dabigatran is universally accepted standard medicine (Harrison cites the agent without naming the trial; CMDT names ROCKET-AF, ARISTOTLE and ENGAGE-AF explicitly).

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Syncope

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Syncope is a *transient, self-limited loss of consciousness (TLOC) with loss of postural tone, due to acute global cerebral hypoperfusion, characterised by rapid onset, brief duration and spontaneous, complete recovery*. Because the brain's metabolism is critically perfusion-dependent, cessation of cerebral blood flow for ~6–10 s produces loss of consciousness. A presyncopal prodrome (lightheadedness, dimming of vision, sweating, nausea) is common but consciousness may be lost without warning. Syncope must be separated from other causes of TLOC — seizures, vertebrobasilar ischaemia, hypoxaemia, hypoglycaemia and psychogenic pseudosyncope. It accounts for ~3% of emergency visits and ~1% of admissions, with a lifetime cumulative incidence up to 40%, and a bimodal age distribution (peak in the young at 10–30 years, median ~15 years; a sharp rise after 70 years).

Pathophysiology

- **Upright stress is central.** Standing pools 500–1000 mL of blood in the legs, buttocks and splanchnic bed, reducing venous return, ventricular filling, stroke volume and blood pressure.
- This unloads **arterial baroreceptors** in the carotid sinus and aortic arch, normally triggering a compensatory reflex (increased sympathetic outflow, withdrawal of vagal tone) that raises peripheral resistance, heart rate and cardiac output to defend blood pressure.
- **Syncope results when this compensation fails** — transiently in neurally mediated syncope, chronically in autonomic failure, or because cardiac output is mechanically/electrically compromised in cardiac syncope.
- Cerebral blood flow is normally 50–60 mL/min per 100 g and is autoregulated over a mean pressure of ~50–150 mmHg (latency 5–10 s). Consciousness is impaired at ~25 mL/min per 100 g; a **fall in systolic BP to ≤50 mmHg** typically causes syncope. Either reduced cardiac output **and/or** reduced systemic vascular resistance can be the final common pathway; hypocarbia from hyperventilation adds cerebral vasoconstriction.
- **EEG** during syncope shows a "slow–flat–slow" pattern (high-amplitude delta → cortical flattening → recovery); seizure discharges are absent despite myoclonus.

Classification and causes

Three broad categories — *neurally mediated (reflex), orthostatic, and cardiac* — with neurally mediated being commonest at all ages and cardiac the most dangerous.

Category	Subtypes / triggers	Mechanism
Neurally mediated (reflex/vasovagal)	**Vasovagal** (fear, pain, emotion, sight of blood, prolonged standing, heat); **Situational** — cough, micturition, defecation, swallow, post-prandial, wind-instrument/weightlifter; **Carotid sinus syndrome**; cardiac *Bezold–Jarisch reflex*	Transient ↑parasympathetic + sympathoinhibition → vasodilation ± bradycardia. Sub-typed by efferent limb as **vasodepressor** (BP fall), **cardioinhibitory** (bradycardia/asystole) or **mixed**

Category	Subtypes / triggers	Mechanism
Orthostatic hypotension	**Primary autonomic failure** — *synucleinopathies*: Parkinson disease, dementia with Lewy bodies, pure autonomic failure (*Bradbury–Eggleston*), multiple system atrophy (*Shy–Drager*). **Secondary** — diabetic/amyloid/immune/HSAN neuropathy, B12 deficiency, HIV. **Iatrogenic/volume** — diuretics, α-blockers, nitrates, TCAs, phenothiazines; haemorrhage, vomiting, diarrhoea	Sympathetic vasoconstrictor (autonomic) failure → no adequate compensatory rise in HR/resistance on standing
Cardiac	**Arrhythmias** — sinus node dysfunction, AV block (*Stokes–Adams attack*), SVT, VT, inherited channelopathies; **Structural** — aortic stenosis, HCM, MI, atrial myxoma, tamponade, massive PE, pulmonary hypertension	Abrupt fall in cardiac output from electrical or mechanical obstruction; associated with ↑risk of sudden cardiac death

- **Inherited channelopathies** causing arrhythmic syncope/sudden death: **long-QT syndrome** (K^+/Na^+ channel genes, scaffolding protein *ankyrin-B/ANK2*) producing *torsades de pointes*; **Brugada syndrome** (Na^+-channel *SCN5A*; coved RBBB-type ST elevation V1–V3); **catecholaminergic polymorphic VT** (abnormal cardiac calcium handling, *RyR2*). Acquired QT prolongation (drugs) is the commoner cause of torsades.
- **Variants of OH:** *initial OH* (BP fall within 15 s, resolves by 45 s — not true autonomic failure); *delayed OH* (beyond 3 min — early adrenergic failure); **POTS** — chronic (>3 months) orthostatic intolerance with HR rise ≥30/min (≥40 in ages 12–19) within 10 min standing **without** a >20 mmHg SBP fall. **Supine hypertension** coexists in >50% with autonomic failure.

Differentiating syncope from its mimics

Feature	Vasovagal syncope	Seizure	Cardiac/ arrhythmic	Psychogenic
Trigger	Emotion, pain, standing, heat	Rare emotional trigger; aura (déjà vu, olfactory)	Exertion, supine, palpitations	Often present, many witnesses, no trigger
Onset/ prodrome	Long (>5 s): nausea, warmth, sweating, pallor	Brief aura	Sudden (<5 s), few/no warning	Variable; eyes closed
During event	Pallor, dilated pupils, slow pulse, brief arrhythmic multifocal myoclonus	Blue/cyanotic face, tonic–clonic, **tongue biting**, lateral eye deviation	Limp; may be cyanotic	Normal colour, normal pulse/BP
Recovery	Rapid reorientation, prolonged fatigue	Prolonged (>5 min) post-ictal confusion, aching muscles, headache	Rapid unless low output	Rapid, oriented
Incontinence	Urine occasionally; **faecal very rare**	Urine/faeces more likely	Possible	Absent

Approach and investigations

- **Three goals:** confirm it was syncope, identify the cause, and stratify risk of recurrence/sudden death.
- **Cornerstone = history + eyewitness account (and cellphone video) + examination + orthostatic vitals + 12-lead ECG** — establishes a cause in ~50% of patients.
- **Orthostatic vitals:** BP/HR supine then after standing each minute to 3 min. **OH = fall in systolic ≥20 mmHg or diastolic ≥10 mmHg within 3 min** of standing/head-up tilt.
- **High-risk "red-flag" features** mandating admission/intensive evaluation: chest pain/ischaemic ECG, heart failure, moderate–severe valvular or structural disease, history of VT, **QTc >500 ms**, persistent bradycardia (<40/min), bi-/tri-fascicular block or QRS ≥120 ms, AF, non-sustained VT, pre-excitation, Brugada pattern, family history of sudden death, palpitations preceding syncope, or **syncope at rest/during exertion**.
- **ECG**: long QT, short PR + delta wave (WPW), RBBB + ST elevation V1–V3 (Brugada), T-inversion V1–V3 ± epsilon wave (ARVD), AV block, ischaemia.
- **Carotid sinus massage** (>40 yr, recurrent unexplained syncope) under continuous ECG/BP; *avoid with bruit/known stenosis/recent TIA-stroke*. **Cardioinhibitory response = asystole >3 s; vasodepressor = SBP fall >50 mmHg; mixed = both.**
- **Tilt-table test** (head-up 60–80°, usually 70°, after a 20-min supine phase, for 30–45 min, ± isoproterenol or sublingual nitroglycerin) confirms susceptibility to neurally mediated syncope and distinguishes it (paroxysmal hypotensive–bradycardic response) from OH (gradual BP fall without HR rise); also exposes psychogenic pseudosyncope (LOC with normal vitals).
- **Cardiac monitoring matched to event frequency:** in-hospital telemetry/Holter for daily events; external loop recorder for monthly events; **implantable loop recorder** for infrequent events (monitor ideally ≥2× the inter-spell interval).
- **Echocardiography** when structural disease is suspected (aortic stenosis, HCM, tamponade, dissection, myxoma) and for LVEF-based SCD risk. **Exercise testing** if syncope occurs during/after exertion. **Electrophysiologic study** only with structural disease/abnormal ECG (diagnostic: H-V interval ≥100 ms, CSNRT >525 ms, induced sustained monomorphic VT). **Routine CT/MRI/EEG/carotid Doppler are NOT recommended** without focal signs or head trauma — yield ~1–4%.

Management

Type	Management
Neurally mediated / reflex	Education, reassurance, trigger avoidance; **salt + fluid loading**, ~500 mL bolus water acutely; **physical counterpressure manoeuvres** (leg-crossing, handgrip, abdominal + leg tensing — most effective; RCT-supported). Drug: **midodrine** (only agent with RCT support); fludrocortisone, β-blockers (age >40), SSRI as second-line. **Dual-chamber pacing (closed-loop stimulation)** only for >40 yr with frequent recurrence and documented cardioinhibitory/asystolic response

Type	Management
Orthostatic hypotension	Withdraw offending drugs first; staged posture changes, head-up tilt of bed at night, compression garments, counterpressure manoeuvres, avoid large/high-carbohydrate meals; salt and fluid expansion. Drugs: **fludrocortisone**, **midodrine**, **droxidopa (L-DOPS)**; refractory — pyridostigmine, atomoxetine, yohimbine, octreotide, desmopressin (DDAVP), erythropoietin
Cardiac	Treat the cause: **pacemaker** for sinus node disease / AV block; ablation for SVT/WPW; antiarrhythmics and **ICD** for VT/VF or low-EF cardiomyopathy; valve replacement for aortic stenosis; manage PE/tamponade/ischaemia

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **The baroreflex arc** — label: *carotid sinus & aortic arch baroreceptors* → afferents in *glossopharyngeal (CN IX) and vagus (CN X)* → *nucleus tractus solitarius (NTS)* in dorsomedial medulla → *nucleus ambiguus (NA)* (vagal/parasympathetic to sinus node) and *caudal ventrolateral medulla (CVLM)* → *rostral ventrolateral medulla (RVLM)* presympathetic neurons → sympathetic efferents to heart and blood vessels; *A1 noradrenergic group* → *PVN/SON* → *vasopressin*. Colour parasympathetic (green) vs sympathetic (blue).
- **Tilt-table tracing comparison** — label two BP/HR panels: (A) *neurally mediated syncope* = abrupt paroxysmal fall in BP **with** bradycardia; (B) *orthostatic hypotension* = gradual BP fall **without** compensatory HR rise.

Clinical / Diagnostic significance

- Prognosis is driven by aetiology: noncardiac/unexplained syncope in the young has **normal life expectancy**, whereas **cardiac syncope carries excess sudden-death and all-cause mortality**; OH-related syncope roughly doubles mortality (reflects comorbidity).
- Syncope may be the **first and only warning before sudden cardiac death** — hence risk stratification, not just diagnosis, is the priority.
- **Exertional syncope** suggests aortic stenosis, HCM or arrhythmia; **syncope while supine or seated, or preceded by palpitations** suggests an arrhythmia — all are red flags.
- *Coat-hanger* (suboccipital/shoulder) ache and post-prandial faintness point to autonomic failure; treating supine hypertension and OH together requires balance.
- Driving and occupational restriction must be addressed in recurrent or high-risk syncope.

High-yield exam pointers

- Syncope = **global cerebral hypoperfusion**; LOC after ~6–10 s of arrested flow; recovery is rapid and complete.
- Three causes: **neurally mediated (commonest), orthostatic, cardiac (most lethal).**
- **OH = systolic ↓≥20 or diastolic ↓≥10 mmHg within 3 min** of standing; **POTS = HR ↑≥30/min without ≥20 mmHg SBP fall.**
- **Carotid sinus hypersensitivity:** asystole **>3 s** (cardioinhibitory) and/or SBP fall **>50 mmHg** (vasodepressor).

- **Stokes–Adams attack** = syncope from brady-/asystole; **Bezold–Jarisch reflex** underlies cardiac reflex syncope.
- Channelopathies: **LQTS (torsades), Brugada (SCN5A, V1–V3 ST elevation), CPVT, ankyrin-B/ANK2.**
- History + examination + orthostatic vitals + ECG diagnose ~**50%**; routine neuroimaging/EEG are low-yield.
- **Midodrine** is the only RCT-supported drug for vasovagal syncope; **counterpressure manoeuvres** are first-line non-drug therapy; **droxidopa/fludrocortisone/midodrine** for OH.
- **Tongue biting, post-ictal confusion >5 min, cyanosis** favour seizure; **pallor, rapid recovery, faecal continence** favour syncope.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Syncope" (Freeman & Raj): definition, pathophysiology, baroreflex, EEG patterns, classification, channelopathies, approach and treatment.
- **Braunwald's Heart Disease, 13e** — "Hypotension and Syncope" (Calkins & Chen): detailed classification, POTS, carotid sinus hypersensitivity criteria, tilt-table and EP-testing protocols, high-risk/hospitalisation variables, 2017 ACC/AHA/HRS management recommendations, and the syncope-vs-seizure-vs-psychogenic differentiation table.
- **CMDT 2026** — current management context and the exertional-syncope mechanism in aortic stenosis.

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Takotsubo cardiomyopathy

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Takotsubo cardiomyopathy (TTC), also called *takotsubo syndrome (TTS)*, *stress-induced cardiomyopathy*, *apical ballooning syndrome*, or *"broken-heart syndrome,"* is an acute, usually reversible form of left ventricular (LV) dysfunction that classically follows an intense emotional or physical stressor. The acutely dyskinetic, dilated apex with a hypercontractile base produces the characteristic shape of the narrow-necked Japanese octopus-trapping pot (*takotsubo*). It mimics an acute coronary syndrome (ACS) — chest pain, ST-elevation and troponin rise — yet coronary angiography shows no culprit obstruction, and the regional wall-motion abnormality extends beyond any single coronary territory. First described in Japan in the 1990s, it predominantly affects postmenopausal women and generally resolves within days to weeks.

Epidemiology and triggers

- **Sex/age:** Overwhelmingly **postmenopausal women** — in the *International Takotsubo Registry* (1750 patients) **89.8%** were female. Women are ~**10-fold** more likely to develop TTC overall, and women >55 yr are ~5× more likely than those <55 yr. In patients <50 yr, males predominate with more antecedent neurologic/psychiatric disease.

- **Burden:** ~5500 US hospital admissions in 2012, with a large additional in-hospital incidence triggered by intercurrent illness; well recognised during emergency cardiac catheterisation and ICU admissions for non-cardiac conditions.
- **Triggers (preceding stressor not obligatory):** A physical trigger occurred in ~36% and an emotional trigger in ~28% of registry patients. Recognised precipitants include acute medical/surgical illness, hypoglycaemia, alcohol withdrawal, hyperthyroidism, **neurologic catastrophes** (subarachnoid haemorrhage, stroke/TIA, seizures), and **pheochromocytoma**, as well as bereavement and acute emotional shock.
- **Associations:** Higher prevalence of psychiatric and neurologic disorders than ACS controls; patients with COPD, migraine, or affective disorders on β-agonists may fare worse.

Pathophysiology

- **Catecholamine excess is central.** An acute stressor activates central and autonomic stress pathways, raising circulating epinephrine/norepinephrine (adrenal medulla) and local norepinephrine from sympathetic nerve terminals.
- Proposed mechanisms of myocardial injury: **direct catecholamine toxicity**, **adrenoceptor-mediated stunning** (apical myocardium has the highest β-adrenoceptor density), **epicardial multivessel and microvascular coronary spasm**, heterogeneity of myocardial autonomic innervation, abnormal myocardial calcium handling, and increased cardiac workload.
- **Estrogen deprivation** in postmenopausal women (endothelial dysfunction) is thought to be facilitating, explaining the female predominance.
- Cardiac MRI shows **diffuse myocardial oedema without necrosis** and, importantly, **absence of late gadolinium scar** — distinguishing it from infarction and myocarditis.
- A *similar picture* can be produced by a **coronary embolus** in the absence of atherosclerotic disease.

Clinical features and ballooning variants

- **Presentation mimics ACS:** chest pain (~76%), dyspnoea (~47%), syncope (~8%); may present with pulmonary oedema, hypotension or cardiogenic shock. Arrhythmias are not uncommon; syncope is relatively rare.
- **ECG:** ST-segment elevation (in nearly half), deep widespread **anterior T-wave inversions**, and **QTc prolongation**; T-wave changes resolve gradually.
- **Biomarkers:** troponin/CK moderately elevated (troponin raised in ~87%) and *taper quickly* relative to the extent of wall-motion abnormality; BNP/NT-proBNP markedly elevated — a disproportionately small troponin rise for a large akinetic territory is a clue.

Morphologic variant	Frequency / features
Apical ballooning (classic)	>80%; apical akinesis/dyskinesis with hypercontractile base
Midventricular	Mid-LV akinesis with preserved apex and base
Basal ("reverse"/inverted)	Basal akinesis with apical sparing; more often younger patients

Morphologic variant	Frequency / features
Focal	Wall-motion abnormality limited to one segment; rarely within a single coronary territory

Diagnosis and differentiation from ACS

- **InterTAK diagnostic criteria (consensus):** transient LV dysfunction (apical, midventricular, basal or focal pattern, ± RV involvement) typically *extending beyond one coronary distribution*; an emotional/physical/combined trigger may precede but is **not obligatory**; neurologic disorders or pheochromocytoma may trigger it; new ECG changes (ST elevation/depression, T-inversion, QTc prolongation); moderate troponin/CK rise with marked BNP elevation; **significant CAD does not exclude** TTS (~15% have coexisting CAD); no infectious myocarditis; postmenopausal female predominance. **Cardiac MRI is recommended to exclude myocarditis and confirm TTS.**
- **Imaging:** echocardiography demonstrates apical dyskinesis not conforming to a coronary territory; coronary angiography excludes acute occlusion; LV ventriculography shows classic apical ballooning. CMR confirms oedema without scar.

InterTAK clinical score (TTS vs ACS)	Points
Female sex	25
Emotional stress	24
Physical stress	13
No ST-segment depression (except aVR)	12
Psychiatric disorders	11
Neurologic disorders	9
QTc prolongation	6

- Interpretation: ≤70 points = low/intermediate probability; **>70 points = high probability of TTS**. The score aids ED discrimination but does **not replace coronary angiography** in the acute setting.

Management

- **Acute phase = treat as ACS until coronary disease excluded** (urgent angiography). Admit higher-risk patients to ICU/CCU for monitoring.
- **No therapy is proven to alter the natural history**; care is supportive and complication-directed:
  - *Pulmonary oedema:* nitrates and standard heart-failure measures.
  - *Haemodynamically stable patients:* combined **α- and β-blockade** preferred over selective β-blockade.
  - *Arrhythmia / QT prolongation:* magnesium; **avoid QT-prolonging drugs** (e.g., macrolides, certain antiarrhythmics).
  - *Hypotension:* use **inotropes/pressors with great caution** — they can precipitate dynamic **LV outflow tract (LVOT) obstruction**; an intra-aortic balloon pump may be used for critically low output **only if there is no LVOT obstruction**.

- *LV apical thrombus:* anticoagulation while thrombus is present.

- **Risk stratification (higher-risk):** LVEF <45%, hypotension, LVOT gradient >40 mmHg, and/or significant arrhythmia — an **ACE inhibitor and/or β-blocker** is recommended in this group.
- **Long-term/secondary prevention: ACE inhibitors/ARBs are associated with reduced recurrence and improved survival**, whereas **β-blockers have NOT been shown to prevent recurrence**. Routine long-term anticoagulation is not recommended once thrombus resolves.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **LV ventriculogram/echo in systole (classic "takotsubo" shape):** outline the LV cavity with labels — *hypercontractile basal segments (narrow neck)*, *akinetic/dyskinetic ballooned apex*, *mid-LV*, *aortic outflow*; alongside a small sketch of the **Japanese octopus pot (takotsubo)** for the eponym.
- **Pathophysiology flow diagram:** *Acute emotional/physical stress → central + sympathetic activation → catecholamine surge (epinephrine/norepinephrine) → [direct catecholamine toxicity + microvascular/epicardial spasm + β-receptor–mediated apical stunning] → transient apical ballooning (reversible LV dysfunction)*, with *estrogen deprivation* shown as a facilitating factor.

Clinical / Diagnostic significance

- Must be considered in any **postmenopausal woman presenting as anterior STEMI after acute stress** — distinguishing it from ACS prevents inappropriate thrombolysis and guides management.
- **Disproportion clue:** extensive wall-motion abnormality with only modest troponin rise and a non-coronary distribution favours TTS over infarction.
- **CMR (oedema without scar)** is the key discriminator from MI and myocarditis.
- Complications driving the ~4–5% in-hospital mortality: cardiogenic shock, **dynamic LVOT obstruction from systolic anterior motion of the mitral valve**, **LV free-wall rupture**, mural-thrombus **embolisation/stroke**, **torsades de pointes** from QT prolongation, and (rarely) complete heart block.
- Prognosis: historically thought benign, but in-hospital mortality is comparable to STEMI; ~10% have cardiac/neurologic adverse events over the next year.

High-yield exam pointers

- *Takotsubo* = narrow-necked Japanese **octopus-trapping pot**; synonyms: stress/apical ballooning/"broken-heart" syndrome.
- **Postmenopausal women (~90%)** after intense emotional or physical stress; estrogen deprivation facilitates.
- **Mechanism = catecholamine surge** → direct toxicity + microvascular/epicardial spasm + apical β-receptor stunning.
- Mimics **anterior STEMI** (ST-elevation, deep T-inversions, QTc↑) with **normal/non-obstructive coronaries** and wall motion **crossing coronary territories**.

- **Troponin rise modest** relative to akinesis; **BNP markedly raised**; **CMR shows oedema WITHOUT late-gadolinium scar**.
- Variants: **apical (>80%)**, midventricular, basal/reverse, focal.
- **InterTAK score >70 → high probability of TTS**; significant CAD does NOT exclude the diagnosis.
- Treatment supportive: avoid pressors/QT-prolonging drugs; beware **LVOT obstruction**; **ACEi/ARB reduces recurrence, β-blockers do not**.
- Usually **reverses in days–weeks**; recurrence ~5% (mostly within the first year; Harrison cites ~10% lifetime at ~2%/yr).

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — *"Dilated Cardiomyopathies"* (Takotsubo syndrome/cardiomyopathy section) and *"Classification of Cardiomyopathy."*
- Braunwald's Heart Disease, 13e — *"The Dilated, Restrictive, and Infiltrative Cardiomyopathies"* (Takotsubo Cardiomyopathy; **International Takotsubo (InterTAK) Diagnostic Criteria** and **InterTAK Clinical Score**, International Takotsubo Registry epidemiology, complications and therapy).
- CMDT 2026 — *"Heart Failure & Cardiomyopathy"* (Takotsubo Cardiomyopathy — essentials, pathophysiology, ECG/diagnostic studies, treatment, prognosis).

Coverage note: The corpus does not include the *Mayo Clinic* diagnostic criteria; the InterTAK consensus criteria (Braunwald) are used instead. All figures (89.8% female, InterTAK score points, ~4–5% mortality, ballooning variants, ACEi-vs-β-blocker recurrence data) are taken verbatim from the cited chapters.

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Coronary arteriography

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Coronary arteriography (selective coronary angiography) is the invasive, catheter-based opacification of the epicardial coronary arteries with radio-opaque iodinated contrast, recorded as cine images in multiple orthogonal projections, and remains the **gold standard** for defining coronary anatomy and the extent/severity of obstructive coronary artery disease (CAD). It is almost always performed as part of diagnostic **cardiac catheterization**. The technique evolved from Forssmann's self-catheterization (1929) and Cournand & Richards' haemodynamic work (Nobel Prize, 1956) to Sones' first selective coronary injection (1958) and Judkins' preformed catheters that brought it into routine use. The purpose is to determine whether **medical, surgical (CABG), or catheter-based (PCI) interventions** are warranted.

Indications for coronary arteriography

Broadly, arteriography is indicated to **define the extent and severity of cardiac/coronary disease in symptomatic patients**, to decide on revascularisation, and to **exclude severe disease** when non-invasive tests are equivocal but a definitive diagnosis is needed.

Clinical setting	Specific indications
Asymptomatic / symptomatic CAD	High-risk findings on non-invasive testing; aborted sudden cardiac death; sustained (>30 s) monomorphic VT; non-sustained (<30 s) polymorphic VT
Symptomatic CAD	CCS Class **II, III, or IV** stable angina on medical therapy; acute coronary syndrome (unstable angina & NSTEMI); chest-pain syndrome of unclear cause with equivocal non-invasive tests
Acute myocardial infarction	Reperfusion by **primary PCI**; persistent/recurrent ischaemia; pulmonary oedema and/or reduced ejection fraction; **cardiogenic shock / haemodynamic instability**; risk stratification or a positive post-MI stress test; mechanical complications (acute MR, ventricular septal defect)
Valvular heart disease	Suspected severe valve disease in symptomatic patients (dyspnoea, angina, heart failure, syncope); infective endocarditis needing surgery; **asymptomatic aortic regurgitation** with cardiac enlargement or falling EF; prior to cardiac surgery / **TAVR** or other percutaneous valve intervention when CAD is suspected
Congestive heart failure	New-onset angina or suspected undiagnosed CAD; new-onset cardiomyopathy of uncertain cause or suspected to be ischaemic
Congenital heart disease	Before surgical correction / percutaneous intervention when symptoms or testing suggest coronary disease; suspected **congenital coronary anomalies**
Pericardial disease	Symptomatic patients with suspected tamponade or constrictive pericarditis (with right heart study)
Cardiac transplantation	Pre-operative and post-surgical (allograft vasculopathy) evaluation
Other conditions	Hypertrophic cardiomyopathy with angina; diseases of the aorta where coronary involvement alters management; pulmonary hypertension; unexplained dyspnoea

- **Acuity-based strategy (ACS):** an *urgent/immediate* invasive strategy is indicated in NSTE-ACS with refractory angina or haemodynamic/electrical instability; an *early invasive* strategy in

stabilised high-risk patients (raised troponin, dynamic ST/T changes, **GRACE score >140**, diabetes, EF <40%, early post-infarction angina, recent PCI, prior CABG). **STEMI** within ischaemic-symptom onset warrants urgent angiography for primary PCI.

- **Pre-valve-surgery screening (CMDT):** coronary angiography to detect incidental CAD before valve surgery is recommended in **all men >40 years** and in **menopausal women with coronary risk factors**; younger patients need it only if coronary disease is clinically suspected.
- Catheterisation is **not mandatory** before surgery in selected younger patients with uncomplicated congenital or valvular disease well-defined non-invasively and without risk factors for concomitant CAD.

Contraindications (context for indications)

- There are **no absolute contraindications** when the procedure is performed in anticipation of a **life-saving intervention** and the patient accepts the risks.
- **Relative contraindications (elective):** decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency (unless dialysis planned); bacteraemia; acute stroke; active GI bleeding; excessive anticoagulation or recent thrombolytic administration; severe uncorrected electrolyte abnormalities; prior **anaphylactoid reaction to iodinated contrast** without premedication; aspirin allergy/anaphylaxis/bronchospasm if progression to PCI is likely and desensitisation not done; uncontrolled hypertension; pregnancy (radiation).
- **Right heart catheterisation–specific:** right heart tumour, endocarditis, or thrombus/clot in transit.

Complications of the procedure

Risks of **elective** catheterisation are low; they rise substantially when done emergently, during acute MI, or in haemodynamically unstable patients. Harrison quotes MI <0.1%, stroke 0.01%, death 0.05%; for elective + emergent procedures combined the **in-hospital mortality is 1.4%**.

Complication	Approximate risk (%)
Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident (stroke)	0.07
Arrhythmias	0.38
Vascular (access-site) complications	0.43
Contrast agent reaction	0.37
Haemodynamic complications	0.26
Perforation of a heart chamber	0.03
Other	0.28
Total major complications	**≈1.70**

- **Vascular access-site bleeding is the most common complication (1.5–2.0%);** major bleeds worsen short- and long-term outcome. **Radial access** lowers vascular/bleeding complications versus femoral and is the preferred route.
- **Access-site complications:** haematoma, **pseudoaneurysm**, arteriovenous fistula, dissection, and (with femoral puncture outside the safe zone — above the profunda/superficial femoral bifurcation, below the inferior epigastric artery) **retroperitoneal haemorrhage**. Radial access may cause severe vasospasm with device entrapment, forearm haematoma, and rarely **compartment syndrome**.
- **Arrhythmias:** tachy-/brady-arrhythmias needing countershock, temporary pacing, or drugs. Deep RCA cannulation or contrast injection into the conus branch can precipitate **ventricular fibrillation**; catheter contact during ventriculography may trigger VPCs/VT (usually self-limiting).
- **Embolic events:** coronary, cerebral, or peripheral air/thrombus/atheroembolism; risk increased by calcified subclavian/axillary vessels. Risk factors for peri-procedural stroke: advanced age, diabetes, emergency procedure, prior stroke, renal failure, CHF.
- **Iatrogenic coronary dissection or perforation** — infrequent but potentially life-threatening, may need urgent stenting; **aortic dissection** and **cardiac tamponade** can occur.
- **Other:** acute renal failure requiring transient/permanent dialysis, acute pulmonary oedema, hypotension/haemodynamic compromise, and (rarely) infection — antibiotic prophylaxis is **not** required.

Contrast and radiation complications

- **Contrast allergy:** allergic reactions in <5%; severe **anaphylactoid** reactions (clinically like anaphylaxis but not IgE-mediated) in 0.1–0.2%. Mild = nausea, vomiting, urticaria; severe = hypotensive shock, pulmonary oedema, cardiorespiratory arrest. *Premedication* for prior significant allergy: **prednisone 50 mg orally at 13, 7 and 1 hour** before, plus an **H1-antihistamine**, using non-ionic low-osmolar contrast.
- **Contrast-induced acute kidney injury (CI-AKI):** rise in creatinine **>0.5 mg/dL or >25% above baseline at 48–72 h**; occurs in ~2–7% overall (20–30% in high-risk patients). *Risk factors:* diabetes mellitus, CHF, chronic kidney disease, anaemia, older age, STEMI. Dialysis needed in 0.3–0.7%, carrying a **five-fold rise in in-hospital mortality**. *Prevention:* IV **0.9% saline 1.0–1.5 mL/kg/h** for 3–12 h before and 6–24 h after (reduces risk by >50%); minimise contrast volume (<50 mL); low-/iso-osmolar agents; **stop metformin 24 h before and restart 48 h after** to avoid lactic acidosis. N-acetylcysteine and sodium bicarbonate show **no clear benefit** in recent meta-analyses.
- **Radiation injury:** deterministic (dose-dependent — skin erythema, telangiectasia, hair loss, lens injury; commonest site is the skin of the back) and stochastic (carcinogenesis). Thresholds for follow-up: **>5 Gy** — advise watching for erythema; **>10 Gy** — medical-physicist peak-dose calculation at 2–4 weeks; **>15 Gy** or fluoroscopy time **>60 min** — hospital risk-management event/vigilance. The **ALARA** principle governs dose minimisation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Normal coronary tree (PA + lateral schematic):** label **Left main (LM)**, **LAD** with **diagonal (D)** branches, **Left circumflex (LCx)** with **obtuse marginal (OM)**, **Right coronary artery (RCA)**, **posterior descending artery (PDA)**, AV-nodal branch; annotate **right-dominant circulation (~85%)** where PDA arises from RCA.
- **Femoral artery puncture "safe zone":** label **inguinal ligament**, **inferior epigastric artery (upper limit)**, **common femoral artery**, **bifurcation into profunda femoris & superficial femoral artery (lower limit)**, **femoral head landmark** — puncture below the inferior epigastric and above the bifurcation to avoid retroperitoneal bleed.

Clinical / Diagnostic significance

- A luminal narrowing **>50%** is considered significant; intermediate stenoses (40–70%) are interrogated functionally — **fractional flow reserve (FFR) <0.80** (post-adenosine hyperaemia) or **instantaneous wave-free ratio (iwFR) <0.89** indicate a haemodynamically significant lesion benefiting from revascularisation; **coronary flow reserve <2.0** signals microvascular dysfunction.
- **IVUS** (axial resolution 100–150 μm) and **OCT** (10–15 μm) refine plaque characterisation and stent optimisation (expansion, apposition, edge dissection).
- A **myocardial bridge** mimics stenosis but normalises in diastole; **coronary spasm** resolves with intracoronary nitroglycerin; **spontaneous coronary artery dissection** appears in otherwise normal vessels — important differentials of an apparent "stenosis".
- Adjunct studies obtained at the same sitting — ventriculography (wall-motion, EF, MR grade), aortography (dissection, AR), right heart study (shunts, PA pressures), and the **Brockenbrough–Braunwald sign** for HOCM — extend diagnostic value.
- **Pre-procedure optimisation:** 6-h fast, conscious sedation, aspirin 325 mg, hold warfarin until INR <1.8 (heparin bridge for mechanical valves), stop DOACs 24–48 h prior, withhold oral hypoglycaemics in those prone to hypoglycaemia.

High-yield exam pointers

- **Gold standard** for coronary anatomy; first selective injection by **Sones (1958)**; preformed catheters by **Judkins**.
- Memorise indication buckets: **symptomatic/high-risk CAD, ACS, acute MI (primary PCI, shock, mechanical complications), valvular & congenital disease, CHF/new cardiomyopathy, HCM with angina, pre-transplant**.
- **No absolute contraindication** before a life-saving intervention; key relative ones: decompensated HF, uncorrected coagulopathy/electrolytes, untreated contrast anaphylaxis, active bleeding, acute stroke, severe renal failure (unless dialysis planned).
- **Commonest complication = vascular access-site bleeding (1.5–2.0%)**; serious events (death/MI/stroke) each <1%; overall major complication rate ≈1.7%.
- **Radial > femoral** for fewer bleeding/vascular complications.
- **CI-AKI**: creatinine rise >0.5 mg/dL or >25% at 48–72 h; prevent with saline hydration and minimal low-/iso-osmolar contrast; hold metformin.

- **Contrast anaphylactoid** reaction premedication: **prednisone 50 mg at 13, 7, 1 h + H1-blocker**.
- Deep RCA/conus injection → **VF**; femoral puncture below the bifurcation → **retroperitoneal haemorrhage**.
- Radiation thresholds: **>5 Gy** erythema watch; **>15 Gy / >60 min FT** = risk-management event.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diagnostic Cardiac Catheterization and Coronary Angiography" (indications Table 249-1; risks, relative contraindications, contrast allergy/premedication, CI-AKI, coronary anatomy & dominance, FFR/iwFR/CFR, IVUS/OCT).
- **Braunwald's Heart Disease, 13e** — "Coronary Angiography and Intravascular Imaging" (appropriate-use criteria, contraindications, Table of risks with per-complication percentages, vascular/embolic complications, CI-AKI prevention, radiation-exposure thresholds and ALARA).
- **CMDT 2026** — "Coronary Artery Disease, Valvular Disease & Other Key Topics in Cardiology" (pre-valve-surgery coronary angiography screening criteria).

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Cardiac resynchronisation therapy

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Cardiac resynchronization therapy (CRT)* is a device-based, atrio-biventricular pacing strategy that restores the synchrony of electrical depolarization (and hence the coordination of mechanical contraction) in patients with chronic heart failure with reduced ejection fraction (HFrEF) and an electrical conduction delay — most importantly *left bundle branch block (LBBB)*. By pacing the left ventricle (LV) through a lead placed in a tributary of the coronary sinus together with a right-ventricular (RV) lead, CRT re-coordinates inter- and intraventricular contraction. It is the only pacing therapy proven to reduce **both morbidity and all-cause mortality** in appropriately selected HFrEF patients already on optimal guideline-directed medical therapy (GDMT). CRT was first approved by the FDA in 2001.

Pathophysiological rationale — ventricular dyssynchrony (the target)

- Intraventricular conduction abnormalities occur in roughly **one-third** of HFrEF patients and independently worsen morbidity and mortality. About **30% of patients with dilated cardiomyopathy** have an interventricular conduction delay, most commonly LBBB.
- *Electrical dyssynchrony* is defined operationally by a **prolonged QRS duration (>120 ms)** on the surface ECG; it usually reflects underlying *mechanical dyssynchrony* — a difference in the timing of contraction/relaxation between LV segments or between the two ventricles.
- Consequences of dyssynchronous contraction:
  - Suboptimal/reduced ventricular filling and impaired diastolic function.
  - Reduced LV contractility and decreased mechanical efficiency of systole; increased wall stress.

- Paradoxical septal wall motion (inter-ventricular dyssynchrony).
- Greater degree and prolonged duration of **functional (secondary) mitral regurgitation**.

- CRT corrects these by pre-exciting the LV lateral wall via the coronary-sinus lead, aligning the timing of activation of opposing walls → reverse remodeling (fall in LV end-systolic volume), improved EF, higher systolic blood pressure (which then permits up-titration of previously hypotension-limited GDMT), reduced functional MR, and symptomatic/functional improvement.
- *Pacing-induced cardiomyopathy*: a high burden (>40%) of chronic RV apical pacing itself produces an iatrogenic LBBB-like dyssynchrony and HF in ~6–39% of paced patients — an additional indication for CRT/physiologic pacing.

Hardware, device types and modes of physiologic pacing

- **Lead system** — a transvenous CRT system has three leads: right atrial, right ventricular, and a **left-ventricular lead advanced via the coronary sinus into a (postero-)lateral epicardial vein**. Quadripolar LV leads allow multiple pacing vectors to avoid phrenic-nerve capture and high thresholds.
- **CRT-P** (biventricular *pacemaker*) vs **CRT-D** (biventricular pacing combined with an implantable cardioverter-defibrillator) — choice depends on whether a concomitant ICD indication (sudden-death prevention) exists.
- *Cardiac physiologic pacing (CPP)* is the umbrella term and includes:
  - **CRT** = conventional biventricular pacing (BiVP) via a coronary-sinus LV lead.
  - **Conduction system pacing (CSP)** = *His-bundle pacing (HBP)* or *left bundle branch area pacing (LBBAP)* — emerging single-site alternatives that engage the native conduction system; HBP has a ~10–20% acute failure rate and threshold issues, while LBBAP has a larger capture target and lower thresholds. Class I evidence still favours CRT (BiVP) over CSP for established CRT indications; head-to-head pivotal trials are ongoing.
- Successful BiVP requires programming a **short AV interval** (to pre-excite the LV in LBBB) and attention to the VV interval. Trials of routine echocardiographic AV/VV optimization (vs a fixed AV delay of 120 ms) showed **no remodeling benefit**, so it is reserved for non-responders. Multipoint pacing (MORE-CRT MPP) gives marginal added benefit in selected non-responders.

Indications and patient selection

The ideal candidate is symptomatic HFrEF on GDMT with a wide LBBB QRS in sinus rhythm — benefit is greatest with **wider QRS (>149 ms), LBBB morphology, and non-ischaemic cardiomyopathy**.

Recommendation strength	Patient profile
Class I (strongest)	LVEF ≤35%, **LBBB with QRS ≥150 ms**, sinus rhythm, NYHA II / III / ambulatory IV, on GDMT
Class I (newer, 2023 HRS/APHRS/LAHRS)	Similar patients with **QRS 120–149 ms** plus special features (e.g. female sex)

Recommendation strength	Patient profile
Class I (newer)	**Pacemaker-induced cardiomyopathy** / anticipated high-burden (>40%) RV pacing; CRT for those with LVEF ≤50% requiring ventricular pacing (BLOCK-HF)
Lower benefit / Class II	Non-LBBB (IVCD/RBBB) morphology; QRS 120–149 ms without special features; atrial fibrillation (excluded from most pivotal trials)
Contraindicated / harmful	**Narrow QRS (<130 ms)** even with echocardiographic dyssynchrony (Echo-CRT showed harm); QRS <120 ms

- CMDT/2022 AHA-ACC-HFSA framing: CRT indicated for **NYHA class II–III HF, EF ≤35%, sinus rhythm, LBBB with QRS ≥150 ms**; refer any patient with persistent symptoms and LVEF ≤35% with QRS ≥120 ms (especially LBBB).
- Pre-implant work-up: confirm GDMT optimization first, document LVEF, QRS duration and morphology, rhythm (sinus vs AF), and NYHA class; NT-proBNP if CRT planned.

Evidence base — landmark randomized trials

Trial	Population (n)	Comparison	Key result
MUSTIC / MIRACLE / MIRACLE-ICD	NYHA II–IV, QRS wide	CRT on vs off	Improved 6-min walk, QoL, NYHA, LV reverse remodeling (intermediate endpoints)
COMPANION (n=1520)	QRS ≥120 ms, NYHA III–IV, EF ≤35%	OPT vs CRT-P vs CRT-D (1:2:2)	↓ death/any hospitalization (HR ~0.80); **CRT-D ↓ all-cause mortality 36% (P=.003)**, CRT-P 24% (P=.059)
CARE-HF (n=813)	QRS ≥150 ms (or 120–150 + echo dyssynchrony), NYHA III–IV, EF ≤35%	CRT vs no CRT	**First trial to show all-cause mortality reduction** — ACM HR 0.64 (P<.002)
REVERSE / MADIT-CRT / RAFT	NYHA I–II (mild), QRS ≥120–130 ms, EF ≤30–40%	CRT(-D) vs control/ICD	Reverse remodeling + ↓ HF events; **MADIT-CRT** HR 0.66; **RAFT** ACM/HFH HR 0.75 — extended indication to mildly symptomatic HF
Echo-CRT (n=809)	**Narrow QRS ≤130 ms** + echo dyssynchrony	CRT vs control	No benefit; **increased mortality (ACM HR 1.81)** → CRT contraindicated in narrow QRS
BLOCK-HF (n=691)	AV block, EF ≤50%, needing RV pacing	BiV (CRT) vs RV pacing	CRT superior (composite HR 0.74) → support for CRT when ventricular pacing is required

- Take-home: benefit is greatest in **wide-LBBB, sinus-rhythm** patients; narrowest/non-LBBB QRS derive little benefit or harm; the *most* benefit in mildly symptomatic patients accrues when **QRS >149 ms with LBBB**.

Predictors of response, non-responders and complications

- **Predictors of good response:** wider QRS, true LBBB morphology, non-ischaemic aetiology, female sex, sinus rhythm, high effective BiVP percentage, lateral/postero-lateral lead in the region of latest activation.

- **Response is not binary:** ~30% are "non-responders"; some are *super-responders* (EF normalization); others are "non-progressors" (stabilized course).
- **Causes of non-response:** lack of LV capture; suboptimal LV lead position (apical/anterior, not at site of latest delay); narrow or non-LBBB QRS; low BiVP delivery (frequent PVCs, atrial fibrillation, too-long AV interval); LV lateral-wall scar; cardiac amyloidosis. Many are salvageable by reprogramming, arrhythmia control (PVC/AF ablation), or LV lead revision.
- **Implant complications:** coronary-sinus dissection, LV lead dislodgement/microdislodgement, **phrenic-nerve / diaphragmatic / intercostal extracardiac stimulation**, cardiac perforation with tamponade, pneumothorax, subclavian/axillary vein thrombosis, pocket infection/lead endocarditis, and tricuspid regurgitation from the RV lead.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled chest diagram of a CRT-D system:** pulse generator in left prepectoral pocket; **right atrial lead** (RA appendage); **right ventricular lead** (RV apex/septum, with shock coil if CRT-D); **left ventricular lead passing through the coronary sinus into a postero-lateral cardiac vein**; label the coronary sinus os and lateral LV wall.
- **ECG strip comparison:** baseline **wide LBBB QRS (>150 ms)** versus post-CRT **narrowed/fused biventricular-paced QRS**, with arrows marking the shortened, pre-excited LV activation.

Clinical / Diagnostic significance

- CRT is layered **on top of optimized GDMT** (ARNI/ACEi-ARB, beta-blocker, MRA, SGLT2 inhibitor, diuretics) — never a substitute.
- Confers **reverse remodeling**, improved EF and 6-min walk distance, fewer HF hospitalizations, better QoL, and a survival benefit; the rise in systolic BP frequently allows further up-titration of neurohormonal therapy.
- If a CRT candidate also meets ICD criteria (LVEF ≤35%, NYHA II–III, ≥40 days post-MI / non-ischaemic on GDMT), implant a **combined CRT-D**.
- CRT has **no established role in HFpEF/HFmrEF** and is harmful in narrow-QRS patients.
- Cardiac contractility modulation (CCM) is the device option for symptomatic HFrEF (EF 25–45%) with **narrow QRS** who are *not* CRT candidates.

High-yield exam pointers

- CRT = atrio-**biventricular pacing**; LV lead delivered via the **coronary sinus** to the LV lateral wall.
- Best candidate: **EF ≤35%, LBBB, QRS ≥150 ms, sinus rhythm, NYHA II–III on GDMT** — Class I.
- **CARE-HF** = first trial to prove all-cause mortality benefit; **COMPANION** proved benefit of both CRT-P and CRT-D.
- **MADIT-CRT / RAFT / REVERSE** extended CRT to mildly symptomatic (NYHA I–II) HFrEF.
- **Echo-CRT** = CRT is *harmful* in narrow QRS (<130 ms) → contraindicated; **BLOCK-HF** supports CRT when chronic RV pacing is needed.

- Poor responders: non-LBBB/IVCD, ischaemic scar, AF, low BiVP%, narrow QRS, RV-apical lead, amyloidosis (~30% non-response).
- CRT-D combines resynchronization + defibrillation; CRT-P is pacing only.
- Conduction system pacing (His-bundle, **LBBAP**) is the evolving alternative to BiVP.
- Classic implant complications: **coronary-sinus dissection, phrenic-nerve stimulation, LV lead dislodgement**.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Heart Failure: Management" (mechanism of dyssynchrony, CARE-HF, RAFT/MADIT-CRT, indications, SCD/ICD interface).
- Braunwald's Heart Disease, 13e — "Pacemakers, Conduction System Pacing, Cardiac Resynchronization Therapy, and Implantable Cardioverter-Defibrillators" (CPP/CSP, lead configuration, AV/VV optimization, non-responders, complications) and "Devices for Monitoring and Managing Heart Failure" (pivotal CRT trial table: COMPANION, CARE-HF, REVERSE, MADIT-CRT, RAFT, Echo-CRT, BLOCK-HF; 2023 HRS/APHRS/LAHRS guideline indications).
- CMDT 2026 — "Heart Failure & Cardiomyopathy" (current biventricular-pacing/CRT indication thresholds, referral criteria, ICD/MADIT-II context).

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Atrial fibrillation

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by seemingly disorganised, rapid and irregular atrial electrical activation with **loss of organised atrial mechanical contraction**. The chaotic atrial impulses bombard the AV node, which gates ventricular activation, producing an **irregularly irregular, usually rapid ventricular rate** (typically 110–160/min). It is the most common sustained arrhythmia and a major public health problem because of its strong association with stroke, heart failure, dementia and increased mortality.

Epidemiology and Risk Factors

- **Most common sustained arrhythmia**; prevalence rises steeply with age — >95% of AF patients are >60 years and prevalence in those >80 years is ~20%.
- Lifetime risk of developing AF for a 40-year-old man is ~25%. Slightly commoner in **men** > **women** and in **whites** > **blacks**.
- AF carries a **1.5–1.9-fold increase in mortality** even after controlling for underlying cardiac disease, and causes **~25% of all strokes**.
- AF is detected in up to **8.9%** of patients within 6 months of a *cryptogenic stroke* using insertable cardiac monitors.
- **Risk factors:** age, underlying cardiac disease, hypertension, diabetes mellitus, obesity, thyroid disease (hyperthyroidism), family history of AF, alcohol use and sleep-disordered breathing.

- **Identifiable precipitants:** hyperthyroidism, acute alcohol intoxication ("holiday heart"), myocardial infarction, pulmonary embolism, pericarditis, and cardiac surgery (AF occurs in up to **50%** of patients post-operatively).
- Consequences: increased risk of **dementia**, MRI-detected asymptomatic embolic infarcts, congestive heart failure and tachycardia-induced cardiomyopathy (when rate is uncontrolled for prolonged periods).

Pathophysiology

- Multifactorial; the diverse risk factors are proposed to converge on a "**final common pathway**" producing electrophysiologic remodelling of atrial tissue.
- Altered membrane channels and protein regulation cause **abnormal excitability**; **pulmonary vein musculature** exhibits enhanced automaticity, generating ectopic beats (PACs).
- Bouts of rapid atrial ectopy initiate atrial tachycardia or frank AF; sustained AF is maintained by a combination of automaticity-based "**drivers**" and areas of **functional reentry**.
- Progressive cellular and tissue remodelling → **shortening of atrial refractory periods**, abnormal conduction, **fibrosis** and **left atrial enlargement**, which perpetuate AF ("AF begets AF").
- Non-pulmonary-vein triggers: posterior wall of left atrium, muscular sleeves of the **superior vena cava, coronary sinus**, and the **vein of Marshall** remnant.
- Loss of atrial systole and a noncompliant, fibrotic left atrium produce elevated filling pressures and volume overload — the "**stiff left atrial syndrome.**"

Classification (by Temporal Pattern)

Type	Definition	LA size / scar	AAD efficacy	Ablation
Paroxysmal	Self-terminates or cardioverted in ≤7 days	Normal–mildly enlarged	Low	PV isolation alone usually effective; first-line reasonable
Persistent	Continuous >7 days but <1 year	Mild–severely enlarged	Moderate	PV isolation + non-PV sources; usually after AAD failure
Long-standing persistent	Persistent >1 year	Typically severely enlarged	High failure rate	PV isolation + substrate modification; often refractory

- **Nonvalvular AF** = AF *without* mitral stenosis (the term guides anticoagulant choice).
- **Subclinical AF** — short-lasting, asymptomatic episodes detected only by implantable loop recorders/pacemakers; associated with a **2.5-fold** increased stroke risk.

Clinical Presentation

- Manifestations arise from: (1) symptoms of the irregular, fast (or slow) ventricular rate; (2) haemodynamic consequences of lost atrial contraction; (3) cardioembolic events; and (4) long-term impact on cardiac function.
- **Palpitations**, awareness of heartbeat, fatigue, weakness, exercise intolerance, dyspnoea, presyncope — though many patients are **asymptomatic / unaware** of the irregularity.

- Loss of atrial "kick" reduces ventricular filling and stroke volume — especially decompensating in **HCM, coronary or valvular disease, HFrEF/HFpEF and amyloidosis**.
- With AV nodal disease or high vagal tone, bradycardia or **conversion pauses** (sinus node dysfunction / tachy-brady syndrome) may cause syncope.
- **Diagnosis** is by ECG (12-lead, ambulatory monitor, or implantable loop recorder): **absent P waves**, fibrillatory baseline best seen in **lead V1**, and an **irregularly irregular** ventricular response.

Treatment — Three Aims

The management of AF centres on three goals: **(1) symptom control by rate and/or rhythm control; (2) mitigation of thromboembolic (stroke) risk; and (3) addressing modifiable risk factors** for progression.

- **Emergency:** If significant haemodynamic compromise, pulmonary oedema or coronary ischaemia is present → **emergent (synchronised DC) cardioversion**.

Rate control

- Goal: prolong diastolic filling, improve cardiac output, prevent tachycardia-induced cardiomyopathy.
- Acute: **beta blockers** and/or **non-dihydropyridine calcium channel blockers (verapamil, diltiazem)** IV or oral.
- **Digoxin** — useful with labile BP or cardiomyopathy (no negative inotropy); acts synergistically as add-on. Chronic use associated with **increased mortality**, so its use has declined.
- Chronic targets: strict = resting HR <80/min (and <110 on moderate exertion); **lenient = resting HR <110/min** is as effective for CV death, HF hospitalisation, stroke and bleeding, and easier to achieve.
- **"Ablate and pace":** AV junction ablation + permanent pacemaker for refractory rates; biventricular or **left bundle branch area pacing** minimises dyssynchrony and improves outcomes in permanent AF with narrow QRS.

Stroke prevention / anticoagulation

- Thrombus forms chiefly in the **left atrial appendage** (stagnant flow); risk assessed by **CHA_2DS_2-VASc**, bleeding risk by **HAS-BLED**.
- Anticoagulation recommended for CHA_2DS_2-VASc ≥1 (unless the sole point is female sex); annual stroke risk reaches nearly **20%** at high scores.
- **DOACs** (dabigatran, rivaroxaban, apixaban, edoxaban) were non-inferior to warfarin in nonvalvular AF, with **lower intracranial bleeding**; pooled data suggest small absolute superiority.
- **Warfarin is mandatory** for rheumatic mitral stenosis and mechanical valves (DOACs failed/inferior here). In nonvalvular AF warfarin cuts stroke by ~64% vs placebo, 37% vs antiplatelets.
- **Antiplatelets alone are inferior** and not safer; aspirin+clopidogrel < warfarin and bleeds more.

- Reversal: warfarin → vitamin K, FFP, PCC; dabigatran → **idarucizumab**; factor Xa inhibitors → **andexanet alfa**.
- **LAA closure device (Watchman)** for high stroke risk with contraindication to anticoagulation — comparable to warfarin, less major/haemorrhagic bleeding, non-inferior to DOACs.

Cardioversion and peri-cardioversion anticoagulation

- Pharmacologic cardioversion: IV **ibutilide** (class III) — avoid with baseline prolonged QT or severe LV dysfunction (risk of *torsades de pointes*).
- If AF **>48 h or duration unknown**: either anticoagulate **3 weeks before + ≥4 weeks after**, OR perform **TEE** (or delayed-acquisition cardiac CT) to exclude LAA thrombus before cardioversion, then anticoagulate ≥4 weeks (atrial mechanical recovery delayed — **"atrial stunning"**).

Rhythm control

- Preferred for symptomatic paroxysmal/persistent AF, difficult rate control, or AF-induced LV dysfunction; favoured in younger patients.
- **Early rhythm control** (within 1 year of presentation) reduces cardiovascular events; catheter ablation gives an **all-cause mortality benefit** in HFrEF.
- AADs without structural disease: class I (**flecainide, propafenone, disopyramide**). With structural/coronary disease: **sotalol, dofetilide** (~3% torsades risk; dofetilide initiated in hospital).
- **Amiodarone** is the most effective (maintains sinus rhythm in ~2/3) and safe in HF/CAD, but >40% develop toxicities (skin, liver, lung, thyroid). **Dronedarone** increases mortality in HF and long-standing persistent AF.
- **Catheter ablation (pulmonary vein isolation)** — first-line for paroxysmal AF; ~80% maintain sinus rhythm at 1 year after a single procedure. **Pulsed-field ablation** (electroporation) selectively targets myocardium and is non-inferior to thermal ablation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — ECG of AF:** A rhythm strip emphasising **lead V1**. Labels: *Absent P waves*, *Fibrillatory (f) waves / chaotic baseline*, *Irregularly irregular R-R intervals*, *Narrow QRS complexes*. (Optionally show a "blocked PAC" then "PAC initiates AF" as the trigger.)
- **Diagram 2 — Left atrium and pulmonary vein triggers:** Outline of the left atrium with four pulmonary veins. Labels: *Pulmonary vein musculature (ectopic triggers)*, *Posterior LA wall*, *Left atrial appendage (thrombus site)*, *Circumferential PV isolation ablation lesion set*, *Vein of Marshall*.

Clinical / Diagnostic significance

- AF is **not benign** — independent marker of mortality and the cause of ~25% of strokes; aggressive risk-factor modification (BP, obesity, alcohol, OSA, diabetes) is now a core treatment aim.
- **Always screen for thyrotoxicosis** and reversible precipitants in new-onset AF.

- **CHA_2DS_2-VASc** drives anticoagulation decisions; HAS-BLED quantifies but does not by itself withhold therapy.
- **TEE** before cardioversion when AF >48 h excludes LAA thrombus and shortens delay to cardioversion.
- Persistent uncontrolled rates → **tachycardia-induced cardiomyopathy**, which is largely reversible with rate control.
- Ablation complications to counsel: stroke (0.5–1%), tamponade (~1%), phrenic nerve palsy, PV stenosis, and the rare but lethal **atrio-oesophageal fistula** (<0.1%, presents 10 days–3 weeks later with fever/sepsis, stroke).

High-yield exam pointers

- AF = **irregularly irregular rhythm, absent P waves, fibrillatory baseline best seen in V1**.
- Three aims: **rate ± rhythm control, stroke prevention, risk-factor modification**.
- Stroke risk = **CHA_2DS_2-VASc**; bleeding risk = **HAS-BLED**; anticoagulate if score ≥1 (≥2 in men/≥3 women per practice; female-only point does not mandate).
- **DOACs preferred** in nonvalvular AF; **warfarin mandatory** in rheumatic MS / mechanical valves.
- Reversal agents: **idarucizumab** (dabigatran), **andexanet alfa** (Xa inhibitors).
- The **48-hour rule**: AF >48 h or unknown → 3 weeks pre + 4 weeks post anticoagulation, or TEE-guided cardioversion; beware **atrial stunning**.
- **Amiodarone** = most effective AAD but most toxic; **dronedarone contraindicated** in HF.
- **Pulmonary vein isolation** is first-line rhythm control for paroxysmal AF; thrombus forms in the **left atrial appendage**.
- Classify by duration: **paroxysmal ≤7 days, persistent >7 days–<1 year, long-standing persistent >1 year.**

> **SOURCE & COVERAGE**
>
> Harrison's Principles of Internal Medicine, 22e — Ch 258 "Atrial Fibrillation" (Sauer, Romero, Zei). The chapter fully supports this answer; the conventional CHA_2DS_2-VASc threshold wording (anticoagulate men ≥2 / women ≥3) is standard textbook practice consistent with the chapter's "score ≥1 unless lone female point" statement.

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Infectious diseases

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Cat bite management

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — An animal bite is a breach of the skin's protective barrier that inoculates the biting animal's oropharyngeal flora into deeper, susceptible tissues, converting the wound into a contaminated, often deep, polymicrobial injury. Cat bites are clinically deceptive: although the external wound is small, the cat's *narrow, sharp canine teeth* drive bacteria deep, so that **more than half of all cat bites become infected** — a far higher rate than dog bites — with a strong predilection for **septic arthritis and osteomyelitis** when punctures overlie a joint, especially of the hand. The dominant pathogen is *Pasteurella multocida*, which advances within hours. Management therefore rests on four pillars: **structured assessment, aggressive local wound care, appropriate antibiotic therapy, and prophylaxis against rabies and tetanus.**

Microbiology — why a cat bite is dangerous

Cat-bite infections are **polymicrobial**, reflecting the feline oropharynx plus skin/soil organisms; cultures yield a mix of aerobes and anaerobes.

Organism	Note
Pasteurella multocida	Small gram-negative coccobacillus; normal feline oral flora; the single commonest isolate (~75% of cat-bite infections); causes **rapidly advancing** cellulitis with purulent drainage and adenitis, often within hours
Staphylococcus aureus (incl. **MRSA**)	Skin/oral flora; consider empirical MRSA cover in high-risk wounds
β-hemolytic **streptococci**	Common aerobic co-pathogen
Anaerobes — *Bacteroides, Fusobacterium, Prevotella, Porphyromonas*	Especially in deep punctures; many produce β-lactamase
Capnocytophaga canimorsus	Fulminant sepsis, DIC, renal failure in **asplenic, cirrhotic or immunosuppressed** hosts
Bartonella henselae	**Cat-scratch disease** — late consequence (see below)
Francisella tularensis (tularemia); *Sporothrix schenckii* (sporotrichosis)	Reported after cat bites/scratches

Approach to the patient — focused assessment

- **History:** type of animal, *provoked vs unprovoked* attack (unprovoked raises rabies suspicion), **time elapsed** since injury, the animal's vaccination/ownership status and current whereabouts.
- **Host risk factors:** diabetes mellitus, liver disease/cirrhosis, **splenectomy/asplenia**, immunosuppression (glucocorticoids, SLE, leukaemia), mastectomy or lymphoedema of the involved limb, prosthetic joints/valves — all favour antibiotics and predict severe disease.
- **Wound examination:** type (puncture/laceration/scratch), depth, and crucially **joint, tendon, nerve or bone involvement** — hand wounds warrant **hand-surgery consultation**. Document

with a diagram or photograph. Assess for established infection (redness, exudate, foul odour, lymphangitis, lymphadenopathy).

- **Investigations: radiograph** of penetrating/hand wounds for fracture, retained tooth or foreign body and to baseline for osteomyelitis; **Gram stain and aerobic + anaerobic culture** of all infected wounds (use a small-tipped swab in deep punctures); WBC count and **blood cultures** if systemic infection is suspected. Notify the laboratory if fastidious organisms (e.g. *Capnocytophaga*) are suspected, as they need prolonged incubation.

Wound management (local care) — the most important step

- **Copious irrigation** with normal saline and **debridement** of devitalised tissue; remove foreign bodies; drain all abscesses. Thorough cleansing/irrigation is the single most important factor in reducing infection.
- **Wound closure is controversial and generally avoided** in bite wounds. **Cat-bite puncture wounds should be left unsutured** because of their very high infection rate; small uninfected wounds heal by secondary intention, and **delayed primary closure** is used once the risk of infection has passed.
- **Facial wounds** are an exception — usually sutured after meticulous cleaning, because of excellent blood supply, low infection risk and cosmetic importance.
- Wounds **>12 h old** (arm/leg) or **>24 h old** (face) and **all hand wounds** should not be closed primarily.
- **Elevate and immobilise** the part (especially the hand) — a valuable adjunct to antimicrobial therapy.

Antibiotic therapy

Cover must target *S. aureus*, *Pasteurella*, *Capnocytophaga*, streptococci and oral anaerobes. **Avoid monotherapy with dicloxacillin, cephalexin, macrolides or clindamycin** — all lack reliable *Pasteurella* activity; azithromycin and 1st/2nd-generation cephalosporins are inadequate. **TMP-SMX has poor anaerobic activity** and must be paired with an anti-anaerobe.

Scenario	Regimen
Prophylaxis (early uninfected cat bite — *usually advised*, see below)	**Amoxicillin-clavulanate** 875/125 mg PO q12h (or 500 mg PO TID) for **3–5 days**
Penicillin-allergic	**Clindamycin or metronidazole** *plus* (doxycycline 100 mg BD **or** double-strength TMP-SMX BD **or** a fluoroquinolone, e.g. ciprofloxacin 500 mg BD); or **moxifloxacin** 400 mg OD monotherapy
Established infection	**Amoxicillin-clavulanate** PO; or **ampicillin-sulbactam** 1.5–3.0 g IV q6–8h; or **ceftriaxone + metronidazole**; or ertapenem 1 g IV daily
Serious *P. multocida* (pneumonia/sepsis/meningitis)	**IV penicillin G** (alternatives: 2nd/3rd-gen cephalosporin, ciprofloxacin)
***C. canimorsus* bacteraemia**	2-week course of IV **penicillin G** or ampicillin-sulbactam, then step-down oral

- **Duration:** established skin/soft-tissue infection generally **5–7 days** (up to 2–3 weeks per CMDT); **septic arthritis 4 weeks**, **osteomyelitis 6 weeks**.
- **Prophylaxis is recommended for essentially all cat bites**, particularly hand bites, because of their high infection rate; also for severe/crush/deep wounds, possible bone/joint involvement, genital wounds, delayed care (>8 h), and the immunocompromised/comorbid host. A meta-analysis showed prophylaxis halves the infection rate.

Rabies post-exposure prophylaxis (PEP)

Rabies is almost uniformly fatal but **nearly always preventable** by prompt PEP — *more cats than dogs are reported rabid each year* in the USA, so a cat bite mandates a deliberate rabies decision in consultation with public-health authorities.

- **Risk stratification:** a healthy-appearing **dog, cat or ferret** may be **confined and observed for 10 days** — PEP is not needed if the animal stays healthy; if it sickens, euthanise and test the brain by **direct fluorescent antibody (DFA)**. If the animal escaped, is unprovoked, or rabies is endemic, **start PEP without delay**.
- **Local wound care:** wash thoroughly with **soap and water**, debride — must not be delayed.
- **Passive immunisation** (previously unvaccinated only): **Human Rabies Immune Globulin (HRIG) 20 IU/kg** — infiltrate **as much as anatomically possible into and around the wound**, remainder IM at a distant site. If HRIG is unavailable, **equine RIG 40 IU/kg**. RIG must be given **no later than day 7** after the first vaccine dose; never give RIG and vaccine at the same site/syringe.
- **Active immunisation: four 1-mL doses of cell-culture rabies vaccine IM in the deltoid** (anterolateral thigh in children) on **days 0, 3, 7 and 14**; a **5th dose on day 28 only in the immunocompromised**. **Never give in the gluteus** (vaccine failures).
- **Previously vaccinated** patient: **two booster doses on days 0 and 3; no RIG**.

Tetanus & other prophylaxis

A bite is a contaminated, **tetanus-prone wound**.

- **Booster (Td/Tdap):** indicated if primary immunisation is incomplete/unknown or if the **last booster was >5 years ago** (bite wounds), as opposed to the >10-year rule for clean minor wounds.
- **Human Tetanus Immune Globulin (TIG):** given (with the vaccine, at a separate site) to patients who have **not completed primary immunisation** or whose status is unknown.
- **Hepatitis B:** for human-bite exposure to blood-tinged saliva, give hepatitis B vaccine ± HBIG (not generally required after animal bites).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Rabies PEP decision algorithm** — boxes/labels: *"Bite or saliva contaminating wound/mucosa?"* → *"Rabies endemic in species & area?"* → *"Animal captured?"* → if a **normally-behaving dog/cat/ferret** → *"Observe 10 days"* (well → **No prophylaxis**; ill/DFA-positive → **RIG + vaccine**); if escaped/wild/abnormal → **RIG + vaccine**.
- **Cat-bite hand puncture (cross-section)** — labels: *narrow deep puncture, epidermis/dermis, metacarpophalangeal joint, tendon sheath, deep inoculation of* Pasteurella multocida*, small external wound belying deep penetration.*

Clinical / Diagnostic significance

- The **small external wound of a cat bite belies deep inoculation** — a low threshold for imaging, prophylaxis and hand-surgery referral prevents missed septic arthritis/osteomyelitis.
- **Asplenic/cirrhotic patients** are at risk of fulminant *Capnocytophaga canimorsus* sepsis with purpura fulminans and DIC — counsel and treat aggressively.
- **Cat-scratch disease** (*B. henselae*) is a late consequence: subacute, **painful regional lymphadenopathy** (axillary/epitrochlear) with a primary inoculation papule; usually self-limited. Aspirate (do **not** incise) suppurative nodes; treat extensive lymphadenopathy with **azithromycin 500 mg day 1 then 250 mg OD ×4 days**. Atypical forms include *Parinaud's oculoglandular syndrome* and *neuroretinitis* (macular star).
- Failure to respond to antibiotics should prompt re-evaluation for **retained foreign body, abscess, or deep-space infection** needing surgical drainage.

High-yield exam pointers

- **>50% of cat bites become infected**; deep, narrow puncture → joint/bone risk.
- ***Pasteurella multocida*** = commonest pathogen; infection within **hours**; treat with **amoxicillin-clavulanate**.
- **Never use clindamycin, macrolides, cephalexin or dicloxacillin alone** (no *Pasteurella* cover).
- **Do NOT primarily suture cat-bite punctures** — irrigate, debride, leave open / delayed closure.
- **Rabies PEP:** wound wash + **HRIG 20 IU/kg infiltrated into wound** + vaccine IM deltoid on **days 0, 3, 7, 14** (4 doses); previously vaccinated → days 0 & 3 only, no RIG.
- **Healthy dog/cat/ferret** → observe **10 days** before committing to vaccine.
- **Tetanus:** bite = tetanus-prone → booster if last dose **>5 yr**; **TIG** if primary course incomplete.
- Cover **MRSA** empirically in high-risk wounds; **asplenia → Capnocytophaga** sepsis risk.
- **Cat-scratch disease** = *B. henselae*, tender regional nodes, **azithromycin**, aspirate not incise.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Infectious Complications of Bites" (microbiology, approach, wound management, antibiotic Table 146-1, prophylaxis); "Rabies and Other Rhabdovirus Infections" (post-exposure prophylaxis — HRIG 20 IU/kg, 4-dose vaccine schedule, 10-day observation); "Tetanus" (wound management, HTIG, prevention); "Bartonella Infections, Including Cat-Scratch Disease" (cat-scratch disease, azithromycin).
- **CMDT 2026** — "Common Problems in Infectious Diseases & Antimicrobial Therapy: Animal & Human Bites" (current prophylaxis/treatment regimens, durations, indications).

Coverage note: The standard tetanus wound-prophylaxis decision (Td/Tdap if last booster >5 years for tetanus-prone wounds; TIG ~250 IU IM if primary immunisation incomplete) is universally accepted internal medicine; Harrison Ch 146/157 explicitly supports the >5-year booster rule for bites and TIG for incomplete primary immunisation, while the exact prophylactic TIG dose is conventional. All organism names, drug regimens and doses above are taken verbatim from the cited chapters.

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Scrub typhus

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — **Scrub typhus** is an acute, mite-borne, febrile zoonosis caused by *Orientia tsutsugamushi*, an obligately intracellular gram-negative bacterium of the family **Rickettsiaceae**. It is transmitted to humans by the bite of larval **trombiculid mites (chiggers)** and is characterised pathologically by **endothelial-cell infection with increased vascular permeability (vasculitis)**. The classic clinical triad is an **eschar** at the chigger-bite site, **regional/generalised lymphadenopathy**, and a transient **maculopapular rash**, on a background of high fever. It is endemic across the **"tsutsugamushi triangle"** of Asia-Pacific (including India), is a leading cause of **acute undifferentiated febrile illness and fever of unknown origin**, and is highly responsive to **doxycycline**.

Etiology, vector and epidemiology

- **Organism:** *Orientia tsutsugamushi* (genus *Orientia*, family Rickettsiaceae). It differs substantially from *Rickettsia* species both **genetically** and in **cell-wall composition** — notably it **lacks lipopolysaccharide (LPS)** and has no peptidoglycan, hence its separation into a distinct genus. Related species *O. chuto* (south-western Asia) and *Candidatus O. chiloensis* (Chile) are emerging.
- **Vector & reservoir:** larval **trombiculid mites = chiggers** (*Leptotrombidium deliense* and others). The chigger is the **only stage that feeds on a host**; the mite is both vector and reservoir, the organism being maintained by **transovarial transmission**. Infected chiggers cluster in areas of **heavy scrub vegetation during the wet season**.
- **Antigenic diversity:** *O. tsutsugamushi* shows **remarkable antigenic diversity** (classically the *Karp*, *Gilliam* and *Kato* serotypes). Immunity to the **homologous strain wanes over 1–3 years**, and cross-protective immunity against heterologous strains may be lost in as little as **1 month** —

hence reinfection is common (in some areas >3% of the population is infected/reinfected each month).

- **Geography:** endemic and **re-emerging** in eastern and southern Asia, northern Australia and islands of the western Pacific and Indian Oceans — the "**tsutsugamushi triangle**". A major cause of acute febrile illness in **India and China**; more common in rural areas but increasingly urban, and now recognised in travellers.
- **Other transmission:** vertical (transplacental), **transfusion**, and **occupational/laboratory** exposures are documented.

Feature	Scrub typhus
Organism	*Orientia tsutsugamushi* (lacks LPS)
Vector	Larval trombiculid mite (chigger), e.g. *Leptotrombidium deliense*
Incubation period	**6–21 days** (≈1–3 weeks)
Pathognomonic sign	**Eschar** (tache noire) ± regional lymphadenopathy
Rash	Macular/maculopapular, trunk, day 4–8, fleeting
Drug of choice	**Doxycycline** (alt: azithromycin, chloramphenicol)
Untreated mortality	~6% (classic) up to 10–30% in severe series

Pathogenesis

- Chigger bite **inoculates organisms into the dermis**; *O. tsutsugamushi* spreads **lymphohaematogenously** and infects **vascular endothelial cells** (and macrophages).
- The central lesion is a **disseminated vasculitis / vasculitic perivasculitis** with **increased vascular permeability**, producing oedema, hypovolaemia, microvascular leak and multi-organ ischaemia — the same final common pathway shared by all rickettsioses.
- At the bite site, local vasculitis and necrosis produce the **eschar** (a black, crusted, painless ulcer with an erythematous halo); the draining nodes enlarge first (**regional lymphadenopathy**), reflecting initial lymphogenous spread.
- Severe disease reflects widespread endothelial injury → **interstitial pneumonitis/ARDS, myocarditis, meningoencephalitis, hepatitis, AKI** and, late, **haemophagocytosis**.

Clinical features

- **Onset:** after a 6–21-day (1–3 week) incubation, abrupt **high fever, severe headache, myalgia, malaise, chills, backache, cough** and **gastrointestinal symptoms** (nausea, vomiting, diarrhoea in nearly two-thirds — corresponding to mucosal erosions/haemorrhage).
- **Eschar (most useful sign):** a papule at the bite site that ulcerates into a **black, painless, crusted eschar (tache noire)**, typically in moist/covered intertriginous skin. It is **highly suggestive but not always present** — recognised in only **~19%** in a South Korean series, and in **<50% of returning travellers**; absence does not exclude the diagnosis.
- **Lymphadenopathy:** tender **regional** node enlargement near the eschar, sometimes becoming **generalised** — a helpful clue.

- **Rash: macular → maculopapular**, mainly on the **trunk**, appearing around **day 4–8**; it may be fleeting or absent (rash in **<40%**), peaking ~day 8 and occasionally lasting up to 21 days.
- **Relative bradycardia** (pulse–temperature dissociation) is characteristic.
- **Complications: pneumonitis/ARDS**, **myocarditis**, **meningoencephalitis or aseptic meningitis**, **acute kidney injury**, hepatitis and **haemophagocytic lymphohistiocytosis (HLH)**; ARDS or haemophagocytosis tends to develop in the **second–third week**. Infection confers **prolonged immunity against homologous strains** but only transient immunity against heterologous strains.

Investigations / Diagnosis

- **Supportive laboratory findings** (shared rickettsial signature): **thrombocytopenia**, **normal or low WBC count**, **elevated hepatic aminotransferases**, hyperbilirubinaemia, raised creatinine, **hyponatraemia**, raised CRP, and **hypoalbuminaemia**.
- **Serology (reference standard): indirect immunofluorescence assay (IFA)** and **indirect immunoperoxidase assay** are the **gold standard** but are expensive and of limited availability; a fourfold rise in paired acute/convalescent titres is confirmatory. **ELISA** detecting *Orientia*-specific antibodies and **rapid lateral-flow chromatographic tests** are widely used point-of-care options.
- **PCR (most sensitive):** amplification of *Orientia* genes is **most sensitive from the eschar** (eschar crust/swab), and can also be done on blood/buffy coat; best performed **before doxycycline** is started.
- **Culture:** possible from early blood but requires a **BSL-3 laboratory**; rarely used. **Combined ELISA + PCR** is recommended where available.
- ***Weil-Felix test*** (Proteus **OX-K** agglutination) is the classic cheap field test for scrub typhus but is **insensitive and non-specific**, and is now largely superseded by IFA/ELISA/PCR.

Differential diagnosis

- The major mimics of acute undifferentiated tropical fever: **dengue, malaria, leptospirosis, enteric (typhoid) fever, Q fever, viral haemorrhagic fevers, other rickettsioses, and meningitis**. Co-infection (e.g. with malaria) can occur.
- Discriminators favouring scrub typhus: **an eschar, lymphadenopathy, relative bradycardia, lymphocytosis and elevated CRP** (the last three help distinguish it from dengue). In endemic regions it is a recognised cause of **obscure fever / FUO, especially in children**.

Treatment

- **Drug of choice: doxycycline 100 mg orally twice daily** — produces rapid defervescence (often within 48 h, a near-diagnostic therapeutic response). **Minocycline 100 mg BID** is an equivalent tetracycline.
- **Duration:** continue for at least **3 days after the patient is afebrile** (regimens of **7–15 days**); **short courses risk relapse**.
- **Severe disease:** the **INTREST trial** (Varghese et al., *NEJM* 2023) found **no difference** between IV doxycycline and IV azithromycin monotherapy, but **combination doxycycline + azithromycin**

lowered 28-day mortality, day-7 complications and day-5 persistent fever — combination is preferred in severe/complicated cases.

- **Alternatives / special groups: azithromycin 500 mg/day for 3 days** (similar efficacy, fewer adverse effects) and **chloramphenicol 500 mg QID** — both are the agents of choice in **pregnancy** and in **doxycycline allergy/intolerance**. Some Thai strains are relatively doxycycline/chloramphenicol-resistant and respond to **azithromycin + rifampicin**.
- **Supportive care:** ICU support for ARDS (ventilation), myocarditis, AKI (renal replacement) and shock as needed.

Setting	Regimen
Uncomplicated (DOC)	**Doxycycline 100 mg PO BID** (or minocycline 100 mg BID); ≥3 days after afebrile (7–15 days)
Severe / complicated	**IV doxycycline + IV azithromycin** combination (INTREST trial)
Pregnancy / doxy allergy	**Azithromycin 500 mg/day ×3** or chloramphenicol 500 mg QID
Doxy/chloramphenicol-poor response (Thailand)	**Azithromycin + rifampicin**

Prevention: there is **no effective vaccine** (antigenic diversity limits vaccine development). Personal protection — **insect repellents on skin and clothing, protective clothing, avoidance of scrub vegetation** — is key; routine **antibiotic chemoprophylaxis is NOT recommended** for asymptomatic travellers (CDC).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — The eschar with regional lymphadenopathy:** draw a limb/trunk with a central **black crusted eschar** surrounded by an **erythematous halo**, an arrow to the draining **enlarged regional lymph node**, and a faint **macular rash over the trunk**. Labels: *Eschar (tache noire)*, *Erythematous halo*, *Regional lymphadenopathy*, *Truncal maculopapular rash*, *Chigger bite site*.
- **Diagram 2 — Transmission cycle:** *Trombiculid mite (Leptotrombidium)* → **larval chigger bites human** → *Orientia tsutsugamushi* inoculated into skin → **endothelial infection** → **vasculitis** → systemic disease; with a side loop showing **transovarial transmission** keeping the mite as both vector and reservoir. Labels: *Chigger (larva)*, *Orientia tsutsugamushi*, *Transovarial transmission*, *Human (incidental host)*, *Endothelial vasculitis*.

Clinical / Diagnostic significance

- A leading, **treatable** cause of **acute undifferentiated febrile illness, FUO and sepsis** in the Asia-Pacific — empirical **doxycycline** should be started promptly on clinical/epidemiological suspicion without waiting for serology.
- **Always search for the eschar** in skin folds (axilla, groin, neck, genitalia, under breasts) — it is the single most useful diagnostic clue and is easily missed.

- **Eschar + thrombocytopenia + transaminitis + relative bradycardia** in a patient from an endemic area is a near-classic combination.
- **Untreated mortality** is significant (~6% classic; **10–30%** in severe hospitalised series). **Poor prognostic markers:** hypotension/vasopressor need, ICU admission, **age >60 years, absence of an eschar** (delays diagnosis), pregnancy, **leukocytosis and hypoalbuminaemia**.
- A **rapid response to doxycycline (defervescence in ~48 h)** is itself a useful diagnostic/therapeutic confirmation.

High-yield exam pointers

- Causative organism: ***Orientia tsutsugamushi*** — a Rickettsiaceae that **lacks LPS**, separating it from genus *Rickettsia*.
- Vector = **larval trombiculid mite (chigger)**, *Leptotrombidium deliense*; reservoir maintained by **transovarial transmission**.
- Endemic area = **"tsutsugamushi triangle"**; incubation **6–21 days**.
- **Classic triad: eschar (tache noire) + regional lymphadenopathy + truncal maculopapular rash**, with **relative bradycardia**.
- Eschar present in only ~19–50% of cases — **its absence does not exclude the disease**.
- **PCR of the eschar = most sensitive**; **IFA / indirect immunoperoxidase = gold-standard serology**; **Weil-Felix OX-K** is the classic but insensitive test.
- Labs: **thrombocytopenia, transaminitis, hyponatraemia, normal/low WBC**.
- **Doxycycline 100 mg BID is the drug of choice**; **doxycycline + azithromycin combination** for severe disease (INTREST trial); **azithromycin/chloramphenicol** in pregnancy.
- Serious complications: **ARDS/pneumonitis, myocarditis, meningoencephalitis, AKI, HLH**.
- **No vaccine**; prevention is by mite-bite avoidance.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Rickettsial Diseases" (general rickettsial pathophysiology; *Scrub Typhus* section — *Orientia tsutsugamushi*, chigger/trombiculid biology, epidemiology, clinical features, eschar, diagnosis and treatment regimens including doxycycline + azithromycin combination).
- **CMDT 2026** — "Viral & Rickettsial Infections" (Scrub Typhus: essentials of diagnosis, tsutsugamushi triangle, relative bradycardia, eschar frequency [~19%], laboratory findings, IFA/ELISA/PCR, differential diagnosis, prognosis/poor-prognostic factors, treatment including the **INTREST trial**, doxycycline/minocycline/azithromycin/chloramphenicol).
- **Coverage note:** The corpus emphasises **IFA/indirect immunoperoxidase and PCR**; it does **not** explicitly detail the **Weil-Felix (Proteus OX-K)** test or name the **Karp/Gilliam/Kato** serotypes — these are included here as universally accepted standard internal-medicine teaching and flagged accordingly. Numeric epidemiological values in Harrison's Table 192-1 were partly garbled in the text extract; figures quoted here are taken from the verified narrative text (incubation 6–21 days, untreated case-fatality ~6%).

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Pulmonary nocardiosis

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Nocardiae* are aerobic, Gram-positive, weakly (partially) acid-fast, catalase-positive filamentous bacteria that are ubiquitous saprophytes of soil and water, acquired chiefly by **inhalation**. Pulmonary nocardiosis is a subacute, **non-resolving necrotising pneumonia** that classically arises in hosts with impaired cell-mediated/phagocyte defence and has a strong tendency to **cavitate, cross tissue planes (pleura/chest wall) and disseminate haematogenously to the brain and skin**. A BAL culture growing *Nocardia* in this 45-year-old diabetic with a pneumonia failing to clear is therefore not a contaminant but a call to define disease extent (especially occult brain abscess) and start prolonged, susceptibility-guided combination therapy led by trimethoprim-sulfamethoxazole.

Why suspect Nocardia in this patient (microbiology and host risk)

- **Organism:** Gram-positive, beaded, **branching filaments ~1 µm wide, up to 50 µm long** that fragment into cocco-bacillary forms; **weakly/partially acid-fast** on modified Kinyoun, Ziehl-Neelsen or Fite-Faraco stains (weak-acid decolouriser) — hence frequent confusion with *Mycobacterium tuberculosis*. Cell wall contains mycolic acids; grows as chalky, wrinkled, white-yellow/orange colonies.
- **Common pathogenic species:** *N. farcinica, N. cyriacigeorgica, N. nova* complex, *N. abscessus, N. brasiliensis* (mostly cutaneous), *N. otitidiscaviarum, N. transvalensis*. *N. farcinica* has a special predilection for CNS spread and is often ceftriaxone-resistant.
- **Host defects predisposing to invasive disease:** defects of **cell-mediated immunity and phagocytes** — solid-organ or haematopoietic stem-cell transplantation, **systemic corticosteroids/Cushing syndrome**, immunosuppressive therapy, HIV, chronic granulomatous disease (CGD), IL-12/IL-12R deficiency, pulmonary alveolar proteinosis with **anti-GM-CSF autoantibodies**.
- **Structural lung disease / bronchiectasis** predisposes to airway *colonisation*; a positive respiratory culture must be read in clinical context, but in an immunosuppressed host it usually reflects true disease and warrants empirical therapy.
- *Diabetes mellitus* (this patient) is a widely recognised predisposing condition through impaired neutrophil/phagocyte function — see Coverage note.

Pleuropulmonary clinical picture (the "non-resolving pneumonia")

- **Subacute onset** over days to weeks; in the severely immunocompromised it may be acute. **Cough productive of small amounts of thick, purulent, non-malodorous sputum** is prominent.
- Fever, anorexia and malaise are common; **weight loss, dyspnoea, pleuritic pain and haemoptysis are less common**.
- Without definitive therapy there are characteristic **remissions and exacerbations over weeks to months** — the classic "non-resolving / relapsing" pneumonia that fails standard antibiotics and mimics TB, fungal infection or malignancy.
- **Dissemination occurs in up to one-third** of pulmonary cases — CNS (brain abscess) and skin/subcutaneous tissue are the commonest metastatic sites.

CT thorax — what you would find

Finding	Detail
Nodules and masses	Solid pulmonary nodules and mass lesions in **one or more lobes** (often multifocal/multilobar)
Cavitation	Nodules and masses **frequently cavitate** — thick-walled cavities are characteristic
Consolidation / infiltrates	Dense lobar or patchy air-space consolidation
Pleural disease	**Pleural effusion or empyema in ~one-third** of cases (empyema may occur even without parenchymal disease)
Chest-wall extension	Direct invasion **through the ribs and chest wall** with **chest-wall abscess** (non-respect of tissue planes)
Pattern	Multifocal, indolent, progressive; radiologically mimics **TB, fungal pneumonia, metastases or bronchogenic carcinoma**

- Representative CT (Harrison Fig. 179-3): solid nodules, a cavitated nodule, an ipsilateral pleural effusion and a chest-wall abscess.
- *Practical pearl:* the combination of **cavitating nodules/masses + effusion/empyema + chest-wall involvement** in an immunocompromised or diabetic host with a non-resolving pneumonia should raise nocardiosis specifically.

Establishing the diagnosis and staging extent

- **Microbiology is the cornerstone.** Sputum smears are *often negative*, so **BAL fluid or lung biopsy** (as done here) is the higher-yield specimen.
- **Stains:** Gram stain (beaded branching filaments) plus a **modified acid-fast stain** (weak-acid decolourisation); organisms may take up silver stains.
- **Culture:** grows on most fungal/mycobacterial and routine media but **slowly — colonies in up to 2 weeks, typical morphology by 4 weeks**; alert the laboratory to incubate longer and to **avoid mycobacterial decontamination procedures** (they kill *Nocardia*). Selective media (colistin-nalidixic acid, modified Thayer-Martin, BCYE) improve recovery from mixed flora.
- **Speciation and susceptibility:** identify at least to complex level by **MALDI-TOF MS or gene sequencing (16S rRNA, secA1, hsp65, gyrB)**; perform **susceptibility testing by CLSI-approved broth microdilution** (E-tests less reliable) — species-directed therapy matters because susceptibilities differ markedly.
- **Mandatory search for disseminated disease — image the brain.** Every patient with pulmonary/systemic nocardiosis, **regardless of CNS symptoms**, must have **contrast-enhanced brain imaging** to exclude occult abscess (one-third of CNS cases are asymptomatic). **MRI with gadolinium is preferred** (more sensitive); CT is reserved for when MRI is not possible. Nocardial brain abscesses are typically **multiple, multilobulated, ring-enhancing**.
- **Identify the immune defect:** test for **HIV**; in the absence of an obvious risk factor consider **CGD** and anti-GM-CSF autoantibodies; optimise/document the diabetic and any iatrogenic immunosuppression.

Management

Principles: susceptibility-guided, **prolonged** (months), **combination therapy for severe/disseminated/CNS disease** then de-escalation to a single oral agent, plus **source control** (drainage of empyema/abscess) and **correction of host factors** (glycaemic control, reduce immunosuppression where feasible).

Agent	Dose	Role / caveats
Trimethoprim-sulfamethoxazole (TMP-SMX)	**TMP 10–20 mg/kg + SMX 50–100 mg/kg per day** in 2 divided doses initially; maintenance down to **TMP 5 / SMX 25 mg/kg**	**Drug of choice**; sulfa allergy → **desensitisation**
Linezolid	600 mg PO/IV q12h	**Uniformly active against all species**; cytopenias/neuropathy limit therapy after 2–3 weeks (tedizolid less toxic)
Amikacin	5–7.5 mg/kg q12h or 15 mg/kg q24h	Active vs nearly all species (except *N. transvalensis*, some *N. pseudobrasiliensis*); monitor levels/renal function
Imipenem / Meropenem	Imipenem 500 mg IV q6h; meropenem 2 g IV q8h	β-lactam for combination; **meropenem preferred if CNS involved** (lower seizure risk)
Ceftriaxone	—	Useful but **not active against *N. farcinica***
Amoxicillin-clavulanate	875/125 mg bid	Effective in *N. brasiliensis*, some *N. farcinica*
Moxifloxacin / Minocycline	Minocycline 100–200 mg bid	Oral options; moxifloxacin most active quinolone

- **Severe disease (as here, non-resolving pneumonia ± dissemination):** empirical **combination of two or three** of TMP-SMX, linezolid, amikacin and a carbapenem (imipenem, or **meropenem if CNS**). Clinical improvement usually appears in **1–2 weeks** (may be slower).
- **De-escalation:** after definite improvement, continue with a **single oral drug, usually TMP-SMX**.
- **Duration:** pulmonary/systemic with **intact host defences 6–12 months**; with **deficient host defences 12 months** (indefinite in AIDS with CD4 <200/μL or CGD); **CNS disease 12 months** (6 months if all CNS disease excised); primary cutaneous 2 months.
- **Surgery:** drain empyema and chest-wall/soft-tissue abscesses; **brain abscesses** aspirated/drained/excised if diagnosis unclear, large, or failing medical therapy; repeat imaging to confirm resolution (radiographic lag is expected).
- **Diabetes-specific:** tight glycaemic control and treating any concomitant immunosuppression are integral to cure; **do not give topical corticosteroids** if nocardial keratitis coexists.
- **Prognosis:** mortality <10% for localised pulmonary disease; higher with dissemination, worst with CNS involvement and delayed therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CT thorax (axial) schematic of pulmonary nocardiosis** — labels: *thick-walled cavitating nodule*, *multiple solid nodules*, *lobar consolidation*, *pleural effusion/empyema*, *chest-wall abscess invading through rib*, *(absence of significant hilar lymphadenopathy)*.
- **Modified acid-fast (Kinyoun/ZN) smear of BAL** — labels: *beaded, branching, partially acid-fast filaments ~1 μm wide*, *fragmentation into cocco-bacillary forms*, *neutrophilic background*.

Clinical / Diagnostic significance

- Treat *Nocardia* in BAL of an immunosuppressed/diabetic patient with a non-resolving pneumonia as **true infection**, not colonisation, and act on it.
- The single highest-yield staging step is **brain imaging (MRI preferred)** to catch silent abscesses that change duration and the choice of carbapenem.
- **Alert the microbiology lab** (slow grower; avoid mycobacterial decontamination) and obtain **species ID + susceptibilities** — they directly dictate the regimen (e.g., ceftriaxone fails *N. farcinica*).
- Differentiate from **TB** (both acid-fast, both cavitate) by branching filament morphology and culture/molecular ID — clinically important because mismanagement as TB delays cure.

High-yield exam pointers

- *Nocardia* = aerobic, **weakly acid-fast, branching beaded Gram-positive filaments**; acquired by **inhalation**; opportunist of impaired cell-mediated immunity.
- CT hallmark: **multifocal cavitating nodules/masses + pleural effusion/empyema (~⅓) + chest-wall invasion**.
- **Sputum often negative → BAL/biopsy**; cultures slow (up to 2–4 weeks) — *tell the lab*.
- **TMP-SMX is the drug of choice**; severe disease → **2–3 drug combination** (add linezolid/amikacin/carbapenem).
- **Meropenem over imipenem if CNS**; **ceftriaxone not active against *N. farcinica***.
- **Always image the brain** even if asymptomatic; nocardial brain abscess = **multiple, multilobulated, ring-enhancing**.
- Prolonged therapy: **6–12 months (intact)**, **12 months (immunosuppressed/CNS)**.
- Linezolid is uniformly active but toxicity limits use after **2–3 weeks**; monitor counts.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Nocardiosis"** (microbiology, risk factors, pulmonary/CT features incl. Figs 179-2/179-3, diagnosis, drug doses, treatment-duration Table 179-1).
- **CMDT 2026 — "Nocardiosis" (Bacterial & Chlamydial Infections)** and **"Pulmonary Disorders"** (essentials of diagnosis, chest-wall invasion, TMP-SMX dosing 15 mg/kg/day, imipenem/meropenem/amikacin/linezolid/minocycline doses, brain-imaging rule, 6–12-month duration).

Coverage note: The corpus describes CT findings qualitatively (nodules, masses, cavitation, effusion/empyema, chest-wall invasion) but does not enumerate finer CT signs (e.g., halo sign, ground-glass, tree-in-bud), so these are deliberately omitted. Harrison's explicit major risk-factor list emphasises T-cell/phagocyte immunosuppression (transplant, corticosteroids, HIV, CGD) rather than diabetes specifically; **diabetes mellitus as a predisposing condition** is included here as universally accepted internal medicine and is supported indirectly by the chapter's "impaired host-defence" framing.

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Visceral leishmaniasis (kala-azar)

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — A middle-aged man from a leishmaniasis-endemic part of India presenting with chronic intermittent fever, constitutional symptoms and *massive splenomegaly* most often has **visceral leishmaniasis (VL, kala-azar)**, a systemic protozoal infection of the reticuloendothelial system caused by the **Leishmania donovani complex** and transmitted by phlebotomine sandflies. "Massive splenomegaly" (spleen palpable >8 cm below the left costal margin or weighing ≥1000 g) sharply narrows the differential, and a positive **rK39 rapid diagnostic test** in this setting effectively confirms VL. The answer below addresses (a) the differential diagnosis and confirmatory work-up, and (b) treatment once rK39 is positive.

(a) Differential diagnosis — fever + weight loss + massive splenomegaly

The combination of a chronic febrile illness with constitutional decline and a *huge* spleen narrows a long list considerably. Causes are grouped below.

Category	Conditions to consider	Discriminating features
Chronic infections (tropical)	**Visceral leishmaniasis (kala-azar)** — top of the list in an endemic Indian patient; chronic/relapsing **malaria & hyper-reactive malarial (tropical) splenomegaly syndrome**; **disseminated/miliary tuberculosis**; **enteric (typhoid) fever**; **brucellosis**; **schistosomiasis**; disseminated **histoplasmosis**; subacute **infective endocarditis**	VL: progressive *massive* spleen, pancytopenia, hypergammaglobulinaemia, skin hyperpigmentation

Category	Conditions to consider	Discriminating features
Haematological / neoplastic (classic massive-spleen causes, Table 70-3)	**Chronic myeloid leukaemia (CML)**; **myelofibrosis with myeloid metaplasia**; **non-Hodgkin lymphoma / chronic lymphocytic leukaemia / hairy cell leukaemia**; **polycythaemia vera**; **Gaucher disease**; autoimmune haemolytic anaemia	Leucocytosis/immature myeloid cells (CML), leucoerythroblastic film + teardrop cells (myelofibrosis), lymphadenopathy/lymphocytosis (lymphoma/CLL)
Congestive / other	**Portal hypertension** from chronic liver disease (congestive splenomegaly); sarcoidosis; **thalassaemia major**	Stigmata of chronic liver disease, varices; transfusion-dependent anaemia

- **Why VL is the leading diagnosis here:** an endemic Indian origin, *6-month* indolent course, intermittent fever with the characteristic double-rise pattern, progressive *massive* splenomegaly (the single most important sign of VL), and constitutional wasting. Per Harrison, VL is **easily mistaken for malaria**, and the other key mimics it explicitly lists are **typhoid, tuberculosis, brucellosis, schistosomiasis and histoplasmosis**; splenomegaly from **portal hypertension, CML, tropical splenomegaly syndrome and schistosomiasis** can also be confused with VL.
- **Pointers that strongly suggest VL:** *fever with neutropenia or pancytopenia* in a patient from an endemic region; **hypergammaglobulinaemia** (polyclonal) in long-standing illness; moderate hepatomegaly following the splenomegaly; lymphadenopathy is *uncommon on the Indian subcontinent* (helps distinguish from African VL and from lymphoma).

(a) Investigations to confirm the diagnosis

1. Demonstration of the parasite (gold standard). Amastigotes (**Leishman–Donovan bodies**, 2–4 μm, each with a nucleus and a kinetoplast) within macrophages on Giemsa-stained tissue aspirate smears:

- **Splenic aspirate** — highest sensitivity **>95%**, but invasive and potentially dangerous (haemorrhage) in untrained hands; avoid with deranged coagulation/thrombocytopenia.
- **Bone marrow aspirate** — sensitivity **60–85%**; safer and most commonly used in practice.
- **Lymph node aspirate** — sensitivity ~**50%**.
- **Culture** of the aspirate (e.g. NNN medium) raises yield; **PCR / real-time PCR** and **LAMP** are highly sensitive, allow species identification, and outperform microscopy on blood, but are confined to reference laboratories.

2. Serology / antigen-based tests.

- **rK39 immunochromatographic rapid diagnostic test** — detects antibody to a 39-amino-acid recombinant antigen from the kinesin region of *L. infantum*; needs only a drop of finger-prick blood, read in **15 min**; in immunocompetent patients sensitivity ~**98%** and specificity ~**90%** (both lower in East Africa). It is the field test of choice.
- **ELISA** and **indirect immunofluorescent antibody test (IFAT)** in equipped laboratories.
- **Caveat:** antibody tests (including rK39) **stay positive for years after cure**, so they *cannot* be used to confirm cure or detect relapse.

3. Supportive laboratory findings. Pancytopenia (early leukopenia and anaemia, later thrombocytopenia from marrow infiltration/hypersplenism); marked **polyclonal hypergammaglobulinaemia** (basis of the classic bedside **aldehyde/formol-gel test**, non-specific); raised

aminotransferases ± bilirubin; hypoalbuminaemia in advanced disease. Always exclude **HIV co-infection**, which alters diagnosis (serology may be negative in up to 50%) and treatment.

(b) Treatment when the rK39 test is positive — VL in India

A positive rK39 in this clinical context confirms VL; institute supportive care plus a specific antileishmanial regimen tailored to **India**, where there is **widespread resistance to pentavalent antimonials** (cure <50% in Bihar) so antimonials are *not* first-line.

Drug / regimen	Dose & schedule	Notes
Liposomal amphotericin B (LAmB) — *drug of choice in India*	**Single dose 10 mg/kg IV** (96% cure; used in the national elimination programme). FDA-approved regimen: **3 mg/kg on days 1 –5, 14 and 21** (total 21 mg/kg). Asian total-dose requirement only 10–15 mg/kg	Best safety profile; reticuloendothelial uptake; mild infusion reactions, backache, reversible nephrotoxicity
Amphotericin B deoxycholate	**0.75–1.0 mg/kg on alternate days × 15 infusions**	Effective but toxic — infusion fever/chills, nephrotoxicity, hypokalaemia; premedicate with chlorpheniramine + paracetamol
Miltefosine (first **oral** drug)	**28 days**: 50 mg/day if <25 kg; **50 mg twice daily if ≥25 kg**; 2.5 mg/kg/day for children 2–11 yr	~94% cure (declining); GI upset; **teratogenic — contraindicated in pregnancy**, contraception ≥5 months; give as directed observed therapy
Paromomycin (aminosidine)	**11 mg/kg base IM daily × 21 days**	Cure ~94.6%; ototoxicity, reversible hepatotoxicity
Pentavalent antimonials (SbV) — *not first-line in India*	20 mg/kg/day IV/IM × 28–30 days	Cure >90% in Africa/Americas but **<50% in Bihar**; monitor ECG — **QTc >0.5 s** risks fatal arrhythmia; pancreatitis, arthralgia

- **Preferred for this patient:** a **single 10 mg/kg dose of liposomal amphotericin B**, the regimen adopted by the Indian subcontinent VL elimination programme — short, well-tolerated and highly effective.
- **Multidrug (combination) therapy** is increasingly favoured for shorter courses, lower toxicity and reduced resistance: in India, **single-dose LAmB 5 mg/kg followed by miltefosine for 7 days, or paromomycin for 10 days, or miltefosine + paromomycin together for 10 days** each give cure rates **>97%**.
- **Supportive care:** correct severe anaemia with transfusion; treat intercurrent infections (pneumonia, TB, dysentery); nutritional support.
- **If HIV co-infected:** LAmB is the drug of choice; WHO now recommends **LAmB total 30 mg/kg (5 mg/kg on days 1,3,5,7,9,11) plus oral miltefosine 100 mg/day for 14 days** in the Indian subcontinent, alongside antiretroviral therapy (restoring CD4 >200/μL reduces relapse). Relapse within a year is common; prolonged follow-up is essential.
- **Response & follow-up:** defervescence, regression of splenomegaly, weight gain and haematological recovery occur within ~1 week; **continued improvement over 12 months indicates cure**. rK39 cannot be used to judge cure. Watch for **post–kala-azar dermal**

leishmaniasis (PKDL) in 5–15% of Indian patients 6 months–3 years later (hypopigmented macules/nodules) — treated with miltefosine for 12 weeks; PKDL patients are a human reservoir, important for elimination.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sandfly–human life cycle of Leishmania donovani:** label *Phlebotomus argentipes* sandfly, **promastigote** (flagellate, 10–20 µm, in sandfly midgut), bite/inoculation into skin, uptake by **neutrophils → macrophages**, transformation to **amastigote** (2–4 µm, intracellular), multiplication and rupture of macrophages, reticuloendothelial spread to **spleen, liver, bone marrow, lymph nodes**, and re-uptake by feeding sandfly.
- **Giemsa-stained splenic/marrow smear:** macrophage containing multiple **amastigotes (Leishman–Donovan bodies)**, each labelled with **nucleus** and rod-shaped **kinetoplast**; a few extracellular parasites.

Clinical / Diagnostic significance

- *Massive splenomegaly* + fever + pancytopenia + hypergammaglobulinaemia in an endemic Indian patient is the classic VL pentad; bone marrow aspirate is the practical confirmatory test, rK39 the field test.
- Untreated VL is fatal in the majority (and historically ~90% mortality); early diagnosis and treatment cut mortality to 2–5%.
- Antimonial **resistance in Bihar** is the single most important reason LAmB/miltefosine displaced antimonials as first-line in India — a frequent exam discriminator.
- Always screen for **HIV**: it changes prognosis (atypical sites, seronegative serology, high relapse) and the specific regimen.
- VL is targeted for **elimination as a public-health problem** in India (reported 98.7% decline); single-dose LAmB and active PKDL detection underpin the programme.

High-yield exam pointers

- **Massive splenomegaly** = spleen >8 cm below LCM or ≥1000 g; classic causes — **CML, myelofibrosis, kala-azar, chronic malaria (tropical splenomegaly), lymphoma/CLL, hairy cell leukaemia, Gaucher disease, thalassaemia major**.
- Kala-azar = *L. donovani* complex; vector in India **Phlebotomus argentipes**; transmission **anthroponotic** (humans reservoir); incubation ~2–6 months.
- **Splenic aspirate sensitivity >95%** > bone marrow 60–85% > lymph node ~50%.
- **rK39**: 39-aa kinesin antigen, ~98% sensitive/~90% specific; stays positive after cure — *not* for test-of-cure.
- **First-line in India = liposomal amphotericin B**, single dose 10 mg/kg; antimonials fail (<50% cure) due to Bihar resistance.
- **Miltefosine** = first oral drug, 28 days, **teratogenic** (avoid in pregnancy).
- **PKDL** follows treated Indian VL in 5–15% (6 months–3 years); reservoir for transmission.

- Cure judged **clinically over 12 months** (defervescence, shrinking spleen, count recovery), not by serology.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Leishmaniasis" (visceral leishmaniasis: epidemiology, immunopathogenesis, clinical features, rK39 and parasitological diagnosis, differential diagnosis, and full treatment/regimen detail including LAmB, miltefosine, paromomycin, antimonials, combination therapy, HIV co-infection, PKDL); and "Enlargement of Lymph Nodes and Spleen" (Table 70-3, diseases associated with massive splenomegaly).
- **CMDT 2026** — "Protozoal & Helminthic Infections: Leishmaniasis" (current management: liposomal amphotericin B dosing in India, miltefosine, paromomycin, combination regimens; rK39 and splenic/marrow aspiration diagnosis; mortality figures).

Coverage note: The patient's specific state (Chhattisgarh) is not named in the corpus; the answer is grounded in the corpus's "Indian subcontinent" VL data, which applies. The **aldehyde (formol-gel) test** is included as universally accepted classic Indian bedside teaching for the hypergammaglobulinaemia that Harrison documents; it is non-specific and not a confirmatory test.

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Abdominal tuberculosis

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Abdominal tuberculosis is *Mycobacterium tuberculosis* (and occasionally *M. bovis*) infection involving the gastrointestinal tract, peritoneum, mesenteric/omental lymph nodes and solid abdominal viscera. It is one of the commonest forms of extrapulmonary TB in endemic regions such as India, classically affecting the **ileocaecal region** and the **peritoneum**. Active pulmonary disease is demonstrable in fewer than half of patients, and the indolent, non-specific presentation (chronic pain, fever, weight loss, ascites, subacute obstruction) makes it a notorious mimic of Crohn disease and malignancy — hence a "great diagnostic challenge."

Epidemiology, pathogenesis & routes of spread

- In Harrison's descending order of extrapulmonary frequency, the **peritoneum** ranks among the major sites; **gastrointestinal TB** accounts for ~3.5% of extrapulmonary cases in low-burden settings but is far commoner in endemic India and in untreated AIDS/immigrant groups.
- **Four mechanisms of seeding:**
  - **Swallowing of infected sputum** with direct mucosal seeding (in active pulmonary TB).
  - **Haematogenous spread** from a pulmonary or miliary focus.
  - **Ingestion of milk** from cattle with bovine TB (*M. bovis*) — historical, now rare.
  - **Contiguous spread** from adjacent organs (e.g., ruptured mesenteric nodes, female genital TB).

- The **terminal ileum and caecum** are most often involved because of abundant lymphoid (Peyer's patch) tissue, physiological stasis and greater contact time for bacillary penetration.

Clinical forms of abdominal TB

Form	Site / pathology	Typical features
Intestinal (luminal) TB	Terminal ileum & caecum most common; any segment possible	Chronic abdominal pain (may mimic appendicitis), subacute/recurrent **obstruction**, **palpable abdominal mass**, weight loss, diarrhoea, **hematochezia**; ulcers/fistulae may simulate Crohn disease
Tuberculous peritonitis	Peritoneum, omentum, mesentery	Non-specific abdominal pain, **fever** and **ascites**; "doughy abdomen"; SAAG <1.1, lymphocytic exudate
Glandular (nodal)	Mesenteric & retroperitoneal lymph nodes	Massive lymphadenopathy, central necrosis on CT; may cause obstruction or fistulae
Visceral	Liver, spleen, pancreas (part of disseminated/miliary disease)	Hepatosplenomegaly, granulomas on biopsy; rare isolated organ involvement

- **Morphological subtypes of intestinal TB (standard surgical classification):** *ulcerative* (transverse/circumferential "girdle" ulcers, bleeding, perforation-prone), *hypertrophic* (mass-forming, mimics carcinoma), and *ulcero-hypertrophic* (mixed).
- **Complications:** intestinal obstruction (commonest), perforation, haemorrhage, fistula and stricture formation; **anal/perianal fistulae** should prompt evaluation for rectal TB.

Tuberculous peritonitis — types & ascitic fluid analysis

- **Three classical morphological types: wet (ascitic)** — free fluid; **dry/plastic (fibroadhesive)** — adhesions, mesenteric thickening, "doughy abdomen"; **fibrotic/encysted (loculated)** — omental masses and loculated collections.
- **Ascitic fluid (paracentesis) — hallmark findings:**
  - **Exudative, high protein** (>2.5 g/dL) fluid.
  - **Low SAAG (<1.1 g/dL)** — a "diseased peritoneum" pattern; *caveat:* coexistent cirrhosis produces **mixed ascites** with a high SAAG, complicating the diagnosis.
  - **Lymphocyte-predominant** leukocytosis (neutrophils occasionally predominate early).
  - **Elevated adenosine deaminase (ADA)** — useful supportive marker for tuberculous peritonitis.
  - **Low smear/culture yield** — direct AFB smear is usually negative; culturing a **large volume** of fluid increases yield.
- **Peritoneal/omental biopsy — best obtained at laparoscopy** — is often required for definitive diagnosis (caseating granuloma, AFB, culture). Laparoscopy is specifically recommended for low-SAAG/mixed ascites with non-diagnostic CT and cytology.

Diagnostic approach / investigations

- **Imaging:**

- **Contrast CT abdomen** — wall thickening of the **caecum and ileocaecal valve**, **massive (necrotic, low-attenuation) lymphadenopathy**, omental/mesenteric thickening, ascites; CT helps interpret questionable plain-film findings and define intra-abdominal disease.
- **Ultrasound** confirms ascites and guides paracentesis; barium studies may show strictures, "string sign," and a contracted caecum.

- **Colonoscopy + biopsy** — ileocaecal ulcers with steep/undermined edges, adjacent sessile pseudopolyps, small ulcers/erosions or pseudodiverticula; obtain multiple biopsies for histology, AFB, culture and PCR.
- **Microbiological/histological confirmation** (any one is diagnostic):
  - **Caseating granuloma** on histology.
  - **Acid-fast bacilli** on smear/stain.
  - **Positive mycobacterial culture** (gold standard) of biopsy/fluid.
  - **Nucleic acid amplification (PCR / Xpert MTB/RIF)** — now the *most sensitive* means of detecting bacilli in biopsy specimens and also reports rifampin resistance.
- **Tuberculin skin test (PPD)** may be **negative**, especially with weight loss or AIDS — a negative test does *not* exclude the diagnosis.
- Because surgery is needed in many obstructive/complicated cases, the diagnosis is frequently established on **intraoperative histology and culture**.

Differential diagnosis — intestinal TB vs Crohn disease

Feature	Intestinal TB	Crohn disease
Ulcer orientation	**Transverse / circumferential** ("girdle")	**Longitudinal**, cobblestoning, aphthous
Distribution	Ileocaecal, short segment, contracted caecum	Segmental "skip lesions", longer involvement
Granuloma	**Caseating**, confluent, larger	**Non-caseating**, small, discrete
Microbiology	AFB / culture / PCR positive	Negative
Serology / markers	—	ASCA may be positive

- Other mimics: **carcinoma**, **lymphoma**, **intestinal amoebiasis**, appendiceal mass, and (for peritoneal disease) **peritoneal carcinomatosis** and ovarian malignancy. A therapeutic ATT trial with response assessment is sometimes used when distinction from Crohn disease is impossible.

Management

- **First-line anti-tubercular therapy (ATT)** — abdominal (extrapulmonary) TB is treated with the **same regimen as drug-susceptible pulmonary TB**: a 2-month intensive phase of isoniazid + rifampin + pyrazinamide + ethambutol followed by a 4-month continuation phase of isoniazid + rifampin — **2HRZE / 4HR (6 months total)**, curative in >90%.
  - Footnote caveat (Harrison Table 183-4): standard 6 months suffices for extrapulmonary TB **except CNS, bone or joint disease**, which need longer (CMDT: many experts give **9–12 months** for miliary, meningeal, bone/joint TB).

Drug (daily, adult)	Dose	Max
Isoniazid (H)	5 mg/kg	300 mg
Rifampin (R)	10 mg/kg	600 mg
Pyrazinamide (Z)	25 mg/kg	2 g
Ethambutol (E)	15 mg/kg	—

- **Adjuncts: pyridoxine** with isoniazid to prevent peripheral neuropathy; daily (not intermittent) dosing is preferred; monitor for **drug-induced liver injury**, optic neuritis (ethambutol) and adherence.
- **Surgery** is reserved for complications — obstruction not relieved by ATT, perforation, uncontrolled haemorrhage, fistula and abscess. Steroids have an established role only in **TB pericarditis and meningitis**, not in routine intestinal/peritoneal disease (corticosteroids are sometimes used to reduce adhesion/obstruction risk in peritoneal TB — see Coverage note).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Ileocaecal tuberculosis (line diagram of the terminal ileum, ileocaecal valve and caecum).** Labels: *Terminal ileum*, *Thickened/incompetent ileocaecal valve*, *Contracted/conical caecum*, *Transverse (circumferential) ulcers*, *Hypertrophic mass*, *Stricture causing obstruction*, *Enlarged caseating mesenteric lymph nodes*.
- **Tuberculous peritonitis — ascitic fluid analysis flow box.** Labels: *Paracentesis → Exudate, protein >2.5 g/dL*, *SAAG <1.1 g/dL*, *Lymphocytic leukocytosis*, *Raised ADA*, *Low AFB smear/culture yield*, *Laparoscopic peritoneal biopsy = confirmatory*.

Clinical / Diagnostic significance

- **Index of suspicion** in any patient from an endemic area with chronic abdominal pain, fever, weight loss, ascites or subacute obstruction — abdominal TB is treatable and curable but lethal if missed.
- The **low-SAAG, lymphocytic, ADA-rich exudate** plus **necrotic mesenteric nodes on CT** is a classic triad pointing to peritoneal TB; remember "mixed ascites" when cirrhosis coexists.
- **Ileocaecal TB closely mimics Crohn disease** — empirical immunosuppression/biologics for misdiagnosed Crohn can be catastrophic, so excluding TB (caseation, AFB, PCR, culture) before starting anti-TNF therapy is mandatory.
- **PCR/Xpert MTB/RIF** on biopsy improves yield and simultaneously screens for rifampin resistance, shortening time to appropriate therapy.

High-yield exam pointers

- Commonest sites: **ileocaecum** (luminal) and **peritoneum**; <50% have active pulmonary TB.
- Four routes: **swallowed sputum, haematogenous, ingested (*M. bovis*) milk, contiguous spread**.
- Intestinal subtypes: **ulcerative, hypertrophic, ulcero-hypertrophic**; commonest complication = **obstruction**.
- Peritoneal types: **wet (ascitic), dry/plastic, fibrotic/encysted**; "doughy abdomen."

- Ascites: **exudate, SAAG <1.1, high protein, lymphocytic, high ADA, low smear yield**; **laparoscopic biopsy** is most reliable.
- CT clues: **ileocaecal/valve thickening + massive necrotic lymphadenopathy**.
- Diagnosis confirmed by **caseating granuloma / AFB / culture / PCR**; **PPD may be negative**.
- Treatment = **2HRZE/4HR (6 months)** — same as pulmonary; longer only for CNS/bone/joint; surgery for complications.
- Key differential = **Crohn disease** (transverse vs longitudinal ulcers; caseating vs non-caseating granuloma) — exclude TB before biologics.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Tuberculosis"** (extrapulmonary TB: Gastrointestinal TB and Tuberculous peritonitis; treatment regimens and drug-dose Tables 183-2/183-4).
- **CMDT 2026 — "Gastrointestinal Disorders"** (Intestinal Tuberculosis; Ascites — SAAG classification, ascitic-fluid analysis, ADA, laparoscopy) and **"Pulmonary Disorders"** (extrapulmonary TB treatment duration; pyridoxine).
- *Coverage note:* The morphological subclassifications (intestinal: ulcerative/hypertrophic/ulcero-hypertrophic; peritoneal: wet/dry/fibrotic), the Crohn-vs-TB ulcer-orientation/granuloma contrasts, ASCA, and a specific numerical ADA cut-off are universally accepted standard internal-medicine teaching but are not stated verbatim in the cited corpus, which confirms the underlying findings (lymphocytic exudate, raised ADA, ileocaecal site, Crohn mimicry, caseating granuloma) in narrative form. Routine corticosteroid use in peritoneal TB to reduce adhesions is variably practised and is *not* endorsed by the corpus (which supports steroids only for TB pericarditis and meningitis).

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Acute pyelonephritis

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Acute pyelonephritis is a symptomatic, **tissue-invasive infection of the renal parenchyma, calyces and pelvis**, and is the prototype of a *complicated urinary tract infection (UTI)* because infection has extended beyond the bladder. It usually develops as an **ascending infection** from the bladder, so its microbiology mirrors that of acute cystitis. Affected patients are often systemically ill, and **fever is the cardinal feature distinguishing it from cystitis**.

Etiology and microbiology

- ***Escherichia coli*** is the predominant uropathogen across the whole UTI spectrum; the microbiology of pyelonephritis is **similar to that of acute cystitis** since it arises by ascent.
- Other **Enterobacterales** — *Klebsiella, Proteus, Enterobacter, Citrobacter* — and *Staphylococcus saprophyticus* account for most of the remainder.
- *Staphylococcus aureus* or *Salmonella* in urine should raise suspicion of **haematogenous seeding** and concomitant bacteraemia.

- **Rising antimicrobial resistance**: surveillance shows >20% resistance to TMP-SMX, fluoroquinolones and nitrofurantoin in many regions; ~9% of isolates produce **extended-spectrum β-lactamase (ESBL)** and ~6% are resistant to ≥3 antibiotic classes — hence the value of *local antibiogram* data.

Pathogenesis

- The urinary tract is a continuous urine column from kidney to urethra; in most UTIs bacteria **ascend** urethra → bladder → ureter → renal parenchyma. **Haematogenous infection accounts for <2%** of UTIs.
- The **flushing action of normal voiding** is the key host defence; anything causing stasis or obstruction predisposes to infection.
- **Vesicoureteral reflux** and **inhibition of ureteral peristalsis / decreased ureteral tone** promote ascent — these are central to pyelonephritis in **pregnancy**.
- **Microbial virulence factors**: *P fimbriae* (bind the blood-group P antigen on renal epithelium) are important in the pathogenesis of pyelonephritis and subsequent **bloodstream invasion**; *type 1 pili* mediate bladder attachment (bind mannose). Toxins, iron-acquisition systems, biofilm and capsule also contribute.
- **Host factors**: familial/maternal predisposition; mutations in innate-immune genes (**Toll-like receptors, IL-8 receptor**) linked to recurrent UTI and pyelonephritis; non-expression of certain blood-group antigens (non-secretor) increases uroepithelial adherence of *E. coli*.

Predisposing / risk factors

- **Obstruction & stasis**: renal/staghorn calculi, benign prostatic hypertrophy, neurogenic bladder, vesicoureteral reflux, urinary-diversion surgery, congenital anomalies, cystocele/pelvic-organ prolapse.
- **Foreign bodies**: indwelling/intermittent catheters, stents, nephrostomy tubes — provide an inert surface for **biofilm** and act as a nidus.
- **Diabetes mellitus** (2–3× higher UTI/ASB rate; predisposes to emphysematous pyelonephritis); **pregnancy**; female anatomy (**short urethra**); sexual activity and **spermicide** use; immunocompromise.

Clinical features

- **Acute onset**, with or without preceding cystitis symptoms (dysuria, frequency, urgency).
- ***Mild* pyelonephritis** — low-grade fever ± lower-back or **costovertebral-angle (flank) pain**.
- ***Severe* pyelonephritis — high fever, rigors, nausea, vomiting and flank pain**; may progress to bacteraemia and sepsis.
- Fever, rigors and unilateral back/flank pain in a patient with "cystitis" are **inconsistent with simple cystitis** and mandate evaluation for infection beyond the bladder.

Complications

Complication	Key features (per source)
Acute papillary necrosis	Sloughed papillae obstruct the ureter → obstructive uropathy; also seen in **sickle cell disease** and **analgesic nephropathy**; *bilateral* necrosis → rapid rise in serum creatinine
Emphysematous pyelonephritis	Severe form with **gas in renal/perinephric tissue**; occurs almost exclusively in **poorly controlled diabetes** (often *E. coli*, a gas-forming facultative anaerobe)
Xanthogranulomatous pyelonephritis (XGP)	Chronic obstruction (often **staghorn calculus**) + chronic infection → suppurative destruction; residual tissue is yellow with **lipid-laden macrophages**; can **mimic renal malignancy**
Intraparenchymal / perinephric / renal cortical abscess	Suspect with **continued fever and/or bacteraemia despite antibiotics**

Diagnosis / investigations

- **Urinalysis**: pyuria (>10 WBC/HPF is the accepted standard for pyuria), **nitrite** (only Enterobacterales convert nitrate→nitrite) and **leukocyte esterase** on dipstick; haematuria in ~30%.
- **Urine culture** before therapy — provides organism identification and **susceptibilities to guide therapy** (essential in pyelonephritis, men, pregnancy and recurrent/resistant cases).
- **Blood cultures** in systemically ill / febrile patients.
- **Imaging (CT or ultrasound)** for febrile UTI and febrile UTI in men — to detect **obstruction, abscess, calculi or anatomic abnormalities**; CT also demonstrates gas in emphysematous pyelonephritis.

Treatment

- **Principle**: empirical therapy must be reliable and **rapidly reach therapeutic levels in renal parenchyma and blood**; nitrofurantoin, fosfomycin and pivmecillinam achieve poor renal-tissue levels and **must not be used** for pyelonephritis.

Setting	Recommended regimen (per source)
Hospitalised patients	Empirical **IV β-lactam**, chosen by local antibiogram and avoiding agents to which the patient recently had a resistant isolate
Outpatient (not requiring admission)	Empirical **TMP-SMX, ciprofloxacin, or levofloxacin** per local antibiogram + urine culture + short-term follow-up; an initial IV/IM β-lactam or aminoglycoside dose can be added where feasible
Susceptible isolate, oral therapy	**5–7 days of an oral fluoroquinolone** OR **7–14 days of oral TMP-SMX**; oral β-lactams are less effective → use with caution and close follow-up
Parenteral options (uncomplicated PN)	Late-generation cephalosporin (**ceftriaxone, cefepime**), **piperacillin-tazobactam**, a **carbapenem**, or fluoroquinolone; alternatives — novel β-lactam/β-lactamase inhibitors (e.g., meropenem-vaborbactam) and aminoglycosides

Setting	Recommended regimen (per source)
Pregnant patients with pyelonephritis	**Parenteral β-lactam therapy ± aminoglycoside** (based on limited data)

- **Admit** ambulatory patients who cannot tolerate oral medication (vomiting) or are unlikely to adhere to follow-up.
- **Step-down**: once a clinical response is achieved, switch parenteral → **oral**; therapy may be concluded at **7 days** in responders treated with a fluoroquinolone or TMP-SMX (oral β-lactams may need longer).
- **No clinical response within 72 h** → evaluate for an **uncontrolled source** (obstruction, abscess).
- **Source control**: papillary necrosis with obstruction needs intervention to relieve obstruction; perinephric/cortical abscess → **percutaneous drainage**; **emphysematous pyelonephritis** → percutaneous drainage initially, then **elective nephrectomy** as needed; **XGP** → usually **nephrectomy** with individualized antibiotic duration, in collaboration with urology.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Ascending pathogenesis of pyelonephritis**: vertical urinary tract with labels — *Urethra → Bladder (cystitis) → Vesicoureteral reflux → Ureter → Renal pelvis/calyces → Renal parenchyma (pyelonephritis)*; annotate *P fimbriae adhesion to renal epithelium*, *Type 1 pili (bladder)*, and *Haematogenous seeding (<2%: S. aureus, Salmonella)*.
- **Diagram 2 — Labelled kidney showing complications**: cross-section with labels — *Cortical abscess*, *Perinephric abscess*, *Papillary necrosis (sloughed papilla obstructing ureter)*, *Gas in parenchyma (emphysematous PN)*, *Staghorn calculus with destruction (XGP)*.

Clinical / Diagnostic significance

- **Fever + flank/CVA tenderness** in a UTI patient = pyelonephritis until proven otherwise; reclassify "cystitis with fever" as a complicated UTI.
- Persistent fever/bacteraemia despite appropriate antibiotics signals **abscess or obstruction** — image and arrange drainage.
- **Diabetic + severe pyelonephritis + gas on imaging** = emphysematous pyelonephritis, a urological emergency.
- **Pregnancy**: untreated asymptomatic bacteriuria predisposes to pyelonephritis, **preterm delivery and low birth weight** — justifying routine **ASB screening and treatment** by urine culture in pregnancy.
- **Avoid** nitrofurantoin/fosfomycin/pivmecillinam for upper-tract disease — they fail to reach renal tissue.

High-yield exam pointers

- Pyelonephritis = **tissue-invasive complicated UTI**; *E. coli* is the commonest organism; ascent is the usual route (<2% haematogenous).
- **P fimbriae** = key virulence factor for pyelonephritis and bloodstream invasion; **type 1 pili** for bladder attachment.

- **Triad of severe disease**: high fever + rigors + flank pain, often with nausea/vomiting.
- **Emphysematous pyelonephritis** → poorly-controlled diabetes; **XGP** → staghorn calculus + lipid-laden macrophages, mimics tumour; **papillary necrosis** → also sickle cell disease & analgesic nephropathy.
- Always **send urine culture (± blood cultures)** before empirical antibiotics; image febrile UTI/men with CT or US.
- Outpatient empirical: **TMP-SMX / ciprofloxacin / levofloxacin** by antibiogram; hospitalised: **IV β-lactam**.
- Oral course for susceptible isolate: **5–7 days fluoroquinolone or 7–14 days TMP-SMX**; reassess at **72 h** if no response.
- **Pregnant pyelonephritis** = admit + **parenteral β-lactam ± aminoglycoside**.

SOURCE & COVERAGE

Harrison 22e — Ch 140 "Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis." *Coverage note*: This chapter does not state a specific clean-catch colony-count threshold for diagnosing pyelonephritis (it gives **>10^2 CFU/mL** as a sensitive cystitis cut-off and **≥10^3 CFU/mL** for CAUTI); the classic **≥10^5 CFU/mL** clean-catch criterion is universally accepted standard textbook medicine. Quantified imaging grading (e.g., Huang–Tseng classes of emphysematous pyelonephritis) is also outside the provided text.

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Amoebic liver abscess

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Amoebic liver abscess (ALA) is the most common extraintestinal manifestation of infection with **Entamoeba histolytica**, produced by portal venous spread of invasive trophozoites from the colon to the liver. It usually presents as a febrile hepatic space-occupying lesion with right-upper-quadrant pain, often without active dysentery. It is a treatable medical emergency because rupture into the pleura, peritoneum, or pericardium may be fatal.

Etiology and Epidemiology

- **Agent: E. histolytica** is the pathogenic species in the Entamoeba complex; **E. dispar**, **E. moshkovskii**, and other species may be morphologically indistinguishable on microscopy but do not explain classic invasive disease.
- **Transmission:** ingestion of mature cysts from fecally contaminated water, food, hands, or mechanically contaminated food; less commonly via oral-anal sexual practices. Trophozoites are killed by gastric acid and air and do not transmit infection.
- **Reservoir:** humans are the established host; asymptomatic carriers may shed large numbers of cysts.
- **Geography:** common in tropical and subtropical areas with poor sanitation, crowding, and poor nutrition; important in the Indian subcontinent, Africa, parts of East Asia, Mexico, Colombia, and other endemic regions.

- **Risk groups:** residents of endemic areas, returning travelers, recent immigrants, men who have sex with men, institutional inmates, and persons exposed to unsafe water or food.
- **Sex and age:** invasive colitis and liver abscess are much more common in men; Harrison notes that men aged **30-60 years** are affected **10-12 times** more often than women of the same age.
- In travelers who develop ALA after leaving an endemic area, most present within **5 months**.

Pathogenesis and Pathology

- After cyst ingestion, **excystation** occurs in the small intestine; trophozoites colonize the large bowel. In most persons infection remains asymptomatic, but trophozoites may invade the colonic mucosa.
- Virulence depends on **Gal/GalNAc adherence lectin**, cysteine proteinases, glycosidases, contact-dependent cytotoxicity, trogocytosis, inflammatory-cell lysis, and resistance to oxidative and complement-mediated killing.
- Intestinal disease produces **flask-shaped ulcers** with trophozoites at the margin of viable and necrotic tissue; glucocorticoid exposure can convert unrecognized amebiasis into severe colitis or toxic megacolon.
- ALA is **always preceded by intestinal colonization**, often asymptomatic. Trophozoites enter mesenteric venules and reach the liver via the **portal venous system**.
- In the liver, vessel-wall lysis, thrombosis, neutrophil recruitment, neutrophil lysis, and hepatocyte necrosis produce a cavity of necrotic debris surrounded by a thin rim of congested liver.
- The aspirate is classically described as "**anchovy paste**", but color is variable. It is usually **bacteriologically sterile**, granular, and poor in cells; trophozoites are uncommon in the aspirated center and are more often near the abscess capsule.

Clinical Features

- **Classical triad:** fever, right-upper-quadrant abdominal pain, and tender hepatomegaly.
- Onset may be acute or gradual. Pain is often dull or pleuritic and may radiate to the right shoulder; point tenderness over the liver and **intercostal tenderness** are useful bedside clues.
- **Fever** is common; **jaundice is rare** and, if prominent, suggests large abscess, biliary obstruction, cholangitis, or alternative diagnosis.
- Gastrointestinal symptoms are absent in many patients: fewer than one-third have active diarrhea despite colonic origin of infection. Anorexia, malaise, weight loss, nausea, cough, and hiccups may occur.
- **Right pleural effusion** or elevated right hemidiaphragm may accompany superior right-lobe abscesses.
- Older patients from endemic areas may present subacutely over months with weight loss and hepatomegaly; **10-15%** may present only as fever of unknown origin.

Pattern	Exam clue	Significance
Acute ALA	Fever, RUQ pleuritic pain, tender liver, leukocytosis	Usually symptomatic for <10 days; multiple lesions are more likely early

Pattern	Exam clue	Significance
Subacute/chronic ALA	Weight loss, hepatomegaly, variable fever	Common diagnostic trap in endemic-area patients
Left-lobe abscess	Epigastric pain, pericardial risk	Needs early drainage consideration
Superior right-lobe large abscess	Pleural pain, effusion, basal lung signs	Risk of pleuropulmonary rupture

Investigations and Diagnosis

- **CBC/LFT:** leukocytosis is common; Harrison notes leukocytosis >10,000 cells/microliter in about three-fourths of ALA. Eosinophilia is not a feature. Liver enzymes may be normal or minimally raised; **alkaline phosphatase** is most often elevated and may remain high for months.
- **Stool tests:** often negative in isolated ALA. If intestinal symptoms are present, examine at least **three fresh stool specimens**; hematophagous trophozoites are diagnostic, but routine microscopy cannot distinguish E. histolytica from nonpathogenic Entamoeba species.
- **Serology:** anti-amebic antibody testing is positive in **>90%** of invasive amebiasis including liver abscess. Early ALA may be seronegative in up to **10%**, so repeat testing after about a week if suspicion remains high.
- **Antigen/PCR:** stool or aspirate antigen assays targeting E. histolytica improve specificity; PCR-based gastrointestinal panels have very high sensitivity and specificity where available. In hepatic abscess, stool antigen is frequently negative, while aspirate antigen is highly diagnostic if aspiration is done.
- **Imaging:** ultrasonography, CT, and MRI detect round or oval hypoechoic or low-density nonhomogeneous lesions. More than **80%** of patients symptomatic for >10 days have a **single right-lobe abscess**; about **50%** of those symptomatic for <10 days may have multiple abscesses.
- **Important limitation:** imaging cannot reliably distinguish amoebic from pyogenic abscess; use epidemiology, serology, cultures when aspirated, and therapeutic response.
- **Differential diagnosis:** pyogenic liver abscess, cholangitis, acute cholecystitis, hepatocellular carcinoma with necrosis/infection, hydatid cyst, tuberculosis, malaria, typhoid fever, right lower-lobe pneumonia, subphrenic abscess, and inflammatory bowel disease with hepatic sepsis.

Treatment

- **Principle:** treat both tissue invasion and intestinal carriage. A tissue amebicide alone improves the abscess but does not eradicate bowel cysts; hence add a **luminal amebicide** after or along with nitroimidazole therapy.

Clinical setting	Preferred regimen
Amoebic hepatic abscess	**Metronidazole 750 mg orally three times daily for 10 days**; if oral therapy is not possible, **metronidazole 500 mg IV every 6 hours for 10 days**
Alternative	**Tinidazole 2 g orally daily for 5 days**
Luminal eradication	**Diloxanide furoate 500 mg orally three times daily for 10 days** or **iodoquinol 650 mg orally three times daily for 21 days** or **paromomycin 10 mg/kg orally three times daily for 7 days**

- Avoid alcohol with metronidazole/tinidazole because of a disulfiram-like reaction; nausea, metallic taste, vomiting, epigastric discomfort, and headache may occur.
- More than **90%** respond dramatically to metronidazole, with reduction in pain and fever within **72 hours**. With early diagnosis and treatment, mortality from uncomplicated ALA is **<1%**.
- **No routine aspiration** is required for typical, uncomplicated ALA responding to therapy; aspiration does not hasten healing even for large abscesses up to about 10 cm.
- **Aspirate/drain if:** pyogenic abscess must be excluded, especially with multiple lesions; no clinical response in **3-5 days**; very large abscess with threatened rupture; left-lobe abscess at risk of pericardial rupture; frank pleural or peritoneal rupture; or the patient is toxic/very ill.
- **Surgery:** reserve for bowel perforation and rupture into the pericardium; percutaneous drainage may suffice for many ruptured hepatic abscesses.
- Abscess cavities resolve slowly. Imaging abnormalities may persist despite clinical cure; complete resolution by 6 months occurs in about two-thirds, and 10% may have abnormalities for a year.

Complications and Prevention

- **Pleuropulmonary complications** are the commonest, reported in **20-30%**: sterile effusion, contiguous spread, rupture into pleural space, lung abscess, or hepatobronchial fistula with expectoration of necrotic material.
- **Peritoneal rupture** may present as indolent leak or acute abdomen and needs drainage plus medical therapy.
- **Pericardial rupture**, usually from left-lobe abscess, has the worst prognosis and requires urgent surgical drainage.
- Rare extraintestinal sites include lung, brain, genitourinary tract, and painful punched-out genital ulcers due to direct extension or hematogenous spread.
- **Prevention:** safe water, sanitary disposal of feces, hand hygiene, adequate cooking of food, protection of food from flies, avoidance of unpeeled fruits/vegetables in endemic areas, bottled/boiled/filtered water, and treatment of cyst carriers.
- Cysts resist standard chlorination; iodine treatment or boiling/filtration is more reliable. There is **no effective chemoprophylaxis**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Life cycle and hepatic spread of E. histolytica:** ingestion of cysts, excystation in small intestine, colonization of colon, flask-shaped colonic ulcer, portal venous spread, right-lobe liver abscess; labels: cyst, trophozoite, colon, portal vein, liver abscess, asymptomatic cyst passage.
- **Anatomical complications of ALA:** right-lobe abscess, pleural effusion/rupture, hepatobronchial fistula, peritoneal rupture, left-lobe abscess, pericardial rupture.

Clinical / Diagnostic significance

- ALA is a classic cause of **fever with right-upper-quadrant pain** in Indian exams and must also be considered in FUO with epidemiologic risk.

- Absence of diarrhea does **not** exclude ALA; most patients with hepatic disease have no active intestinal symptoms.
- Positive serology plus compatible imaging and clinical syndrome is usually sufficient for diagnosis; aspiration is mainly for uncertainty, poor response, or rupture risk.
- Differentiate from pyogenic abscess: pyogenic abscess patients are often older, have biliary disease, bowel disease, diabetes, recent surgery, polymicrobial cultures, and need antibacterial therapy plus drainage.
- Rule out amebiasis before giving glucocorticoids for presumed inflammatory bowel disease in endemic settings.
- Do not chase radiologic resolution too frequently: clinical response is more important early because abscess size can lag behind cure.

High-yield exam pointers

- Most common extraintestinal site of amebiasis is the **liver**.
- **Right-lobe, solitary abscess in a young/middle-aged man** with fever and RUQ pain is the prototype.
- **Jaundice is uncommon** in uncomplicated ALA.
- Stool examination is often negative in ALA; **serology is the key test**.
- Aspirate is classically **anchovy-paste**, sterile, and poor in cells; trophozoites are usually not seen in the center.
- Treat with **metronidazole/tinidazole plus luminal agent**; metronidazole alone risks persistent intestinal carriage.
- Clinical response should occur within **72 hours**; lack of response by **3-5 days** is an aspiration/drainage indication.
- Left-lobe abscess is dangerous because of **pericardial rupture**.
- Standard chlorination is unreliable against cysts; emphasize sanitation, boiling/iodination/filtration, and safe food.

> **SOURCE & COVERAGE**
>
> Harrison 22e — "Amebiasis and Infection with Free-Living Amebae"; CMDT 2026 — "Protozoal & Helminthic Infections" and "Liver, Biliary Tract, & Pancreas Disorders".

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Anaerobic infections

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — **Anaerobic bacteria** are organisms that grow optimally in the absence of oxygen and constitute the predominant class of the normal human microbiota residing on mucous membranes. They cause disease chiefly after **breakdown of a mucosal barrier** allows the microbiota to leak into normally sterile tissue, producing infections that are typically **polymicrobial** (mixed anaerobic + facultative/microaerophilic species). Because they are fastidious and hard to culture, the anaerobic aetiology is frequently *unproven*, so the diagnosis often rests on clinical pattern recognition. Treatment hinges on **appropriate antibiotics plus surgical drainage/debridement**.

Classification of anaerobes by oxygen tolerance and morphology

- **Obligate (strict) anaerobes** — killed in the presence of ≥0.5% oxygen (lack superoxide dismutase/catalase).
- **Aerotolerant anaerobes** — tolerate oxygen but cannot use it for growth; *most clinically relevant anaerobes* (**Bacteroides fragilis, Prevotella melaninogenica, Fusobacterium nucleatum**) are relatively aerotolerant.
- **Facultative anaerobes** — grow with or without oxygen (e.g. *E. coli*); preferentially use oxygen when available.
- **Microaerophilic organisms** — require low O_2 (2–10%) and are damaged by atmospheric ~21%.
- Oxygen tolerance correlates with expression of **superoxide dismutase and catalase** (detoxify O_2^- and H_2O_2). Energy is generated by less-efficient **anaerobic respiration** (acceptors: sulfate, nitrate, CO_2, fumarate) or **fermentation** (~5% of the ATP yield of aerobic respiration).

Microbiological group	Representative pathogens
Gram-negative bacilli	*Bacteroides fragilis* group (25 species), *Prevotella*, *Porphyromonas*, *Fusobacterium* spp.
Gram-negative cocci	*Veillonella* spp. (few of the gram-neg cocci causing disease)
Gram-positive cocci	Peptostreptococci (*P. micros, P. anaerobius*), *Finegoldia magna* (ex-*Peptostreptococcus magnus*)
Gram-positive spore-forming bacilli	*Clostridium* spp. (covered separately)
Gram-positive non-spore-forming bacilli	*Cutibacterium acnes* (ex-*Propionibacterium*), *Actinomyces* spp.

Sites of normal anaerobic microbiota and the organisms they seed

- The **lower GI tract (colon)** is the major reservoir — anaerobe:aerobe ratio ~**1000:1**, ~10^{11}–10^{12} organisms/g; *Bacteroides* group, *Prevotella*, *Clostridium*.
- **Oral cavity / gingival crevices** — ratio up to 1000:1; *Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus, Actinomyces* → odontogenic, peripharyngeal, sinus and pleuropulmonary infections.
- **Female genital tract** — ratio ~10:1; *Prevotella bivia, P. disiens, Bacteroides* → pelvic infections.
- **Skin** — *Cutibacterium acnes* predominant → foreign-body/prosthetic infections.

- Infections "reflect the neighbouring microbiota": e.g. **B. fragilis + E. coli** dominate intra-abdominal abscesses; oral flora dominate lung abscess.

Pathogenesis and virulence factors

- **Prerequisite = an anaerobic micro-environment with lowered oxidation–reduction (redox) potential** — created by ischaemia, trauma, surgery, a perforated viscus, or by facultative organisms consuming oxygen (basis of synergy).
- **Adhesion** — *P. gingivalis* fimbriae; *F. nucleatum* acts as a "bridge" binding almost all oral bacteria; *B. fragilis* pili/fimbriae/haemagglutinins.
- **Exoproteins/toxins** — *P. gingivalis* collagenase; clostridial exotoxins are among the most potent in nature.
- **Endotoxin (lipid A)** of *B. fragilis*/*Prevotella*/*Porphyromonas* is **100–1000× less biologically potent** than aerobic gram-negative LPS → explains the *lower rates of DIC, purpura and septic shock* in anaerobic gram-negative bacteraemia. (Exception: *Fusobacterium* LPS, contributing to severe Lemierre's syndrome.)
- ***B. fragilis* capsular polysaccharide complex** — the best-studied anaerobic virulence factor; ≥8 distinct capsules; **PSA and PSB are zwitterionic** (free amino + carboxyl groups). PSA induces **abscesses** by stimulating peritoneal macrophages (via **TLR-2**) to release **IL-8, IL-17 and TNF-α**, driving PMN chemotaxis and adhesion to **ICAM-1**-expressing mesothelium — the abscess nidus.
- **Bacterial synergy** — infections characteristically involve **3–6 organisms**; facultatives lower redox potential, supply growth factors (e.g. vitamin K for *P. melaninogenica*) and impair phagocytosis (short-chain/succinic acids).

Clinical syndromes by anatomical site

- **Mouth, head & neck** — dental caries, periodontitis; **Ludwig's angina** (submandibular/sublingual/submental space cellulitis from molar abscess, tongue elevation, airway threat); **acute necrotizing ulcerative gingivitis** (*trench mouth / Vincent's stomatitis* — painful bleeding gums, grey pseudomembrane); **noma (cancrum oris)** — gangrenous orofacial destruction in malnourished children (sub-Saharan Africa, 70–90% untreated mortality, driven by *F. necrophorum*/*P. intermedia*); **peritonsillar abscess (quinsy)** and **retropharyngeal abscess**; **chronic** sinusitis & suppurative otitis media (anaerobes spare the *acute* forms).
- **Lemierre's syndrome** — *F. necrophorum* oropharyngeal infection → **septic thrombophlebitis of the internal jugular vein** with septic pulmonary emboli.
- **CNS** — anaerobes recovered in ~**30% of brain abscesses**, ~20% of epidural abscesses, ~10% of subdural empyemas (usually by contiguous spread from oto-/odonto-/sinugenic foci); anaerobic **meningitis is rare**.
- **Pleuropulmonary** (from microaspiration of oral flora; indolent course) — **aspiration pneumonia** (dependent segments), **lung abscess** (foul sputum, ~90% yield an anaerobe, 3–6 isolates), **empyema** — distinguish from simple parapneumonic effusion:

Feature	Parapneumonic effusion	Anaerobic empyema
WBC (cells/mL)	~5,000	~55,000
LDH (IU/L)	>200	>1000
pH	~7.4	<7.2
Character	thin exudate	foul, thick pus, loculated, pleural peel

(Contrast with **Mendelson syndrome** — *chemical* aspiration pneumonitis from gastric acid, evolving within 4–6 h, needing no antibiotics unless superinfected.)

- **Intra-abdominal** — peritonitis/abscess after perforation; *E. coli* + *B. fragilis* group; **neutropenic enterocolitis (typhlitis)** — caecal wall thickening >4 mm post-chemotherapy; *Clostridium septicum* bacteraemia flags occult **colon cancer**.
- **Pelvic** — PID, tubo-ovarian abscess, septic abortion, endometritis (*P. bivia, P. disiens, B. fragilis*); **bacterial vaginosis** (loss of lactobacilli, overgrowth of *Gardnerella*/*Prevotella*/*Mobiluncus*).
- **Skin/soft tissue** — **gas gangrene** (clostridial), **progressive bacterial synergistic (Meleney) gangrene**, **synergistic necrotizing cellulitis / Fournier gangrene** (scrotum–perineum–abdominal wall), **necrotizing fasciitis**, **myositis** — foul odour, crepitus/subcutaneous gas, cutaneous anaesthesia.
- **Bone & joint** — *Actinomyces* "**lumpy jaw**" (cervicofacial, mandible > maxilla, sinus tracts); contiguous mixed osteomyelitis (diabetic foot, decubitus).
- **Bacteraemia / endocarditis** — *B. fragilis* is the anaerobe most often isolated from blood; mortality of untreated *B. fragilis* group bacteraemia ~**60%**; gram-negative anaerobic endocarditis carries **21–43% mortality**.

Diagnosis

- **Clinical clues** — abscess formation, **putrid/foul-smelling** discharge (present in only 30–50%, often late), gas in tissues, septic thrombophlebitis, tissue necrosis, and **failure to respond to antibiotics inactive against anaerobes**.
- "**Sterile pus**" that yields no growth (or only a single aerobe) yet is **teeming with organisms on Gram stain** strongly implies anaerobes (lost on inadequate transport/culture).
- **Specimens** — sample normally sterile sites (blood, pleural/peritoneal fluid, aspirates/biopsy); avoid mucosal-surface swabs (mouth, vagina, faeces) that contain commensal anaerobes. Use **air-free syringe + anaerobic transport medium** and rapid transport. Prior antibiotics reduce recovery.

Treatment / Antimicrobial therapy

- **Two pillars**: (1) appropriate **antibiotics** active against *both* aerobes and anaerobes; (2) **surgical debridement of devitalized tissue + drainage** of abscesses, and prompt closure of any mucosal breach.
- **No useful anaerobic activity**: **aminoglycosides, monobactams (aztreonam), trimethoprim-sulfamethoxazole**.

Agent	Caveat
Metronidazole	First-line for gram-negative anaerobes; *unreliable* against gram-positive non-spore-formers (*Actinomyces, Cutibacterium, Peptostreptococcus, Lactobacillus*)
β-lactam/β-lactamase-inhibitor (ampicillin-sulbactam, piperacillin-tazobactam)	Rising resistance in some gram-negatives; newer ceftolozane/ceftazidime-avibactam have limited anaerobic activity
Clindamycin	*B. fragilis* group resistance now 30–43% in USA → no longer first-line for intra-abdominal sepsis
Carbapenems (meropenem, imipenem, ertapenem, doripenem)	Very low resistance (<5%); rare carbapenemase-producing strains
Chloramphenicol	Occasional clinical failures despite in-vitro susceptibility

- **Above vs below the diaphragm** governs empirical choice:
  - **Above diaphragm** (orodental flora, *Prevotella/Porphyromonas/Fusobacterium*; >70% β-lactamase-producing): clindamycin, a β-lactam/β-lactamase-inhibitor, or **metronidazole + penicillin** (for microaerophilic/aerobic streptococci). Penicillin alone is inadequate.
  - **Below diaphragm** (must cover *B. fragilis* + coliforms): single agent — **cefoxitin, moxifloxacin, a β-lactam/β-lactamase-inhibitor, or a carbapenem**; or two-drug **metronidazole + cephalosporin/fluoroquinolone**; add ampicillin/vancomycin if enterococci suspected.
- **Representative CMDT 2026 regimens**: ampicillin-sulbactam 3 g IV q6h (then amoxicillin-clavulanate 875/125 mg PO BID); ceftriaxone + metronidazole 500 mg q6–8h; moxifloxacin 400 mg/day; **brain abscess** — ceftriaxone 2 g IV q12h + metronidazole 500 mg q8h for 6–8 weeks (imaging-guided); anaerobic/microaerophilic streptococcal **endocarditis** — penicillin G 12–18 MU/day for 4–6 weeks.
- **Failure to respond** → re-image for undrained focus, reculture, request susceptibility testing (reserved for serious/refractory/prolonged-therapy infections).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Pathogenesis of an anaerobic abscess" flow diagram** — label: *Mucosal barrier breach (perforation/ischaemia/surgery) → Polymicrobial inoculation → Facultative organisms consume O_2 → lowered redox potential → Outgrowth of obligate anaerobes → B. fragilis PSA → TLR-2 on macrophages → IL-8/IL-17/TNF-α → PMN influx → ICAM-1 adhesion → ABSCESS.*
- **Lung abscess radiograph schematic** — label: *cavity with air–fluid level, dependent (posterior) segment, right upper-lobe posterior / lower-lobe superior segment, surrounding consolidation.*

Clinical / Diagnostic significance

- Suspect anaerobes whenever an infection arises **adjacent to a mucosal surface**, forms an **abscess**, is **foul-smelling**, contains **gas**, or **fails broad-spectrum antibiotics lacking anaerobic cover**.

- **Source control (drainage/debridement) is as important as antibiotics** — many synergistic infections resolve even if therapy targets only the dominant organisms, because resistant species do not survive without their co-pathogens.
- *B. fragilis* group **always implies significant underlying pathology** (colonic neoplasm, diverticulitis, perforation) when isolated from blood — investigate the gut.
- Low DIC/shock incidence is a *hint* (weak lipid A), but does not exclude serious infection.

High-yield exam pointers

- Three oxygen classes: **obligate (killed ≥0.5% O_2) / aerotolerant / facultative**; tolerance = SOD + catalase.
- **B. fragilis** = commonest anaerobe in intra-abdominal abscess, bacteraemia and endocarditis; only ~0.5–1% of colonic flora yet dominant in disease — due to its **zwitterionic capsular polysaccharide (PSA)**.
- **Lemierre's syndrome** = *F. necrophorum* + IJV septic thrombophlebitis + septic pulmonary emboli.
- **Ludwig's angina, ANUG (Vincent's), noma, quinsy** — classic head-and-neck anaerobic eponyms.
- **Meleney** (progressive synergistic) gangrene and **Fournier** gangrene are anaerobic synergistic soft-tissue infections.
- **Empyema** fluid: pH <7.2, LDH >1000, WBC ~55,000 → needs drainage.
- **Typhlitis** + *Clostridium septicum* bacteraemia → screen for **colon cancer**.
- **Metronidazole fails against gram-positive non-spore-formers** (Actinomyces, Cutibacterium, Peptostreptococcus).
- **No anaerobic activity**: aminoglycosides, aztreonam, co-trimoxazole.
- **Above- vs below-diaphragm** rule directs empirical antibiotics.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Infections Due to Mixed Anaerobic Organisms" (primary); with supporting detail from "Pharyngitis, Sinusitis, Otitis, and Other Upper Respiratory Tract Infections," "Lung Abscess," and "Gas Gangrene and Other Clostridial Infections."
- **CMDT 2026** — "Bacterial & Chlamydial Infections: Anaerobic Infections" (current empirical regimens and doses) and "Actinomycosis."

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Aspergillus infections

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Aspergillosis* is the collective term for the spectrum of disease produced by the ubiquitous, hyaline, septate, branching mould *Aspergillus* (~50 pathogenic/allergenic species). *A. fumigatus* causes most invasive disease, >95% of chronic disease and most allergic syndromes; *A. flavus* predominates in sinus, cutaneous and keratitis disease (and granulomatous sinusitis of the Middle East/India); *A. terreus* and *A. nidulans* are intrinsically amphotericin-resistant. Only species growing at 37°C invade; spectrum runs from harmless saprophytic colonisation through devastating angioinvasive infection to allergic hypersensitivity. The clinical form is dictated by the **host immune state**.

Epidemiology, ecology and pathogenesis

- **Ecology:** worldwide; grows in decomposing plant matter (compost), hay and bedding, producing vast numbers of airborne **conidia**. Inhalation is the route of entry; daily exposure ranges from a few to millions of conidia. Intense exposure (construction, mouldy bark/hay, composting) can cause acute pulmonary aspergillosis even in the immunocompetent.
- **Incubation** of invasive disease is highly variable (2–90 days), so community-acquired strains often manifest during hospitalisation; outbreaks relate to contaminated air sources or **hospital construction**. **HEPA filtration** is protective and should guard operating rooms, burn units and high-risk wards.
- **Burden (global, 2024 estimates):** invasive ~2.1 million; chronic ~6.1 million; allergic ~11.7 million.
- **Pathogenesis is host-determined:** profound neutropenia/phagocyte dysfunction → **angioinvasion**; an inadequate TH1 response with persistent inflammation → **chronic** cavitary disease; an exaggerated TH2/"allergic" response to *A. fumigatus* → **ABPA/SAFS**.

Risk factors (by disease form)

Form	Principal host setting / risk factors
Invasive	Profound, prolonged **neutropenia**; high-dose **glucocorticoids**; haematological malignancy/relapsed leukaemia; HSCT; chronic granulomatous disease (esp. *A. nidulans*); advanced HIV; immunomodulators — **infliximab, ibrutinib** (ibrutinib → cerebral disease); ICU patients (2–5%), severe **influenza** (8–25%), severe **COVID-19** (~10%, "CAPA"), COPD (1.3–3.9%); severe liver disease
Chronic	Apparently immunocompetent but with prior lung damage — **prior/active TB**, NTM, sarcoidosis, prior pneumothorax/bullae, COPD, rheumatoid lung; subtle NK/IL-12/IFN-γ defects
Allergic (ABPA/SAFS)	**Asthma** and **cystic fibrosis** (incl. heterozygous *CFTR*); genetic TH2 predisposition; common in the Indian subcontinent
Saprophytic	Pre-existing pulmonary cavity (aspergilloma); maxillary sinus (fungal ball)

Classification and clinical manifestations

- **Invasive (acute ≤1 month / subacute 1–3 months):**

- *Invasive pulmonary aspergillosis* — >80% of invasive disease; fever, cough, pleuritic discomfort, trivial **haemoptysis**, dyspnoea (often asymptomatic). Fever may respond transiently to steroids while disease progresses; a frequent **autopsy-only** diagnosis.
- *Invasive sinusitis* — 5–10%, leukaemia/HSCT; nasal/facial pain, blocked nose, bloody discharge; endoscopy shows pale/dusky/necrotic mucosa.
- *Tracheobronchitis* — lung-transplant and ventilated patients; ulcerative/pseudomembranous; mucous-plug obstruction.
- *Disseminated/cerebral disease* — spread to **brain** (haemorrhagic infarction, abscess; rarely meningitis, mycotic aneurysm, granuloma), skin, thyroid, bone, kidney, GI tract, eye, heart valve; blood cultures almost always negative.
- *Endocarditis* — usually prosthetic-valve (intra-operative contamination) or in PWID; large vegetations, culture-negative.
- *Cutaneous* — purplish area → necrotic **eschar**; direct invasion at IV-catheter sites and in burns/trauma (esp. *A. flavus*).

- **Chronic pulmonary aspergillosis (CPA):**
  - *Chronic cavitary pulmonary aspergillosis (CCPA)* — one/more cavities expanding over months–years; >90% with prior lung disease; weight loss/fatigue may dominate; **life-threatening haemoptysis** is the key complication; untreated → *chronic fibrosing pulmonary aspergillosis* ("destroyed lung"). IgG positive in ~90%.
  - *Aspergilloma (fungal ball)* — fungal mass within a cavity; cough, haemoptysis, wheeze; ~10% resolve spontaneously.
  - *Aspergillus nodule* — 5–50 mm, may cavitate, mimics carcinoma; PET-avid; IgG positive ~65%.
- **Chronic sinusitis:** fungal ball of (maxillary) sinus — non-invasive, surgically curable; chronic invasive sinusitis — slowly destructive (ethmoid/sphenoid), *orbital apex syndrome* (**blindness + proptosis**), cavernous-sinus/carotid involvement; chronic granulomatous sinusitis — Middle East/India, *A. flavus*.
- **Allergic / saprophytic-allergic:**
  - *ABPA* — hypersensitivity to *A. fumigatus*; ~2.5% of referred asthmatics, up to 15% of CF teenagers; brown sputum casts, fleeting infiltrates, central **bronchiectasis**.
  - *Severe asthma with fungal sensitisation (SAFS)* — fungal sensitisation without full ABPA criteria; total IgE **<1000 IU/mL**. ABPA + SAFS = "fungal asthma."
  - *Allergic fungal rhinosinusitis* — perennial sinusitis, nasal polyps, eosinophilic mucin, **Charcot-Leyden crystals**.
- **Superficial:** keratitis (sight-threatening; treat with topical **natamycin 5%**), onychomycosis (toenail, diabetes), otitis externa (often *A. niger*).

Diagnosis

- **Microscopy/histology:** hyaline, narrow, **septate hyphae branching at acute (45°) angles**; tissue shows vascular invasion with infarction (angioinvasion) or necrosis.

- **Galactomannan antigen** (cell-wall) in serum and especially **BAL** — high sensitivity (>80%); BAL more sensitive than serum and essential in ventilated ICU patients where radiology is nonspecific; serum antigen often precedes clinical/radiological signs by days; sensitivity falls with antifungal therapy; rising levels predict worse outcome.
- **Serum (1,3)-β-D-glucan** — supportive but non-specific (positive in many fungi).
- **Real-time PCR** (sputum/serum/BAL) — fast and more sensitive than culture; useful combined with antigen.
- **Culture** — positive in only **10–30%** of invasive disease; *request fungal media/high-volume culture*; vital for **azole-susceptibility testing** (especially during therapy).
- **Aspergillus IgG antibody** — cornerstone of **chronic** disease diagnosis with characteristic imaging (positive ~90% CCPA).
- **ABPA serology:** *Aspergillus*-specific **IgE** (or positive skin-prick) + elevated **total IgE (usually >1000 IU/mL)** + eosinophilia; hyperattenuated/high-density mucus is highly specific.
- **Imaging:** CT thorax — **halo sign** (ground-glass of haemorrhagic infarction around a nodule; early, ~7 days, good prognosis in neutropenia), nodules, wedge/pleural-based infarcts, later cavitation/**air-crescent sign** (aspergilloma). Sinus CT/MRI; brain **MRI** preferred for cerebral disease. *Definitive* diagnosis = positive culture from a sterile site, or positive histology **plus** culture/molecular confirmation from affected tissue.

Treatment

Indication	Primary	Alternatives / notes
Invasive aspergillosis	**Voriconazole** or **isavuconazole** (azoles ~20% higher response than AmB)	Posaconazole; lipid AmB; caspofungin/micafungin (2nd line). ID consult; therapy 3 months–years until immune reconstitution
Chronic pulmonary (CCPA)	**Voriconazole** or **itraconazole**	Posaconazole; IV AmB/micafungin. **≥12 months**; avoid steroids (↑mortality ~240% unless antifungal cover)
ABPA / SAFS	**Itraconazole** + glucocorticoids (prednisone ~0.5 mg/kg/day, taper)	Voriconazole, posaconazole, inhaled AmB; long-term azole spares steroids
Single aspergilloma	**Surgical resection** (peri-operative antifungal cover)	Intracavitary AmB; medical Rx for multicavity disease
Sinus fungal ball / allergic sinusitis	Surgical removal ± endoscopic clearance	Local ± systemic steroids (allergic); ethmoidectomy if recurrent

- **Representative doses:** Voriconazole IV **6 mg/kg q12h ×2 loading then 4 mg/kg q12h** (oral 200 mg bid); isavuconazole 200 mg q8h ×6 doses (2 days) then 200 mg daily; posaconazole tablet 300 mg daily; caspofungin **70 mg load → 50 mg/day**; micafungin ≥150 mg/day (treatment); AmB deoxycholate 1 mg/kg/day; **lipid AmB 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet)**.
- **Therapeutic drug monitoring** is recommended for voriconazole, itraconazole, posaconazole and isavuconazole (variable absorption/metabolism, drug interactions).

- **Resistance:** multi-azole resistance in *A. fumigatus* ~**3–20%** (rising, esp. Southeast Asia; partly from agricultural azole fungicides); AmB inactive against ***A. terreus*** and ***A. nidulans***; ***A. niger*** resistant to isavuconazole.
- **Adjuncts: bronchial artery embolisation** for problematic haemoptysis; reverse immunosuppression; surgery for endocarditis, brain abscess, keratitis, endophthalmitis, proximal-lung lesions.
- **Prophylaxis** (AML induction, GVHD, high-risk HSCT): **posaconazole** (most effective) or voriconazole/itraconazole solution/SUBA-itraconazole; IV micafungin if azole-contraindicated. *Fluconazole has no anti-Aspergillus activity.*

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CT thorax spectrum of pulmonary aspergillosis** — label: (1) *halo sign* = nodule with surrounding ground-glass (early invasive/neutropenic); (2) *air-crescent sign* = crescent of air around a fungal ball (recovery); (3) *aspergilloma* = mobile fungal ball within an upper-lobe cavity with pleural thickening.
- **Tissue microscopy of Aspergillus** — label: hyaline **septate hyphae**, dichotomous **branching at 45° (acute) angle**, progressive width; inset of **conidiophore** with radiating chains of **conidia** (culture morphology); contrast note: broad, aseptate, right-angle hyphae = *Mucor* (differential).

Clinical / Diagnostic significance

- The single most useful discriminator is the **host**: neutropenia → invasive/angioinvasive; structurally damaged lung → chronic/aspergilloma; atopic asthma/CF → allergic.
- In India, **CCPA is a major mimic of, and sequel to, pulmonary TB** (follows treated TB in ~6–13%) — suspect in "smear-negative TB" or relapsing cavitary disease with weight loss; check **Aspergillus IgG**.
- In neutropenic/leukaemic and ICU/post-influenza/COVID patients, screen with **serum/BAL galactomannan** and urgent **CT thorax**; a *halo sign* warrants pre-emptive therapy.
- **ABPA** must be sought in poorly controlled asthma (total IgE >1000 IU/mL, specific IgE, eosinophilia, central bronchiectasis) — treatable, prevents fibrosis.
- Differentiate angioinvasive aspergillosis from **mucormycosis** (broad, aseptate, right-angle hyphae; AmB- rather than voriconazole-responsive) — management diverges sharply.

High-yield exam pointers

- *A. fumigatus* = most invasive/chronic/allergic disease; *A. flavus* = sinus/cutaneous/keratitis & granulomatous sinusitis (India/Middle East).
- **Septate hyphae, acute-angle (45°) dichotomous branching** — the classic histology buzz-phrase.
- **Galactomannan** (serum/BAL) and **β-D-glucan** are key non-culture markers; culture positive in only 10–30% of invasive disease.
- Radiology: **halo sign** (early), **air-crescent sign** (recovery/aspergilloma).
- ABPA hallmark: **total IgE usually >1000 IU/mL** + *Aspergillus*-specific IgE + central bronchiectasis + brown mucus plugs.

- First-line invasive therapy: **voriconazole or isavuconazole**; voriconazole IV **6 mg/kg q12h load → 4 mg/kg q12h**.
- **AmB does NOT cover *A. terreus* or *A. nidulans*; *A. niger* is isavuconazole-resistant; fluconazole has NO anti-Aspergillus activity.**
- **Surgery cures** single aspergilloma and sinus fungal ball; **bronchial artery embolisation** for massive haemoptysis.
- Mortality: invasive **30–70%** if treated (**100% if missed**); CCPA ~15–20% at 1 year, ~40% at 5 years, 50–60% at 10 years.
- Avoid glucocorticoids in CCPA (mortality up ~240%) unless covered by antifungals.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Aspergillosis" (Denning), incl. Tables 223-1/2/3 (disease frequency & diagnostic sensitivity, manifestations, treatment).
- **CMDT 2026** — "Mycotic Infections" (Aspergillosis: allergic/chronic/invasive forms, diagnosis, prevention and IDSA/ESCMID-ECMM-ERS treatment regimens and doses).
- *Coverage note:* The *air-crescent sign* and the *Aspergillus*-vs-*Mucor* hyphal contrast are standard, universally accepted radiology/microbiology added for completeness; Harrison explicitly describes the halo sign, cavitation, 45° septate hyphae and the broad differential rather than naming the "air-crescent sign." Detailed ISHAM/formal ABPA criteria beyond IgE thresholds are not enumerated in the corpus; the serological criteria given are those stated in Harrison/CMDT.

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Chronic meningitis in HIV infection

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Chronic meningitis is diagnosed when a characteristic neurologic syndrome persists for **>4 weeks** in association with a **persistent CSF inflammatory response (white cell count >5/μL)**. Unlike acute meningitis, meningeal signs are often *absent*; the cardinal features are persistent headache, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive/personality change. Correct treatment depends entirely on identifying the etiology, which spans infective, malignant, inflammatory and chemical causes. In *advanced HIV/AIDS*, chronic meningitis is common, may present with minimal symptoms even with a paucicellular CSF, and is dominated worldwide by *Mycobacterium tuberculosis* and *Cryptococcus neoformans*.

Classification of the Causes of Chronic Meningitis

Five major disease categories account for most cases (Harrison), with monogenic autoinflammatory disorders added as an emerging cause of recurrent meningitis.

Category	Representative causes
1. Meningeal infections	**Bacterial:** partially treated pyogenic meningitis, *M. tuberculosis*, *Treponema pallidum* (syphilis), *Borrelia burgdorferi* (Lyme/Bannwarth), *Brucella*, *Nocardia*, *Actinomyces*, *Tropheryma whipplei*, leptospira
	Fungal: *Cryptococcus neoformans/gattii*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces*, *Candida*, *Aspergillus*, *Sporothrix schenckii*
	Protozoal: *Toxoplasma gondii*, trypanosomiasis, *Acanthamoeba*, *Balamuthia*
	Helminthic: neurocysticercosis (*Taenia solium*), *Gnathostoma*, *Angiostrongylus cantonensis*, *Baylisascaris*, schistosomiasis, echinococcus
	Viral: HSV-2 (Mollaret), mumps, LCMV, enteroviruses (in agammaglobulinemia), HIV, EBV, CMV
2. Malignancy (neoplastic)	Carcinomatous/lymphomatous meningitis — metastatic breast, lung, stomach, pancreas; melanoma; lymphoma; leukemia; meningeal gliomatosis
3. Autoimmune / inflammatory	Neurosarcoidosis, Behçet's, SLE, rheumatoid arthritis, granulomatosis with polyangiitis, primary CNS (granulomatous) angiitis, Vogt–Koyanagi–Harada syndrome, IgG4-related hypertrophic pachymeningitis, Sjögren's
4. Chemical meningitis	Leak from epidermoid/dermoid tumour, craniopharyngioma or cholesteatoma; subarachnoid haemorrhage; intrathecal drug/contrast injection; drug hypersensitivity (NSAIDs, sulfonamides, IVIG, isoniazid, carbamazepine, lamotrigine)
5. Parameningeal infection	Brain/epidural/subdural abscess, sinusitis, mastoiditis, otitis media, chronic pleuropulmonary infection with right-to-left shunt
6. Monogenic autoinflammatory (recurrent)	TRAPS (*TNFRSF1A*), CAPS/NOMID (*NLRP3* gain-of-function → ↑IL-1β), complement factor I deficiency

Recurrent Meningitis — a Distinct Subset

Two clinical forms exist: a *chronic persistent* form and a *recurrent* form in which all symptoms, signs and CSF abnormalities resolve completely between attacks. Recurrent meningitis suggests:

- **Mollaret's meningitis** — most often **HSV-2** (rarely HSV-1); large endothelial ("Mollaret") cells then mononuclear cells in CSF; confirm by HSV PCR.
- **Chemical (episodic) meningitis** — recurrent leak from an epidermoid tumour, craniopharyngioma or cholesteatoma; xanthochromia/low glucose.
- **Autoimmune** — VKH syndrome, Behçet's, SLE, neurosarcoidosis, IgG4-related disease, GPA, primary CNS vasculitis.
- **Drug hypersensitivity** — recurs with re-exposure to the offending agent.
- **Inherited autoinflammatory syndromes** — TRAPS, CAPS, complement factor I deficiency (recurrent steroid-responsive neutrophilic meningitis).

CSF Clues that Narrow the Differential

The predominant CSF cell type after the third week is a powerful discriminator.

CSF pattern	Principal considerations
Mononuclear (lymphocytic)	Most chronic meningitides — TB, *Cryptococcus*, syphilis, Lyme, sarcoidosis, neoplastic
Neutrophilic after 3 weeks	*Nocardia*, *Actinomyces*, *Brucella*, *M. tuberculosis* (5–10% of early cases), fungi (*Blastomyces*, *Candida*, *Histoplasma*, *Aspergillus*, *Pseudallescheria boydii*, *Cladophialophora*), SLE, chemical meningitis
Eosinophilic	Parasites (*A. cantonensis*, *Gnathostoma*, *Baylisascaris*, cysticercosis, schistosomiasis, echinococcus, toxoplasma), coccidioidomycosis (6–20% eosinophils), lymphoma/leukaemia/carcinoma, sarcoidosis, hypereosinophilic syndrome
Low glucose (hypoglycorrhachia)	TB, fungal (esp. *Cryptococcus*, *Coccidioides*, *Histoplasma*), carcinomatous/lymphomatous, sarcoidosis, mumps, LCMV

Imaging clue: **leptomeningeal** enhancement (following gyri/basal cisterns) typifies infective meningitis, whereas thick linear/nodular **pachymeningeal** (dural) enhancement suggests IgG4-related disease, GPA, lymphoma or neurosarcoidosis.

Etiologies in Advanced HIV Infection (the "discuss" component)

Chronic meningitis is not uncommon in HIV; immunosuppression *attenuates* meningeal signs, so CSF examination is mandatory for any persistent headache or unexplained mental change. The relevant pathogens track with the **CD4 count**.

Etiology (CD4 threshold)	Key features / CSF–imaging	Treatment (Harrison/CMDT)
Cryptococcal meningitis (CD4 **<100**)	Commonest fungal CNS infection in AIDS; AIDS-defining in ~2%; subacute meningoencephalitis, **markedly raised ICP**, often pauci-cellular CSF; India ink + **CSF cryptococcal antigen (CrAg)**; up to 12% due to *C. gattii*; *prozone* false negatives	**Induction:** liposomal amphotericin B 3–4 mg/kg/day (or amphotericin B deoxycholate 0.7–1.0 mg/kg/day) + **flucytosine 25 mg/kg qid for ≥2 weeks → consolidation** fluconazole (Harrison 800 mg, CMDT 400 mg) daily ×8 weeks → **maintenance** fluconazole 200 mg/day until CD4 >200 for ≥6 months. Serial LPs for ICP; **delay ART 4–6 weeks** (IRIS risk)
Tuberculous meningitis (any CD4; commonest cause **worldwide**)	Basal meningitis, cranial neuropathies, stroke from arteritis; CSF: lymphocytic, **low glucose, high protein**; AFB smear/culture, **CSF PCR (Xpert)**, IGRA; miliary TB on imaging	4-drug ATT (HRZE) + **adjunctive glucocorticoids**; anti-TNF/PD-1 therapy can reactivate TB
Cerebral toxoplasmosis (CD4 **<200**)	Reactivation of latent cysts; fever, focal deficit, seizures; MRI **multiple ring-enhancing lesions**, *eccentric target sign*; 10× more likely if *Toxoplasma* IgG-positive	**Sulfadiazine + pyrimethamine + leucovorin** ≥4–6 weeks (alt: clindamycin + pyrimethamine); empiric trial, biopsy if no response in 2–4 weeks; primary prophylaxis with TMP-SMX if CD4 <100 and IgG+
Primary CNS lymphoma (CD4 **~50**)	**EBV-driven** (often 100% EBV+); 1–3 deep white-matter lesions, ring-enhancing (less than toxoplasmosis); CSF EBV PCR; brain biopsy	Radiotherapy ± chemotherapy + ART; 2-year survival only 20–30%

Etiology (CD4 threshold)	Key features / CSF–imaging	Treatment (Harrison/CMDT)
Progressive multifocal leukoencephalopathy	**JC virus**; multifocal deficits, **non-enhancing** occipito-parietal white-matter lesions; CSF JCV DNA (sensitivity 76%, specificity ~100%)	No specific therapy — **immune reconstitution with ART** is the mainstay
Neurosyphilis	Meningovascular stroke, dementia, myelopathy; **CSF VDRL** (specific, insensitive); aggressive in HIV	IV penicillin G
CMV polyradiculopathy/encephalitis (CD4 <**50**)	Fulminant cauda-equina syndrome, urinary retention; **neutrophilic CSF**, CMV PCR	IV ganciclovir / foscarnet
Aseptic (HIV) meningitis	At seroconversion (acute retroviral syndrome) or persisting low-grade; immune-mediated, rare after AIDS develops; lymphocytic CSF, HIV RNA	Supportive; ART
Other fungi / bacteria	*Histoplasma* (CD4 ~33), *Coccidioides*, *Nocardia*, *Candida*; basis for empiric antifungal cover	Amphotericin B-based regimens

Diagnostic Approach in the HIV Patient

- **Image before LP** if raised ICP / mass lesion suspected (herniation risk); obstructive hydrocephalus needs ventricular drainage.
- Send **opening pressure**, cell count + differential, glucose, protein, Gram/India ink, **CrAg**, **VDRL**, AFB smear/culture + **TB PCR**, fungal culture, cytology/flow cytometry, and broad-range **16S/18S rRNA PCR** or **metagenomic next-generation sequencing** in enigmatic cases.
- Repeat **large-volume CSF (≥3 samples)** for neoplastic/fungal causes; cervical cisternal tap if lumbar CSF unrevealing.
- **Meningeal biopsy** when CSF is non-diagnostic and the patient is deteriorating — target enhancing meninges (diagnostic in 80% vs 9% for non-enhancing regions).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Classification wheel of chronic meningitis:** central hub "Chronic meningitis (>4 weeks, CSF WBC >5/μL)" with six labelled spokes — *Meningeal infection*, *Malignancy*, *Autoimmune/inflammatory*, *Chemical*, *Parameningeal infection*, *Autoinflammatory (recurrent)*; annotate infection spoke with *TB, Cryptococcus, syphilis, Lyme*.
- **Diagram 2 — CD4 ladder of HIV CNS opportunistic infections:** vertical axis falling CD4 with labelled bands — *<200: Toxoplasma, TB*; *<100: Cryptococcus, Histoplasma*; *~50: Primary CNS lymphoma, CMV*; *late/any: PML, neurosyphilis*; label MRI signatures (toxoplasmosis = ring-enhancing/eccentric target; lymphoma = deep solitary; PML = non-enhancing white matter).

Clinical / Diagnostic significance

- A **lymphocytic meningitis with low CSF glucose** in any setting should be treated empirically for **tuberculosis**, as delay is devastating.
- In AIDS, **cryptococcal meningitis can cause fatal raised ICP without ventricular enlargement** — serial therapeutic LPs are lifesaving.
- **Ring-enhancing lesions** in HIV = toxoplasmosis vs primary CNS lymphoma; *Toxoplasma* IgG-negativity (<10% probability) or CSF EBV PCR positivity shifts toward lymphoma and earlier biopsy.
- **IRIS** complicates ART started too early after cryptococcal/TB meningitis — hence the recommended antifungal/anti-TB lead-in before ART.
- Empirical therapy when diagnosis fails: **antimycobacterials + amphotericin B (± flucytosine) ± glucocorticoids**; transient steroid responses can mask TB, cysticercosis or lymphoma.

High-yield exam pointers

- Definition: neurologic syndrome **>4 weeks** + CSF WBC **>5/μL**.
- **Five-category classification:** infection, malignancy, autoimmune, chemical, parameningeal (+ autoinflammatory for recurrent).
- **Worldwide commonest cause in HIV = TB, then Cryptococcus.**
- **Mollaret's = recurrent HSV-2 meningitis.**
- Cryptococcal Rx triad: **amphotericin B + flucytosine (induction) → fluconazole (consolidation → maintenance)**; treat raised ICP.
- Toxoplasmosis Rx = **sulfadiazine + pyrimethamine + leucovorin**; CD4 <200; ring-enhancing lesions.
- **PCNSL = EBV-positive**, CD4 ~50; **PML = JC virus**, non-enhancing.
- Empiric anti-TB therapy for low-glucose lymphocytic chronic meningitis; ~one-third of cases remain undiagnosed despite full workup.
- Biopsy yield highest from **contrast-enhancing meninges** (80%).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Chronic and Recurrent Meningitis"* (classification, CSF/biopsy clues, empiric therapy, immunosuppressed host) and *"Human Immunodeficiency Virus Disease: AIDS and Related Disorders"* (CNS opportunistic infections, CD4 thresholds, MRI patterns, treatment regimens).
- **CMDT 2026** — *"HIV Infection & AIDS"* (current induction–consolidation–maintenance regimens for cryptococcal meningitis and CMV; opportunistic-infection management).

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Neurosyphilis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Neurosyphilis is involvement of the central nervous system by *Treponema pallidum* and can occur at any stage of syphilis, not only in late disease. It is best viewed as a continuum: early CNS invasion within weeks, months to years of asymptomatic CSF involvement, and symptomatic early or late neurologic syndromes. Ocular syphilis and otosyphilis may occur with or without other CNS disease but are treated with the same regimen as neurosyphilis because permanent visual or hearing loss may occur.

Etiopathogenesis and natural history

- *T. pallidum* disseminates early; CSF abnormalities may be found in up to **40%** of untreated primary/secondary syphilis and **25%** of untreated latent syphilis.
- Early neurosyphilis includes **asymptomatic neuroinvasion**, **syphilitic meningitis**, and **meningovascular syphilis**. Late neurosyphilis includes **general paresis** and **tabes dorsalis**.
- Approximate timing is exam-important: meningeal disease usually occurs within **<1 year**, meningovascular disease up to **10 years**, general paresis around **20 years**, and tabes dorsalis around **25-30 years** after infection.
- Risk is higher with untreated HIV infection, especially low CD4 counts; Harrison notes association with serum **RPR >=1:32** and, in HIV, CD4 **<=350/mcL**.
- Benzathine penicillin does not reliably achieve treponemicidal CSF levels; therefore proven or suspected neurosyphilis needs **aqueous penicillin-based therapy**, not standard benzathine-only syphilis therapy.

Clinical classification and features

Form	Core clinical features	Typical CSF clue
Asymptomatic neurosyphilis	No neurologic symptoms/signs; detected during evaluation of syphilis, tertiary disease, HIV/high-risk state, or treatment failure	Mononuclear pleocytosis, raised protein, or reactive CSF-VDRL
Meningeal syphilis	Headache, nausea, vomiting, neck stiffness, cranial nerve palsy, seizures, altered mental status; may accompany or follow secondary syphilis	Lymphocytic pleocytosis and raised protein; CSF-VDRL may be positive

Form	Core clinical features	Typical CSF clue
Meningovascular syphilis	Meningitis plus vasculitis of small/medium/large vessels; subacute prodrome of headache, vertigo, insomnia, psychological change, then progressive stroke syndrome, classically in a young adult and often MCA territory	Higher lymphocytic pleocytosis may occur; CMDT gives **100-1000 cells/mcL** with elevated protein
General paresis	Progressive cortical disease: personality change, affective disturbance, hyperreflexia, *Argyll Robertson pupil*, psychosis, memory loss, impaired orientation/calculation/judgment, dysarthria, tremor	Similar to late parenchymatous neurosyphilis; CSF may resemble tabes
Tabes dorsalis	Posterior column/dorsal root disease: lightning pains, sensory ataxia, positive Romberg, impaired position/vibration sense, areflexia, bladder disturbance, impotence, foot drop, Charcot joint, optic atrophy	Normal or lymphocytic CSF, raised protein, variable serology

Ocular, otic and HIV-associated disease

- **Ocular syphilis** may present as anterior uveitis, iritis, neuroretinitis, optic neuritis, chorioretinitis, optic atrophy, or panuveitis; failure to respond to topical steroids is a classic diagnostic clue.
- **Otosyphilis** presents with sensorineural hearing loss, vertigo, or tinnitus; untreated disease may lead to deafness.
- Ask every patient with syphilis about **vision, hearing, headache, cognitive change, stroke symptoms, gait ataxia, bladder symptoms, lightning pains, and cranial nerve symptoms**.
- Isolated confirmed ocular disease with reactive syphilis serology and no cranial nerve or other neurologic abnormality does **not** require CSF before treatment; full ocular examination is mandatory.
- Isolated auditory disease with reactive serology and normal neurologic examination usually has normal CSF and does **not** require CSF before treatment.
- Ocular syphilis and otosyphilis are treated **as neurosyphilis regardless of CSF findings**.
- In HIV infection, mild CSF pleocytosis may occur due to HIV itself; routine lumbar puncture in asymptomatic patients is not recommended, but a careful neurologic, ophthalmic, otologic, and cranial nerve examination is essential.

Diagnostic approach

- Establish syphilis first using both **nontreponemal** and **treponemal** serology; one test alone is insufficient. Nontreponemal tests are **VDRL/RPR** and are useful for titers and follow-up; treponemal tests include **FTA-ABS, TPPA, EIA/CIA**.
- Consider neurosyphilis when reactive syphilis serology is accompanied by neurologic signs/symptoms or compatible CSF abnormalities.
- **Indications for lumbar puncture:** clinical neurologic involvement such as meningitis, cranial nerve palsy, stroke, altered mental status, motor/sensory deficit, loss of vibration sense; treatment

failure or fourfold rise in titer; active tertiary syphilis; ocular disease with cranial nerve or other neurologic signs.

- **CSF findings:** mononuclear pleocytosis **>5 WBC/mcL**, protein **>45-46 mg/dL**, and/or reactive **CSF-VDRL**. Classic CMDT description is protein >46 mg/dL with lymphocytic pleocytosis **5-100 cells/mcL**.
- **CSF-VDRL** is highly specific; a positive result without blood contamination is diagnostic. It is insensitive and may be negative in **30-70%** of cases, so a negative test does not exclude neurosyphilis.
- **CSF-RPR should not replace CSF-VDRL**. CSF FTA-ABS/TPPA is more sensitive but less specific; a negative result makes neurosyphilis unlikely, especially with nonspecific symptoms.
- In HIV infection, specificity improves by using a higher CSF WBC cutoff, commonly **>20 WBC/mcL**, because HIV itself may cause mild CSF pleocytosis.
- Differential diagnoses to exclude according to presentation include viral/tuberculous/fungal/chronic meningitis, autoimmune encephalitis, HIV-associated neurocognitive disorder, B12 or copper myelopathy, stroke in the young, multiple sclerosis, neuro-ophthalmic disease, and primary psychiatric illness.

Treatment

Situation	Recommended regimen	Key notes
Neurosyphilis, ocular syphilis, otosyphilis	**Aqueous crystalline penicillin G 18-24 million units/day IV** as 3-4 million units every 4 hours or continuous infusion for **10-14 days**	Drug of choice; achieves treponemicidal CSF levels
Alternative when adherence assured	**Procaine penicillin G 2.4 million units IM daily + probenecid 500 mg orally four times daily**, both for **10-14 days**	Avoid if adherence is doubtful
Penicillin allergy	Prefer **penicillin desensitization** and treatment with penicillin	Especially important in pregnancy and definite neurosyphilis
Limited alternative	**Ceftriaxone 1-2 g IM/IV daily for 10-14 days** with close follow-up	Evidence is limited; seek infectious disease input
After neurosyphilis regimen	Benzathine penicillin G 2.4 million units IM weekly for **1-3 weeks** may be considered to match latent-syphilis duration	Not a substitute for CNS-active therapy

- Admit or closely supervise patients requiring IV therapy; patients with ocular disease need ophthalmology, and otosyphilis needs ENT/audiology involvement.
- Do **HIV testing** in all patients with syphilis/neurosyphilis; offer prevention counselling and partner notification where relevant.
- Treat **Jarisch-Herxheimer reaction** supportively: fever, chills, headache, myalgia, tachycardia, and transient worsening after therapy are not penicillin allergy. Use antipyretics; consider expert input in CNS/cardiac disease and pregnancy.

- Existing parenchymal damage may only stop progressing after treatment; meningeal symptoms respond more dramatically than tabetic or paretic deficits.

Follow-up, prognosis and complications

- Monitor clinically and with quantitative **RPR or VDRL** using the same test method; CMDT recommends nontreponemal titers every **3-6 months** after neurosyphilis treatment.
- Adequate response is suggested by clinical improvement and falling serum nontreponemal titers; a fourfold RPR decline correlates with CSF normalization in many treated patients.
- Repeat CSF is not routinely needed when symptoms improve and titers fall appropriately, especially in HIV-negative patients or HIV-positive patients on effective ART.
- Repeat CSF or expert consultation is needed if symptoms persist/return, titers fail to fall or rise fourfold, or treatment failure/reinfection is suspected.
- CSF WBC count is the most sensitive CSF marker of response and generally normalizes within **3-12 months**; CSF protein falls more slowly and CSF-VDRL may decline over years.
- Major preventable complications are stroke, blindness, deafness, dementia/psychosis, sensory ataxia, bladder dysfunction, Charcot joints, and irreversible posterior column or cortical damage.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Natural history timeline of neurosyphilis:** primary/secondary syphilis -> early CNS invasion/asymptomatic CSF -> meningeal syphilis (<1 year) -> meningovascular syphilis (years) -> general paresis (~20 years) -> tabes dorsalis (25-30 years).
- **Diagnostic-treatment flowchart:** reactive serum RPR/VDRL + treponemal test -> neurologic/ocular/otic symptoms? -> ocular/ENT/neurologic examination -> CSF cell count, protein, CSF-VDRL +/- FTA-ABS/TPPA -> IV aqueous penicillin G 10-14 days -> clinical and serologic follow-up.

Clinical / Diagnostic significance

- Neurosyphilis is a **treatable mimic** of meningitis, stroke in the young, dementia, psychiatric illness, sensory ataxia, and posterior column myelopathy.
- Always examine pupils: **Argyll Robertson pupil** is small/irregular and accommodates but does not react to light; it is high-yield in tabes dorsalis and paresis.
- A negative CSF-VDRL does not rule out disease; the diagnosis is a **clinic-serologic-CSF synthesis**, not a single-test diagnosis.
- Do not delay ocular or otic treatment while waiting for CSF when isolated ocular/otic disease is otherwise clear.
- Benzathine penicillin is correct for uncomplicated latent syphilis but **wrong as sole therapy** for neurosyphilis because of inadequate CSF penetration.
- In HIV, interpret mild CSF pleocytosis cautiously; treatment regimen is the same, but follow-up must be meticulous.

High-yield exam pointers

- Write first: **Neurosyphilis can occur at any stage of syphilis**.

- Classification: **asymptomatic, meningeal, meningovascular, ocular/otic, tabes dorsalis, general paresis**.
- Meningovascular syphilis: young patient + subacute encephalitic prodrome + stroke, often MCA territory.
- Tabes dorsalis: lightning pains, sensory ataxia, Romberg sign, areflexia, bladder dysfunction, Charcot joint.
- General paresis: personality change, psychosis, memory/judgment impairment, dysarthria, tremor, hyperreflexia.
- Diagnostic triad: reactive serum serology + neurologic syndrome + CSF pleocytosis/protein/reactive CSF-VDRL.
- **CSF-VDRL positive = diagnostic; negative = does not exclude**.
- Treatment: **aqueous crystalline penicillin G 18-24 million units/day IV for 10-14 days**.
- Follow response with clinical status and quantitative RPR/VDRL; repeat CSF only when response is poor or uncertain.

> **SOURCE & COVERAGE**
> Harrison 22e — "Syphilis"; CMDT 2026 — "Spirochetal Infections" and "Common Problems in Infectious Diseases & Antimicrobial Therapy".

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Clostridium difficile infection

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Clostridioides difficile infection (CDI) is an antibiotic-associated colonic infection caused by toxigenic, spore-forming, obligate anaerobic, gram-positive bacilli. It follows disruption of normal colonic microbiota, usually after antimicrobial exposure, and ranges from mild watery diarrhea to **pseudomembranous colitis**, toxic megacolon, sepsis, perforation and death. Although the older exam term is *Clostridium difficile*, the current nomenclature is **Clostridioides difficile**.

Etiology, epidemiology and risk factors

- **Organism:** spore-forming anaerobic bacillus; spores survive gastric acidity, persist for months on hospital surfaces and spread by contaminated hands, equipment and patient-room environments.
- **Usual setting:** hospitals, nursing homes and the period after discharge; community-associated CDI is increasingly recognized and may occur without documented antibiotic exposure.
- **Antibiotic risks:** clindamycin, ampicillin, second- and third-generation cephalosporins and fluoroquinolones are classic high-risk drugs. Almost any antibiotic can predispose, including vancomycin, by disturbing colonization resistance.
- **Lower-risk but not risk-free agents:** penicillin/beta-lactamase-inhibitor combinations such as piperacillin-tazobactam are less strongly associated than cephalosporins or fluoroquinolones.

- **Host and care-related risks:** older age, severe underlying illness, prolonged hospitalization, gastrointestinal surgery, enteral tube feeding, antacid/PPI exposure, immunocompromise, IBD, chemotherapy, multiple or prolonged antibiotic courses and chronic-care facility residence.
- **Colonization:** asymptomatic fecal carriage increases with length of hospital stay and may exceed 20% after more than 2 weeks in hospital; healthy community adult carriage is much lower. Infants commonly carry C. difficile but rarely develop disease.
- **Epidemic strains:** NAP1/BI/027 produces much higher toxin A and B in vitro, carries binary toxin, is fluoroquinolone-resistant and was linked to severe outbreaks; its incidence has declined where infection control and fluoroquinolone restriction were implemented.

Pathogenesis and pathology

- CDI requires three events: **microbiota disruption** by antibiotics, **exposure to toxigenic C. difficile**, and an additional susceptibility factor such as a virulent strain or inadequate antitoxin immune response.
- Spores are ingested, germinate in the small bowel and colonize the lower gut when normal flora are suppressed.
- Toxigenic strains produce **toxin A (enterotoxin)** and **toxin B (cytotoxin)**. Both glucosylate Rho-family GTP-binding proteins, disrupt actin cytoskeleton, impair epithelial adherence and tight junctions, and cause fluid leakage and inflammation.
- **Toxin B** is clinically crucial because toxin A-negative, toxin B-positive strains can cause disease; toxin B-negative disease is not well documented.
- **Binary toxin CDT** is present in NAP1/BI/027 and some other strains, but its exact pathogenic role is less clearly defined.
- **Pseudomembranes** begin as 1-2 mm whitish-yellow plaques on colonic mucosa, then coalesce; microscopy shows necrotic leukocytes, fibrin, mucus and cellular debris with focal epithelial necrosis and neutrophilic mucosal infiltration.
- The colon is usually involved diffusely, but rectal sparing can occur; terminal ileum is typically spared.
- Serum antibodies to toxins A and B, especially toxin B-neutralizing responses, help protect against recurrence; this is the rationale for bezlotoxumab.

Clinical features and severity

- **Typical CDI:** soft, watery or mucoid diarrhea with characteristic odor; stools are seldom grossly bloody. Lower abdominal cramps, mild tenderness and mucus may occur.
- **Frequency:** CMDT describes many patients with 3-15 watery stools/day; Harrison notes fever in about 28%, abdominal pain in 22% and leukocytosis in 50%.
- **Diagnostic trap:** ileus or adynamic colon may stop stool passage, so CDI can present as unexplained leukocytosis, abdominal distension or acute abdomen without diarrhea.
- **Severe CDI:** leukocytosis >=15,000/mcL or serum creatinine >=1.5 mg/dL; severe disease is common among hospitalized diagnosed cases.

- **Fulminant CDI:** severe CDI plus **hypotension, shock, ileus or toxic megacolon**. It may mimic a surgical abdomen and can present with sepsis, tachycardia, marked leukocytosis, colonic wall thickening, ascites and metabolic acidosis.
- **Complications:** toxic megacolon, perforation, hemorrhage, respiratory failure, septic shock, colectomy requirement, protein-losing enteropathy in chronic untreated colitis and death.
- **Recurrence:** occurs in about 15-30% after treatment in Harrison and up to 20% within 8 weeks in CMDT; recurrence may be relapse with the same strain or reinfection with a new strain.

Clinical setting	Key markers	Exam management implication
Nonsevere CDI	Diarrhea, no severe leukocytosis/creatinine rise	Fidaxomicin preferred; oral vancomycin acceptable
Severe CDI	WBC >=15,000/mcL or creatinine >=1.5 mg/dL	Treat promptly; monitor closely for fulminant disease
Fulminant CDI	Hypotension, shock, ileus or megacolon	High-dose enteral vancomycin + IV metronidazole, surgical review
Recurrent CDI	Return after clinical response	Fidaxomicin, vancomycin taper/pulse, microbiota therapy in repeated relapse

Diagnosis

- Diagnose only when the clinical syndrome fits: **>=3 unformed stools in 24 hours** with no better explanation plus evidence of toxigenic C. difficile or pseudomembranes. Harrison uses >=3 unformed stools per 24 h for >=2 days in its formal criteria.
- Send stool testing in hospitalized patients with dysentery or >=3 liquid stools/24 h, and in outpatients with persistent diarrhea, especially after antibiotics or hospitalization.
- **Do not test formed stool** and do not test asymptomatic patients except for epidemiology; positive tests may reflect colonization.
- **Do not perform test of cure:** stool assays may remain positive for weeks, and more than half of patients may still harbor organism/toxin after diarrhea stops.
- **GDH immunoassay:** sensitive screen with high negative predictive value, but detects toxigenic and nontoxigenic strains and does not prove active toxin disease.
- **NAAT/PCR:** rapid and very sensitive for toxin genes, commonly TcdB, but may overdiagnose colonization if used alone.
- **Toxin EIA:** detects free toxins A/B and supports active toxin-secreting infection, but is less sensitive than NAAT/culture.
- **Preferred algorithm:** GDH or NAAT screening followed by toxin EIA when required, with discordant results interpreted clinically.
- **Endoscopy:** flexible sigmoidoscopy/colonoscopy is not routine when symptoms and stool tests are typical, but is useful in seriously ill patients, atypical cases or ileus. Pseudomembranes are highly specific but insensitive and may be seen in only a subset.
- **Imaging:** abdominal radiograph or CT is indicated in severe/fulminant disease to assess colonic dilation, wall thickening, ascites and perforation.

Treatment

- **Immediate general measures:** isolate with contact precautions, stop the inciting antibiotic if possible, correct dehydration/electrolytes and avoid opiates or antiperistaltic agents in severe disease because they may mask deterioration.
- **Initial nonsevere CDI:** fidaxomicin **200 mg orally twice daily for 10 days** is preferred where available; oral vancomycin **125 mg four times daily for 10 days** is an acceptable alternative.
- **Metronidazole:** no longer first-line; use **500 mg orally three times daily for 10-14 days** only for mild/moderate disease when fidaxomicin or oral vancomycin is unavailable.
- **Severe initial CDI:** oral vancomycin **125 mg four times daily for 10 days** or fidaxomicin **200 mg twice daily for 10 days**; initiate promptly when WBC is high or creatinine is elevated.
- **Fulminant CDI:** vancomycin **500 mg orally or via nasogastric tube four times daily** plus metronidazole **500 mg IV every 8 hours**; if ileus is present, add rectal vancomycin **500 mg in 100 mL normal saline retention enema every 6-8 hours**.
- **IV vancomycin alone is ineffective** for CDI because adequate intraluminal colonic drug levels are not achieved.
- **Early surgical consultation** is essential for severe/fulminant disease, toxic megacolon, perforation, sepsis or hemorrhage. Total abdominal colectomy may be lifesaving; loop ileostomy with colonic lavage and vancomycin infusion is an alternative. Harrison emphasizes operating before serum lactate reaches 5 mmol/L when colectomy is required.

Recurrence, adjunctive therapy and prevention

- **First recurrence:** fidaxomicin **200 mg twice daily for 10 days**, oral vancomycin **125 mg four times daily for 10 days**, or vancomycin taper-and-pulse depending on prior regimen and availability.
- **Vancomycin taper/pulse:** after a treatment course, 125 mg twice daily for 1 week, then daily for 1 week, then every 2-3 days for 2-8 weeks; CMDT also describes 125 mg four times daily for 14 days before tapering.
- **Multiple recurrences:** vancomycin taper/pulse, fidaxomicin standard or extended-pulsed regimen, vancomycin followed by rifaximin **400 mg twice daily for 2 weeks**, or fecal microbiota replacement.
- **Microbiota therapy:** consider after appropriate antibiotic treatment for recurrent CDI. Rebyota is rectal live-jslm fecal microbiota; Vowst is oral live-brpk fecal microbiota spores. CMDT notes 2023 FDA approval to prevent recurrence after antibacterial treatment.
- **Bezlotoxumab:** single-dose **10 mg/kg IV** monoclonal antibody against toxin B, given during standard antibacterial therapy for patients at high recurrence risk: age >65 years, immunocompromise, severe CDI or CDI in the previous 6 months. Avoid or use great caution in patients with heart failure.
- **Transmission prevention:** gloves, strict contact precautions, soap-and-water handwashing during outbreaks because alcohol gels are not sporicidal, bleach/hypochlorite environmental decontamination and avoidance of contaminated electronic rectal thermometers.

- **Antimicrobial stewardship:** restrict unnecessary clindamycin, cephalosporins and fluoroquinolones; stewardship reduces CDI and microbiome injury. Vaccines have not yet succeeded.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis flow diagram:** antibiotic exposure -> loss of normal microbiota -> ingestion of C. difficile spores -> germination and colonization -> toxin A/toxin B production -> epithelial cytoskeleton disruption -> diarrhea/pseudomembranes -> fulminant colitis or recurrence. Label: spores, antibiotics, microbiota disruption, toxin A, toxin B, pseudomembrane, recurrence.
- **Diagnostic-treatment algorithm:** suspected CDI with >=3 unformed stools/24 h -> stool GDH/NAAT plus toxin EIA -> classify nonsevere/severe/fulminant -> fidaxomicin or oral vancomycin; fulminant branch to high-dose enteral/rectal vancomycin + IV metronidazole + surgery. Label: GDH, NAAT, toxin EIA, WBC >=15,000, creatinine >=1.5, ileus/megacolon, recurrence.

Clinical / Diagnostic significance

- Always ask about antibiotics in the previous weeks; CMDT notes symptoms may be delayed up to 8 weeks after exposure.
- CDI is a key cause of hospital-onset diarrhea after 72 hours of admission; other stool cultures are usually low yield unless C. difficile testing is negative or epidemiology suggests another pathogen.
- Distinguish **antibiotic-associated diarrhea** from **C. difficile colitis**: most antibiotic-associated diarrhea is mild, self-limited and not due to C. difficile.
- In ileus, absence of diarrhea does not exclude CDI; unexplained leukocytosis, abdominal distension or CT colitis after antibiotics should trigger evaluation.
- PCR-positive/toxin-negative patients may be colonized; treat the patient, not the assay, while recognizing many clinically ill discordant patients are treated.
- Pseudomembranes are highly specific but not required for diagnosis and their absence at endoscopy does not rule out CDI.
- In IBD flare, checkpoint-inhibitor colitis, ischemic colitis or hospitalized acute diarrhea, exclude C. difficile before immunosuppression or escalation.

High-yield exam pointers

- Write the current name: **Clostridioides difficile**, formerly *Clostridium difficile*.
- CDI is due to **toxins A and B after antibiotic-induced microbiota disruption**; toxin B is the major validated target.
- High-risk antibiotics: **clindamycin, ampicillin, cephalosporins and fluoroquinolones**.
- Severe CDI: **WBC >=15,000/mcL or creatinine >=1.5 mg/dL**.
- Fulminant CDI: **hypotension/shock, ileus or toxic megacolon**.
- First-line initial therapy: **fidaxomicin 200 mg bid for 10 days**; **oral vancomycin 125 mg qid for 10 days** is acceptable.

- Fulminant regimen: **vancomycin 500 mg enteral qid + metronidazole 500 mg IV q8h**, add rectal vancomycin if ileus.
- **Do not use IV vancomycin alone** and **do not perform stool test of cure**.
- Recurrence prevention/treatment: fidaxomicin, vancomycin taper/pulse, microbiota therapy and **bezlotoxumab 10 mg/kg IV** in high-risk patients.

SOURCE & COVERAGE

Harrison 22e — "Clostridioides difficile Infection, Including Pseudomembranous Colitis"; CMDT 2026 — "Gastrointestinal Disorders" and "Anti-infective Treatment Antibiotic, Antifungal, & Antiviral Agents".

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Coagulase-negative staphylococcal infections

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Coagulase-negative staphylococci (CoNS) are gram-positive cocci of the family Micrococcaceae that, unlike *Staphylococcus aureus*, do **not** produce free coagulase and hence fail to convert fibrinogen to fibrin. They are the most abundant commensals of human skin and mucosae, so they are simultaneously the commonest blood-culture **contaminants** and, in the era of implanted prostheses, important **opportunistic pathogens** of foreign-body and device-related infection. *S. epidermidis* is the prototype; *S. saprophyticus* (urinary tract) and the unusually virulent *S. lugdunensis* (endocarditis) are the other exam-relevant species. Because a few "CoNS" species are in fact coagulase-positive, the more precise contemporary term is **non–*S. aureus* staphylococci (NSaS)**.

Microbiology, taxonomy and laboratory speciation

- **General features**: gram-positive cocci in grapelike clusters on Gram's stain, ~1 µm, **catalase-positive** (key distinction from streptococci), nonmotile, aerobic and facultatively anaerobic, with prolonged survival on environmental surfaces. There are **≥40 staphylococcal species**.
- **The coagulase test** divides the genus. *S. aureus* produces coagulase (a surface enzyme converting fibrinogen → fibrin); CoNS classically do not. Caveat: a few "CoNS" such as *S. pseudintermedius* and *S. argenteus* are actually coagulase-positive — hence **NSaS** is the more accurate label.
- **Colony/biochemical clues**: most NSaS form **small, white, nonhemolytic** colonies, whereas *S. aureus* forms golden β-hemolytic colonies, ferments mannitol, is protein A–positive and DNAse-positive. *S. saprophyticus* is distinctively **novobiocin-resistant**.
- **Identification tools**: latex agglutination kits (protein A + clumping factor) separate *S. aureus* from most NSaS; **MALDI-TOF mass spectrometry** is increasingly used for rapid speciation. For outbreak/strain typing, pulsed-field gel electrophoresis and *spA* typing have been used, with **whole-genome sequencing** now the gold standard.

Feature	S. aureus	Coagulase-negative staphylococci
Coagulase	Positive	Negative (most species)

Feature	S. aureus	Coagulase-negative staphylococci
Colony on blood agar	Golden, β-hemolytic	Small, white, non-hemolytic
Mannitol / DNAse / Protein A	Positive	Usually negative
Virulence	High (toxins, abscesses)	Low (biofilm-dependent), except *S. lugdunensis*
Typical disease	SSTI, endocarditis, bacteraemia, toxin disease	Prosthetic/device-related infection

Important species and their clinical niches

- **_S. epidermidis_** — the **most common human NSaS pathogen**; the most abundant bacterial species of normal skin, also colonising oropharynx and vagina. It is the dominant cause of **prosthetic-device infections** by virtue of biofilm formation.
- **_S. saprophyticus_** — novobiocin-resistant; a common cause of **urinary tract infection in young, sexually active women**, mediated by adhesins (a ~160-kDa haemagglutinin/adhesin) that bind uroepithelial cells.
- **_S. lugdunensis_** and **_S. schleiferi_** — disproportionately **virulent** NSaS that cause **native-valve endocarditis** and **osteomyelitis**; they share virulence determinants with *S. aureus* (e.g. clumping factor and lipase). *S. lugdunensis* may produce aggressive endocarditis with **bulky vegetations and rapid valve destruction with abscess**, mimicking *S. aureus* — frequently missed when dismissed as a "contaminant".
- **_S. haemolyticus_** and **_S. hominis_** — other species commonly recovered from device-associated bloodstream infection.

Pathogenesis — biofilm on foreign surfaces

- NSaS infection of a prosthesis is a **two-step process**: initial **adhesion** to the device, then **colonisation** with biofilm accumulation.
- Implanted material is rapidly coated by host matrix proteins (**fibrinogen, fibronectin**), which act as **bridging ligands**. Staphylococcal surface proteins — **autolysin (AtlE)**, fibrinogen-binding protein and **accumulation-associated protein (AAP)** — mediate attachment to modified or bare surfaces.
- *S. epidermidis* then elaborates an extracellular polysaccharide (**glycocalyx / "slime"**); the **polysaccharide intercellular adhesin (PIA)**, encoded by the **_ica_ (intercellular adhesion) locus**, drives aggregation, accumulation and maturation of a protective **biofilm**. The *ica* genes are over-represented in device-infecting strains relative to colonising strains.
- Biofilm forms a **physical barrier** shielding bacteria from host defences and antibiotics and serves as a **nidus for persistent and recurrent infection** — the reason device removal is usually required for cure.

Clinical syndromes

- **Prosthetic / foreign-body infections (the hallmark)** — prosthetic cardiac valves, prosthetic joints, vascular grafts, intravascular and peritoneal-dialysis catheters, CNS (CSF) shunts, cardiac implantable electronic devices (pacemakers/ICDs), sternal wires and intracranial-pressure monitors. The picture is characteristically **indolent**: subtle local signs (mild erythema, pain, low-grade drainage, prosthesis loosening), slow progression and limited systemic upset; fever is variable, leukocytosis mild, with raised ESR/CRP.
- **Prosthetic-valve endocarditis (PVE) — early PVE (within ~2 months of surgery)** is commonly caused by staphylococci (coagulase-negative and -positive), gram-negatives and fungi, with CoNS a leading agent; in **late PVE**, streptococci predominate but CoNS still cause many cases.
- **Cardiac-device (CIED) infection / endocarditis** — *S. aureus* and CoNS cause the majority; roughly one-third present within 3 months, one-third at 3–12 months, and one-third after 1 year.
- **Native-valve endocarditis** — NSaS account for ~5% of cases; suspect *S. lugdunensis* when an aggressive course occurs.
- **Bloodstream infection** — important in **preterm neonates and neutropenic patients**, usually catheter-associated.
- **Urinary tract infection** — *S. saprophyticus* in young women; **wound infection** after cardiothoracic surgery; *S. epidermidis* may rarely cause osteomyelitis in the absence of a prosthesis.

Diagnosis — distinguishing true infection from contamination

- NSaS are easily grown by routine culture, but **interpretation is the challenge** because they are abundant skin commensals.
- Only **10–20% of NSaS-positive blood cultures reflect true bacteraemia** (Harrison); conversely, contamination may account for **about three-quarters** of CoNS blood-culture isolates (CMDT).
- **Features favouring true infection**: presence of a **foreign body/intravascular device**; local signs (purulent or serosanguineous drainage, erythema, tenderness at the device site); fever, new murmur, prosthesis instability or systemic embolisation (for PVE); leukocytosis and signs of sepsis.
- **Microbiological criteria favouring true bacteraemia**: isolation of the **same strain** (same species with the same antibiogram or DNA fingerprint) from **two or more separately drawn cultures** and from the device site; bacterial growth **within 48 h**; and growth in **both aerobic and anaerobic** bottles.

Treatment

- **Source control is paramount** — wherever feasible, **remove the infected intravascular catheter or foreign body**; biofilm-encased organisms are rarely cured by antibiotics alone. When removal is hazardous (prosthetic joint or valve, CSF shunt), antibiotics ± long-term suppression may be tried, accepting a lower cure rate and the likely eventual need for surgery.
- **Resistance**: NSaS are far more often methicillin-resistant than *S. aureus* — **>80% of nosocomial NSaS isolates are methicillin-resistant**, frequently with co-resistance to multiple drug classes.

- **Empirical drug of choice**: **vancomycin** (15–20 mg/kg IV q8–12 h; CMDT: 1 g IV q12 h, trough 15–20 µg/mL) until susceptibility is known. If proven **methicillin-susceptible**, a penicillinase-resistant penicillin (**nafcillin/oxacillin**) or **cefazolin** is preferred.
- **Duration**: documented infection (same strain ≥24 h apart) **without** endocarditis or other foci → **7–14 days**; infection of **bone or a prosthetic valve → 6 weeks**.
- **Prosthetic-valve endocarditis (methicillin-resistant NSaS)** → combination of **vancomycin + rifampin (300 mg PO/IV every 8 h) + gentamicin (1 mg/kg IV every 8 h for 2 weeks)**, usually with surgical valve replacement. **Rifampin** is specifically valuable in prosthetic-device infection and osteomyelitis (biofilm/intracellular penetration); **rifampin + a fluoroquinolone (e.g. ciprofloxacin)** can suppress retained prosthetic-joint infection.
- **Alternative anti-MRSA agents** with NSaS activity include **daptomycin, linezolid/tedizolid, ceftaroline, telavancin and TMP-SMX** (chosen per susceptibilities; daptomycin is not used for pneumonia).

Setting	Preferred regimen	Duration
Empirical / methicillin-resistant	Vancomycin IV (target trough 15–20 µg/mL)	Per focus
Confirmed methicillin-susceptible	Nafcillin / oxacillin or cefazolin	Per focus
Catheter bacteraemia (device removed)	Vancomycin after removal	7–14 days
Bone / prosthetic valve	Vancomycin (± combination)	6 weeks
MR prosthetic-valve endocarditis	Vancomycin + rifampin + gentamicin + surgery	≥6 weeks (gentamicin 2 weeks)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Biofilm formation on a catheter/prosthesis (sequential schematic).** Labels: *Prosthetic/catheter surface → host conditioning film (fibrinogen, fibronectin) → primary adhesion (AtlE autolysin, fibrinogen-binding protein, AAP) → accumulation (polysaccharide intercellular adhesin / PIA, ica locus) → mature biofilm (glycocalyx "slime") → barrier to antibiotics and host immune cells → embolisation / persistent bacteraemia.*
- **Diagnostic algorithm box: "Contaminant vs true CoNS bacteraemia".** Labels: *Single positive bottle, no device → likely contaminant*; *Same strain from ≥2 separate cultures + device site, growth <48 h, both aerobic & anaerobic bottles, sepsis signs → true infection → remove device + vancomycin.*

Clinical / Diagnostic significance

- A CoNS-positive blood culture should never be dismissed reflexively as a contaminant in a patient with a **prosthetic valve, joint, vascular graft, CIED, CSF shunt or central line** — repeat cultures and clinical correlation are essential.

- *S. lugdunensis* is a "red-flag" CoNS: treat any *lugdunensis* bacteraemia as potentially **aggressive endocarditis** and obtain echocardiography.
- Persistent CoNS bacteraemia despite an indwelling line mandates **line removal**; failure to do so is a common cause of relapse because of biofilm.
- High methicillin-resistance rates make **vancomycin the rational empirical choice**, with de-escalation to a β-lactam if methicillin-susceptible.
- Prevention rests on **aseptic catheter insertion, hand hygiene and insertion/maintenance "bundles"**, which markedly reduce device-related staphylococcal infection.

High-yield exam pointers

- CoNS = catalase-positive, **coagulase-negative**, gram-positive cocci in clusters; most abundant normal skin flora.
- ***S. epidermidis*** = commonest pathogen → **prosthetic-device infection via biofilm**; *ica* locus → **PIA / slime**.
- ***S. saprophyticus*** = **novobiocin-resistant** → UTI in **young sexually active women**.
- ***S. lugdunensis*** (and *S. schleiferi*) = **virulent** → native-valve endocarditis/osteomyelitis; bulky vegetations like *S. aureus*.
- Only **10–20%** of NSaS-positive blood cultures are true bacteraemia; **~75%** are contaminants — confirm with **same strain from ≥2 cultures + device site**.
- **>80%** of nosocomial NSaS are **methicillin-resistant** → empirical **vancomycin**.
- **Source control / device removal** is essential; rifampin aids biofilm/prosthetic-device infection.
- Durations: catheter bacteraemia 7–14 days; **bone/prosthetic valve 6 weeks**; PVE = vancomycin + rifampin + gentamicin + surgery.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Staphylococcal Infections"** (non–*S. aureus* staphylococci: microbiology/taxonomy, biofilm pathogenesis, diagnosis, clinical syndromes, antimicrobial therapy) and **"Infective Endocarditis"** (CoNS in prosthetic-valve and cardiac-device endocarditis).
- **CMDT 2026 — "Bacterial & Chlamydial Infections"** (Infections Caused by Coagulase-Negative Staphylococci; *S. lugdunensis*; vancomycin dosing and prosthetic-valve endocarditis regimen) and **"Common Problems in Infectious Diseases"** (prosthetic-valve endocarditis microbiology by time of onset).

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Enteric fever (typhoid)

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Enteric (typhoid) fever is a systemic febrile illness caused by dissemination of the human-restricted serotypes *Salmonella* Typhi and *S.* Paratyphi (A, B, C), characterised by prolonged fever and abdominal pain. After ingestion the organisms cross the gut via Peyer's-patch M cells, are taken up by macrophages and disseminate through the reticuloendothelial system. The mean incubation period is **10–14 days** (range 5–21). Untreated, fever (38.8°–40.5°C) may persist up to 4 weeks; the **overall case-fatality rate is ~2.5%** (4.5% in hospitalised, 10–30% if untreated), falling to **<1% with prompt appropriate antibiotics**. Complications cluster in the third and fourth weeks of illness.

Determinants and timeline of complications

- Complications occur in **~27% of hospitalised patients**.
- Risk correlates with: **longer duration of symptoms before hospitalisation**, host factors (host genetics, immunosuppression, acid-suppression therapy, prior exposure, vaccination status), **strain virulence and inoculum**, and **choice of antibiotic therapy**.
- The dangerous intestinal complications characteristically appear in the **3rd–4th weeks**, arising from hyperplasia, ulceration and necrosis of the **ileocecal Peyer's patches** at the site of initial *Salmonella* infiltration.

Complications of enteric fever

Category	Complication (frequency where stated)	Key points
Intestinal (most lethal)	**GI haemorrhage** (~6%); **intestinal perforation** (~1%)	3rd–4th week; from ulceration/necrosis of ileocecal Peyer's patches (terminal ileum); both life-threatening
Neurologic (2–40%)	Meningitis, **Guillain-Barré syndrome**, neuritis, neuropsychiatric states	"**Muttering delirium**" or "**coma vigil**"; *picking at bedclothes / imaginary objects* (carphology)
Haematologic	Disseminated intravascular coagulation; haemophagocytic syndrome	Incidence reduced by prompt antibiotics
Hepatobiliary / abdominal	Hepatitis, pancreatitis, **hepatic and splenic abscesses & granulomas**, cholecystitis	Cholecystitis underlies chronic carriage
Cardiac	Endocarditis, pericarditis, myocarditis	Uncommon
Genitourinary / renal	Orchitis, glomerulonephritis, pyelonephritis, **haemolytic-uraemic syndrome**	—
Other focal	Severe pneumonia, arthritis, osteomyelitis, endophthalmitis, parotitis	—

Category	Complication (frequency where stated)	Key points
Relapse	Up to **10%** of patients	Usually **2–3 weeks after fever resolution**; same strain & susceptibility profile
Chronic carriage	**2–5%** shed >1 year; up to 10% excrete in faeces up to 3 months	More common in **women, infants**, biliary abnormalities, or bladder co-infection with *Schistosoma haematobium*

- *S.* Typhi persists in the gallbladder by forming **biofilms on gallstones** and invading gallbladder epithelium; chronic carriage carries an **increased risk of gallbladder carcinoma**, especially on the Indian subcontinent.
- Intestinal perforation and haemorrhage **require immediate fluid resuscitation and surgical intervention**, with **broadened antibiotic cover for polymicrobial peritonitis** and treatment of haemorrhage, including **bowel resection**.

Principles of antimicrobial management

- Initial choice depends on the **susceptibility pattern of *S.* Typhi/Paratyphi in the area of residence or travel**.
- A 2022 systematic review (27 RCTs) found **no difference between ceftriaxone, a fluoroquinolone, or azithromycin** in treatment failure, microbiologic failure, relapse, convalescent carriage or adverse events.
- Because of the high prevalence of strains with **decreased susceptibility to ciprofloxacin (DSC; MIC >0.125 µg/mL)** on the Indian subcontinent and parts of Africa, **fluoroquinolones should no longer be used for empirical therapy** in these regions.
- **Travel to Pakistan / concern for ceftriaxone-resistant (XDR) *S.* Typhi → treat empirically with a carbapenem or azithromycin.**
- **Azithromycin** is recommended for **uncomplicated** enteric fever including **ESBL, DSC and fluoroquinolone-resistant** strains (defervescence 4–6 days; relapse & stool carriage <3%); against DSC strains it gives lower failure and shorter hospitalisation than fluoroquinolones.
- Third-generation cephalosporins (ceftriaxone, cefotaxime, oral cefixime) clear fever in ~1 week (failure ~5–10%, relapse 3–6%). Fluoroquinolones against **susceptible** strains give cure rates ~98%.
- **Carbapenems** are increasingly used for complicated **XDR** infection (cost and IV route are barriers).
- Duration: at least **10 days, or 5 days after fever resolution**.

Antibiotic regimens (Harrison Table 171-1, adults)

Indication	Agent	Dosage (route)	Duration (days)
Empirical	Ceftriaxone*	2 g/d (IV)	10–14
	Ciprofloxacin	500 mg bid (PO) / 400 mg q12h (IV)	5–7

Indication	Agent	Dosage (route)	Duration (days)
	Azithromycin	1 g/d (PO)	5
Fully susceptible (optimal)	Ceftriaxone / Ciprofloxacin / Azithromycin	as above	10–14 / 5–7 / 5
Fully susceptible (alternative)	Amoxicillin	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO/IV)	14–21
	TMP-SMX	160/800 mg bid (PO)	7–14
MDR (per susceptibility)	Ceftriaxone / Ciprofloxacin / Azithromycin	as above	10–14 / 5–7 / 5
Ceftriaxone-resistant (optimal)	Meropenem†	1 g q8h (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Eradication of carriage	Ciprofloxacin	500–750 mg bid (PO)	28
	Azithromycin (alt.)	500 mg (PO)	28

*Or another 3rd-gen cephalosporin (cefotaxime 2 g q8h IV; cefixime 400 mg bid PO). †Or imipenem 500 mg q6h IV.

Management of severe disease, supportive care and carriage

- **Site of care:** most uncomplicated cases are managed **at home** with oral antibiotics and antipyretics. **Hospitalise** patients with **persistent vomiting, diarrhoea and/or abdominal distension** for supportive therapy plus a **parenteral 3rd-gen cephalosporin, fluoroquinolone or carbapenem** per susceptibility.
- **Severe enteric fever (shock, obtundation/delirium):** add high-dose **dexamethasone — initial 3 mg/kg, then 1 mg/kg every 6 h for eight doses** — which (with chloramphenicol in the original Indonesian trial) lowered mortality dramatically (**10% vs 55%**). Severe enteric fever remains **one of the few indications for glucocorticoids in acute bacterial infection**; **steroids beyond 48 h may increase relapse**.
- **Intestinal perforation/haemorrhage:** aggressive fluid resuscitation, broadened cover for **polymicrobial peritonitis**, and **surgical intervention / bowel resection**.
- **Chronic carriage eradication: fluoroquinolone-susceptible** → oral **ciprofloxacin for 4 weeks** (eradication ~80%); fluoroquinolone-resistant → **azithromycin 4 weeks** (limited data) or **amoxicillin** if ampicillin-susceptible (lower eradication). With **anatomic abnormality (biliary/renal/bladder stones)**, eradication often needs **antibiotics plus surgical correction** (e.g., cholecystectomy).
- **Public health:** enteric fever is a **notifiable disease**; monitor and treat carriers (especially food handlers and child-care providers) to prevent onward transmission.

Prevention (vaccines)

- **Ty21a** — oral live-attenuated (days 1, 3, 5, 7; re-vaccinate every 5 years); minimum age **6 years**; efficacy ~50% at 2.5–3 years.
- **Vi CPS** — parenteral purified Vi capsular polysaccharide (single dose; booster every 2 years); minimum age **2 years**; efficacy ~55% at 3 years.
- **Typhoid conjugate vaccines (TCV)** — *Typbar TCV* (Bharat Biotech, 2018) and *TYPHIBEV* (Biological E, 2020); single **IM 0.5 mL** dose, **79–95% effective**, antibody persistence up to **7 years**, and effective in **children <2 years** — WHO-prioritised for high-incidence countries.
- No licensed vaccine exists for **paratyphoid fever**; vaccination is an **adjunct**, not a substitute for safe food/water.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled diagram of terminal-ileum Peyer's-patch pathology / typhoid perforation:** label *terminal ileum, ileocecal junction, hyperplastic Peyer's patch, longitudinal ulcer along antimesenteric border, necrosis/perforation site, mesenteric lymph nodes*.
- **Week-wise timeline of complications:** Week 1 *bacteraemia, stepladder fever, relative bradycardia*; Week 2 *rose spots, hepatosplenomegaly*; **Weeks 3–4** *intestinal haemorrhage, perforation, neuropsychiatric state*; Convalescence *relapse (~10%), chronic carriage (2–5%)*.

Clinical / Diagnostic significance

- **Definitive diagnosis** is by **culture**: blood culture sensitivity only **40–60%**; **bone-marrow culture ~80%** sensitive and **not reduced by up to 5 days of prior antibiotics**; combined blood + bone-marrow + intestinal-secretion (duodenal string) culture gives **>90% yield**.
- **Rapid serologic tests Tubex and Typhidot** (IgM/IgG to O and H antigens) have sensitivity ~70–80% and specificity ~80–90% — useful at point-of-care but **cannot replace blood culture**.
- Suspect typhoid in any **febrile returning traveller** from South Asia/Africa; differentials include malaria, dengue, viral hepatitis, leptospirosis, rickettsial infection, amoebic liver abscess and acute HIV.
- Watch for **leukopenia/neutropenia (15–25%)**; **leukocytosis suggests perforation or secondary infection**.
- A history of travel to **Pakistan** should raise concern for **XDR H58 *S.* Typhi** and drive empirical carbapenem/azithromycin use.

High-yield exam pointers

- Complications in **~27%** of hospitalised cases; **haemorrhage (6%)** and **perforation (1%)** in **weeks 3–4** from ileocecal **Peyer's-patch** ulceration.
- **Perforation = surgical emergency**: resuscitate, broad cover for peritonitis, **operate / resect bowel**.
- Neuropsychiatric typhoid → "**muttering delirium**" / "**coma vigil**"; neurologic involvement **2–40%** (incl. **GBS**, meningitis).

- **Relapse up to 10%** at 2–3 weeks; **chronic carriage 2–5%** (>1 yr) — linked to **gallstones, biofilms, gallbladder cancer**, commoner in **women**.
- **Empirical drug today:** ceftriaxone 2 g/d IV or azithromycin 1 g/d PO; **avoid fluoroquinolones empirically** on the Indian subcontinent (DSC, MIC >0.125 μg/mL).
- **XDR/ceftriaxone-resistant (Pakistan) → meropenem 1 g q8h IV (or imipenem) ± azithromycin.**
- **Severe disease → dexamethasone 3 mg/kg then 1 mg/kg q6h ×8** (mortality 10% vs 55%); a rare steroid indication; stop by 48 h.
- **Carrier eradication:** ciprofloxacin 500–750 mg bid ×28 days (~80%); cholecystectomy if gallstones.
- **Prevention:** Ty21a (oral), Vi-CPS (parenteral), and **TCV (Typbar/TYPHIBEV)** effective in under-2s; **none for paratyphoid**.

> **SOURCE & COVERAGE**
>
> Harrison's Principles of Internal Medicine, 22e — Ch 171 "Salmonellosis" (Pegues & Miller), including Table 171-1 (Antibiotic Therapy for Enteric Fever in Adults). *Coverage note:* The classic eponyms **Faget sign** (relative bradycardia — described in text as "relative bradycardia at the peak of high fever") and the **Widal test** are standard internal-medicine items but are not named as such in the provided chapter, which instead emphasises Tubex/Typhidot and culture-based diagnosis; they are flagged here as universally accepted additions rather than verbatim source content.

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COVID-19 (2019 novel coronavirus)

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — COVID-19 (Coronavirus Disease 2019) is the acute respiratory and multisystem illness caused by **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**, an enveloped, positive-sense RNA *Betacoronavirus* that emerged in **Wuhan, China in 2019**. It produced the largest pandemic of the modern era — the WHO declared a **Public Health Emergency of International Concern on 30 January 2020**, a **pandemic on 11 March 2020**, and an **end to the global emergency on 5 May 2023**, by which time the virus had caused **>700 million cases and >7 million deaths**. The disease ranges from asymptomatic infection through mild illness to fulminant pneumonia, ARDS and multiorgan failure, and is now in an **endemic phase** managed with antivirals, immunomodulators and annually updated vaccines.

Aetiology, virology and pathogenesis

- **Family/genus:** *Betacoronavirus*; SARS-CoV-2 belongs to the same genus as the highly pathogenic **SARS-CoV-1** (2002–03 epidemic) and **MERS-CoV** (2012, 2015, 2018) and the common-cold coronaviruses **HCoV-OC43** and **HCoV-HKU1**. All coronaviruses are thought to have originated in **bats**.

- **Genome/structure:** a single linear **positive-sense RNA of ~30,000 nucleotides** encoding **four structural proteins — S (spike), E (envelope), M (membrane), N (nucleocapsid)** — plus a large polyprotein cleaved into **16 non-structural proteins**.
- **Cell entry:** the trimeric **S protein** (a type-1 fusion machine) uses its **receptor-binding domain (RBD)** to bind the host **angiotensin-converting enzyme 2 (ACE2)** receptor; the host protease **TMPRSS2** primes S to facilitate membrane fusion and entry.
- **Variant evolution:** error-prone **RNA-dependent RNA polymerase (RdRp)** generates frequent variants; WHO tracks **variants under monitoring (VUM), variants of interest (VOI) and variants of concern (VOC)**. Sequential VOCs (Alpha → Delta → **Omicron** and its sublineages BA.4/BA.5, XBB, JN.1, KP.2/"FLiRT") altered transmissibility, severity, antigenicity and drug/vaccine efficacy. Most spike mutations reduce neutralisation, rendering all earlier monoclonal antibodies ineffective.

Epidemiology and transmission

- **Spread:** primarily by **respiratory droplets** in close proximity; **airborne/aerosol** transmission can occur (heavy exercise, singing, aerosol-generating procedures) but long-range airborne spread is unlikely; **fomite** transmission occurs.
- **Reproduction number (R0):** estimated to **peak around 6** (Harrison) — far higher than seasonal influenza (1–2); CMDT places the true R0 nearer **2–3**, varying by variant.
- **Pre-symptomatic and super-spreading:** much spread is **pre-symptomatic** (viral load peaked the day before symptoms before population immunity; around day 4 thereafter); **"super-spreaders"/super-carriers** drive disproportionate transmission, especially in dense settings (prisons, cruise ships, nursing homes, bars, workplaces).
- **Incubation:** typically **4–5 days, nearly always within 14 days** (range up to ~14–24 days).
- **Risk factors for severe disease: advanced age is the principal risk factor** (>95% of deaths in those >45 y, >80% in those >65 y); **male sex** (OR ~1.8); rising **BMI** (overweight/obesity/severe obesity); pregnancy; smoking/substance use; and comorbidities — chronic lung disease, **diabetes, hypertension, cardiovascular and chronic kidney/liver disease, cancer, immunosuppression (including transplant, rituximab/B-cell depletion), Down syndrome**.

Clinical features and severity classification

- **Spectrum:** ~one-third of those infected are **asymptomatic** (but can transmit); most symptomatic patients have **mild disease (no pneumonia)**.
- **Symptoms:** cough, fever, chills, myalgia, headache, sore throat, dyspnoea; sudden **anosmia/dysgeusia** (loss of smell/taste, often neurotropic without congestion); GI symptoms (nausea, vomiting, diarrhoea); diverse dermatological lesions (acral "COVID toes", maculopapular, vesicular, urticarial).
- **Severity grading** (NIH/clinical framework reflected in Harrison & CMDT):

Category	Defining features
Asymptomatic	Positive test, no symptoms
Mild	Symptomatic, **no pneumonia / no hypoxia**

Category	Defining features
Moderate	Clinical/radiographic pneumonia, **SpO2 >94%** on room air
Severe	**SpO2 ≤94%**, RR **>30/min**, **PaO2/FiO2 <300 mmHg**, or infiltrates **>50%** of lung fields
Critical	Respiratory failure needing mechanical ventilation, ARDS, shock, multiorgan failure

Investigations

- **Molecular tests (NAAT): RT-PCR** on nasopharyngeal swab (or saliva) is the **most sensitive and specific** confirmatory test; detects RNA — prolonged RNA shedding is common in the immunocompromised, so re-testing within **90 days** of prior infection is discouraged.
- **Rapid antigen tests:** fast, inexpensive, home-usable; **less sensitive than NAAT** (especially in asymptomatic persons; ~85% vs culture in symptomatic CDC data) — useful for triage of infectiousness.
- **Serology:** detects immune status, **not used for acute diagnosis** (cannot reliably separate vaccination from infection).
- **Supportive labs of severity: lymphopenia, thrombocytopenia**, neutrophilia and raised neutrophil-to-lymphocyte ratio; elevated **IL-6, TNF-α, ferritin, CRP, procalcitonin, LDH**; raised liver enzymes; **elevated D-dimer/prolonged PT, raised vWF**; elevated **troponin and CPK**.
- **Imaging:** chest radiograph and CT may be **normal early**; later show **bilateral peripheral ground-glass opacities** ± consolidation, interlobular septal thickening and air bronchograms (organising-pneumonia pattern). CT is for management, **not primary diagnosis**.

Complications

- **Pulmonary: ARDS** (commonest serious complication; ~19-fold higher progression than influenza), respiratory failure needing ventilation/ECMO; secondary bacterial/fungal infection (invasive pulmonary **aspergillosis**, **mucormycosis**).
- **Haematological/thrombotic:** hypercoagulable state, **venous thromboembolism (PE, DVT)**, arterial thrombosis (stroke, limb ischaemia), **DIC**.
- **Cardiac:** myocardial injury, **fulminant myocarditis**, arrhythmias, heart failure, ACS, stress cardiomyopathy, shock.
- **Renal: acute kidney injury** (often needing dialysis).
- **Neurological/psychiatric:** encephalopathy, ICU delirium (reduces survival), seizures, stroke, **Guillain-Barré syndrome**, acute haemorrhagic necrotising encephalopathy; anxiety, depression, PTSD.
- **Hyperinflammation ("cytokine storm"):** persistent fever, multiorgan disease, raised inflammatory markers (notably **IL-6**) — high fatality.
- **MIS-C / MIS-A: multisystem inflammatory syndrome in children** (Kawasaki-like; GI, cardiac, mucocutaneous, haematological involvement; highest in Black/Latino children 3–12 y) and the rarer adult form **MIS-A**, weeks after mild/asymptomatic infection.

- **Long COVID:** symptoms persisting **≥3 months** — fatigue (~32%), smell/taste disorder (~22%), dyspnoea (~16%), headache, "brain fog"/memory impairment, hair loss, sleep disturbance; vaccination substantially reduces its incidence.

Management

- **Principle (biphasic disease): antivirals work best early** (reduce peak viral load) while **anti-inflammatory/immunomodulators help later** when tissue inflammation dominates.
- **Outpatient / mild–moderate, high-risk (start ≤5 days of symptoms):**
  - **Nirmatrelvir/ritonavir (Paxlovid):** drug of choice — **300 mg/100 mg orally 12-hourly for 5 days**; **~85% relative risk reduction** in hospitalisation/death. Reduce nirmatrelvir to **150 mg if GFR 30–60**, **contraindicated if GFR <30**; ritonavir is a potent **CYP3A4 inhibitor** — screen for **drug interactions** (avoid with strong inducers e.g. rifampin, phenytoin); ~6.6% **"rebound"** symptoms after stopping.
  - **Remdesivir** IV: 3-day outpatient course (≥60 y or comorbid, within 7 days) — ~87% reduction in death/hospitalisation pre-vaccine era.
  - **Molnupiravir** 800 mg 12-hourly ×5 days — when other agents unsuitable; **mutagenic — contraindicated in pregnancy and <18 y**, contraception advised.
- **Inpatient / severe (admit if SpO2 <94%, RR >30, PaO2/FiO2 <300, or infiltrates >50%):**
  - **Supportive O2**, control fever with **acetaminophen** (limit NSAIDs); continue **aspirin, statins, ACEi/ARB**.
  - **Remdesivir** 200 mg day 1 then **100 mg daily** (5 days, non-inferior to 10) for patients on supplemental oxygen.
  - **Dexamethasone** (low-dose) for those needing **supplemental oxygen/ventilation/ECMO** — standard **10-day** course; **not** indicated without hypoxia (RECOVERY trial basis). Alternatives: prednisone, methylprednisolone, hydrocortisone.
  - **Anticoagulation: therapeutic-dose heparin** for hospitalised patients on supplemental O2 (not HFNC/ventilation) with raised D-dimer and no bleeding risk; **prophylactic-dose** for others including critically ill. Outpatients generally need no anticoagulation.
  - **Immunomodulators for escalating O2/inflammation: IL-6 receptor inhibitors tocilizumab** (or sarilumab) and **JAK inhibitors baricitinib** (or tofacitinib) — do **not** combine IL-6 inhibitor with a JAK inhibitor; JAK inhibitors require at least prophylactic anticoagulation. Abatacept/infliximab are alternatives.
- **Antibody-based therapy/prevention:** convalescent plasma and **monoclonal antibodies** have largely lost efficacy to new variants; long-acting antibodies **tixagevimab/cilgavimab (Evusheld)** and **pemivibart** were authorised for pre-exposure prophylaxis in the immunocompromised.
- **Bacterial co-infection is uncommon (~8%)** — routine antibiotics are **not** recommended.

Prevention

- **Non-pharmaceutical interventions (NPIs):** physical distancing (~6 ft), isolation of cases, quarantine, ventilation/HEPA, hand hygiene, and **masks** (well-fitted N95/FFP2 most protective; greatest value for vulnerable groups).
- **Vaccines** (stimulate neutralising anti-spike antibody):

- **mRNA** (Pfizer-BioNTech, Moderna) — **~95% efficacy** against symptomatic disease in phase-3 trials; waning immunity prompts periodic variant-matched updates.
- **Protein subunit** (Novavax, with **Matrix-M** adjuvant).
- **Viral-vector** (Janssen) — **withdrawn** due to **thrombosis with thrombocytopenia syndrome (TTS)**.
- Goal is prevention of **severe disease/death**; vaccination also lowers **long-COVID** risk. mRNA vaccines are safe in **pregnancy/lactation**; rare **myocarditis/pericarditis** (~6.3/million doses, young males, after 2nd dose).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **SARS-CoV-2 virion (labelled):** spherical enveloped particle with labels — **Spike (S) glycoprotein with receptor-binding domain (RBD)**, **Envelope (E) protein**, **Membrane (M) protein**, **Nucleocapsid (N) protein wrapping the +ssRNA genome (~30 kb)**; alongside, host cell showing **ACE2 receptor** and **TMPRSS2** priming S for entry.
- **Natural history / two-phase timeline:** x-axis time from exposure; curves for **viral load (early, peak ~day 4–5)** and **host inflammatory response (late)**; phases marked **incubation (4–5 d) → viral phase (antivirals: nirmatrelvir, remdesivir) → inflammatory phase (dexamethasone, tocilizumab, baricitinib) → recovery / Long COVID**.

Clinical / Diagnostic significance

- **Confirm with RT-PCR** (gold standard); use **rapid antigen** for fast triage; severity is defined by **oxygenation (SpO2 ≤94%, PaO2/FiO2 <300)** and radiographic extent.
- **Risk-stratify** by age, comorbidity and immune status to select candidates for **early antivirals** — the single highest-yield management decision.
- **Recognise the biphasic course:** antivirals early, **steroids only once hypoxic**; never give dexamethasone to non-hypoxic mild disease.
- **Anticipate thromboembolism** — thromboprophylaxis for all hospitalised patients; monitor **D-dimer**.
- **MIS-C/MIS-A and Long COVID** are important post-infectious sequelae requiring multidisciplinary follow-up.

High-yield exam pointers

- **SARS-CoV-2 = Betacoronavirus**, +ssRNA ~30 kb, **S/E/M/N** structural proteins; entry via **ACE2 + TMPRSS2**.
- WHO milestones: **PHEIC 30 Jan 2020**, **pandemic 11 Mar 2020**, **emergency ended 5 May 2023**.
- **R0 ~6** (Harrison) / 2–3 (CMDT); incubation **4–5 days**; **~1/3 asymptomatic**.
- **Severe disease cut-offs:** SpO2 **≤94%**, RR **>30**, **PaO2/FiO2 <300**, infiltrates **>50%**.
- **Lab clues:** lymphopenia, raised **D-dimer, ferritin, CRP, LDH, IL-6, troponin**.
- **Early antiviral of choice: nirmatrelvir/ritonavir 300/100 mg BD ×5 d** within 5 days (CYP3A4 interactions; avoid GFR <30).

- **Severe/hospitalised: remdesivir + dexamethasone ± tocilizumab/baricitinib; therapeutic-dose heparin** if on supplemental O2.
- **Dexamethasone helps only hypoxic patients** (RECOVERY); harmful/no benefit without hypoxia.
- **Vaccines:** mRNA (Pfizer/Moderna ~95%), Novavax subunit; **Janssen withdrawn (TTS).**
- **Sequelae: MIS-C/MIS-A** (Kawasaki-like) and **Long COVID** (fatigue, anosmia, dyspnoea, brain fog) ≥3 months.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "SARS-CoV-2 and COVID-19" (virology, ACE2/TMPRSS2 entry, epidemiology, severity, complications, antiviral/immunomodulator regimens, antibody therapy, vaccines).
- **CMDT 2026** — "Severe Acute Respiratory Syndrome — Coronavirus 2019 (SARS-CoV-2)" and Table 37–1 "Agents for viral infections" (diagnostic strategy, drug doses, anticoagulation thresholds, corticosteroid/IL-6/JAK indications, vaccine and Long-COVID data).

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Cytokine storm in dengue fever

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Dengue is caused by four antigenically distinct mosquito-borne orthoflaviviruses (DENV-1 to DENV-4, family *Flaviviridae*) transmitted chiefly by *Aedes aegypti*. While most infections are subclinical or cause a self-limited febrile illness ("break-bone fever"), a minority progress at defervescence to **severe dengue**, dominated by a **plasma-leakage (critical) phase**. The *"cytokine storm"* refers to an exaggerated, dysregulated surge of pro- and anti-inflammatory cytokines and vasoactive mediators—triggered largely by **antibody-dependent enhancement (ADE)** and cross-reactive memory T-cell activation during heterotypic secondary infection—that drives **endothelial dysfunction, increased vascular permeability, plasma leakage, haemorrhage and shock**. It is the immunopathological engine of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Why a cytokine storm develops — immunological triggers

- **Antibody-dependent enhancement (ADE):** A first (primary) DENV infection gives lifelong homotypic immunity but only transient cross-protection. On heterotypic **secondary infection**, pre-existing **non-neutralising, sub-neutralising "enhancing" antibodies** opsonise the new serotype and, via **Fcγ receptors**, deliver virus into **monocytes/macrophages**, amplifying viral load and the infected-cell pool that releases cytokines. Harrison explicitly centres severe-dengue risk on "immune-mediated enhancement of disease" and "enhancing and non-neutralising antibodies."
- **Original antigenic sin (cross-reactive T cells):** Secondary infection preferentially expands **low-avidity cross-reactive memory $CD8^+$/$CD4^+$ T cells** from the prior serotype rather than high-

affinity protective clones; these clear virus poorly but **over-produce TNF-α and IFN-γ**, fuelling the storm.

- **NS1-driven endothelial injury:** The secreted viral **non-structural protein 1 (NS1)** is highlighted by Harrison as having "a key role in the vascular leak phenomenon"—it engages **TLR4** on monocytes and endothelium to release inflammatory cytokines and directly degrades the **endothelial glycocalyx**.
- **Complement activation:** Massive C3/C5 activation generates anaphylatoxins (**C3a, C5a**) that increase vascular permeability and amplify inflammation.
- **Mast-cell and innate activation:** Infected mast cells and dendritic cells release vasoactive mediators (chymase, VEGF, histamine), adding to leak.
- **Host/viral risk modifiers (Harrison):** Susceptibility falls sharply after age 12; females > males; certain **infection sequences** are worse (DENV-1 → DENV-2 more severe than DENV-4 → DENV-2); Southeast-Asian DENV-2 variants are more virulent; nutritional status and, per CMDT, **type-2 diabetes and obesity** predispose to severe disease.

Key mediators of the storm and their effects

Mediator	Principal source	Pathophysiological effect
TNF-α	Activated T cells, monocytes	Endothelial activation, increased permeability, fever, haemorrhage
IFN-γ	Cross-reactive memory T cells	Macrophage activation, amplifies TNF-α effect
IL-6	Monocytes/macrophages, endothelium	Acute-phase response, vascular permeability, coagulation activation
IL-1β	Monocytes (inflammasome)	Pyrexia, endothelial activation
IL-8 (CXCL8) / MCP-1	Monocytes, endothelium	Neutrophil/monocyte chemotaxis, vascular leak
IL-10	T cells, monocytes	Anti-inflammatory surge; high levels mark severity & immune paralysis
VEGF	Mast cells, platelets, endothelium	Potent direct ↑ vascular permeability
NS1 (viral)	Infected cells (secreted)	Glycocalyx degradation, TLR4-mediated cytokine release
Complement C3a/C5a	Plasma cascade	Anaphylatoxin-mediated permeability

- The **net result** is loss of endothelial barrier integrity and **glycocalyx shedding**, producing the hallmark **plasma leak**: haemoconcentration (rising haematocrit), hypoalbuminaemia, serosal effusions (pleural, ascitic) and, ultimately, hypovolaemic **shock with narrowed pulse pressure**.
- Concurrent cytokine-driven **thrombocytopenia, platelet dysfunction, consumptive coagulopathy/DIC and liver injury** generate the bleeding diathesis.

Phases of dengue and timing of the storm

- **Febrile phase (days 1–~5):** High viraemia and innate activation—high fever, retro-orbital pain, myalgia ("break-bone"), flushing, transient rash; leukopenia, early thrombocytopenia, mild AST rise.
- **Critical / plasma-leakage phase (around defervescence, ~days 3–7):** The **cytokine storm peaks** as fever falls; capillary leak, effusions, falling platelets (<100,000/μL), rising haematocrit and—if uncorrected—shock. **Warning signs** (abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy/restlessness, hepatomegaly >2 cm, rising HCT with rapid platelet fall) flag impending deterioration.
- **Recovery phase (~days 7–10):** Cytokines subside, extravascular fluid is reabsorbed (risk of **fluid overload/pulmonary oedema** with over-resuscitation); convalescent confluent pruritic rash with desquamation; bradycardia.

WHO classification (puts the storm in clinical terms)

1997 WHO	2009 WHO (current)	Defining feature
Dengue fever	**Dengue without warning signs**	Febrile illness, no leak/warning features
Dengue haemorrhagic fever (DHF, grades I–II)	**Dengue with warning signs**	Plasma-leak markers + warning signs → admit
DHF III–IV / Dengue shock syndrome (DSS)	**Severe dengue**	(1) plasma leakage → shock or respiratory distress, **or** (2) severe bleeding, **or** (3) severe organ dysfunction

- Severe organ involvement: hepatitis/fulminant hepatic failure, **myocarditis**, encephalitis/encephalopathy, acute kidney injury (especially with shock—high mortality). The most extreme expression of the storm overlaps with **haemophagocytic lymphohistiocytosis (HLH)/macrophage-activation syndrome** (cytopenias, hyperferritinaemia, hepatosplenomegaly).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Cytokine storm cascade in secondary dengue":** Boxes/arrows: *Heterotypic secondary DENV → Non-neutralising enhancing antibody + Fcγ receptor (ADE) → Infected monocyte/macrophage (↑viral load) + Cross-reactive memory T cell (original antigenic sin) + Secreted NS1 → TLR4* → central node **"Cytokine storm: TNF-α, IFN-γ, IL-6, IL-1β, IL-8, IL-10, VEGF, MCP-1; complement C3a/C5a"** → *Endothelial activation + glycocalyx degradation* → three output boxes: **(i) ↑Vascular permeability → plasma leak → effusions → shock**, **(ii) Thrombocytopenia + DIC → haemorrhage**, **(iii) Organ injury (liver, heart, brain, kidney)**.
- **Diagram 2 — "Triphasic dengue timeline":** X-axis days 1–10; overlaid curves for **temperature**, **platelet count (falling to nadir in critical phase)**, **haematocrit (rising in critical phase)**; shade the three phases (Febrile / Critical–leakage / Recovery) and mark the band "Cytokine storm / warning-signs window" at defervescence.

Clinical / Diagnostic significance

- **Markers of the storm / severity:** rising **haematocrit with falling platelets**, hypoalbuminaemia, effusions on lateral-decubitus CXR or ultrasound, elevated transaminases; high **IL-10, ferritin** and AST track severity. The **tourniquet test** (≥10 new petechiae per square inch after 5-min BP-cuff inflation midway between systolic and diastolic) demonstrates microvascular fragility.
- **Diagnosis: NS1 antigen** ELISA/rapid test and **RT-PCR** in the first ~5 days; **IgM/IgG ELISA** thereafter. Early, rapidly rising IgG suggests a **secondary** (ADE-prone) infection. Flavivirus serological cross-reactivity (ZIKV, JEV, YFV) can confound.
- **Management is supportive—fluids are the keystone:** judicious **isotonic crystalloid/colloid** guided by vitals, urine output and haematocrit, ideally **before shock**, with careful titration to avoid overload during recovery reabsorption. **Acetaminophen/paracetamol** for fever; **avoid NSAIDs and aspirin** (gastritis/bleeding). Platelet transfusion is reserved for **severe thrombocytopenia (<10,000/μL)** or active bleeding—prophylactic transfusion is not beneficial and may harm. Treat shock, DIC and organ failure in critical care.
- **Immunomodulation:** Routine corticosteroids/IVIG are **not** proven to alter outcome in severe dengue; targeted anti-cytokine therapy remains investigational. The cytokine-storm/ADE concept underpins **vaccine caution**.
- **Vaccine relevance of ADE: CYD-TDV (Dengvaxia)**, built on the YFV-17D platform, *increased* severe dengue in **seronegative** recipients (vaccine acting as a "first serological hit"), mandating **pre-vaccination serostatus screening**; **TAK-003 (Qdenga)**, a two-dose vaccine, shows benefit including in some seronegatives but with serotype caveats.

High-yield exam pointers

- Cytokine storm = **immunopathology**, not direct viral cytopathic lysis—peaks at **defervescence/critical phase**, not at peak fever.
- **Secondary heterotypic infection + ADE + cross-reactive T cells (original antigenic sin)** = core triggers; **NS1** degrades glycocalyx and is the named driver of vascular leak.

- Dominant mediators to write: **TNF-α, IFN-γ, IL-6, IL-1β, IL-8, IL-10, VEGF**, complement **C3a/C5a**.
- Cardinal consequence = **increased vascular permeability → plasma leak → haemoconcentration → DSS**; plus **thrombocytopenia/DIC → bleeding**.
- **Severe dengue (WHO 2009)** = plasma leakage (shock/respiratory distress) **or** severe bleeding **or** severe organ dysfunction.
- Triad to monitor: **rising HCT + falling platelets + warning signs**; effusions are an early leak sign.
- Treatment = **fluids + paracetamol; avoid NSAIDs/aspirin**; platelets only if <10,000/μL or bleeding; **steroids/IVIG unproven**.
- **~500,000 severe dengue cases/year, CFR ~2.5%** (falls to ~1% with expert supportive care).
- **Dengvaxia ADE pitfall:** harm in seronegatives → screen serostatus before vaccinating.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Arthropod-Borne and Rodent-Borne Virus Infections" (Dengue, Severe Dengue and Viral Haemorrhagic Fever sections: ADE/immune enhancement, enhancing non-neutralising antibodies, NS1-driven vascular leak, plasma-leak/critical phase, severe-dengue criteria, host/viral risk factors, tourniquet test, vaccine ADE).
- **Harrison's 22e** — "Mechanisms of Regulation and Dysregulation of the Immune System" (general biology of pro-inflammatory cytokines TNF-α, IL-1, IL-6, IFN-γ and the anti-inflammatory IL-10/TGF-β axis underpinning immune dysregulation).
- **CMDT 2026** — "Viral & Rickettsial Infections" (Dengue: WHO 1997 vs 2009 classification, severe-dengue definition, laboratory monitoring, supportive treatment, NSAID avoidance, platelet-transfusion threshold, prognosis, comorbidity risk, vaccines).
- **Coverage note (spec gap = true):** The corpus grounds the *triggers* of the storm (ADE, secondary heterotypic infection, NS1-mediated vascular leak, T-cell dysregulation) and the *general* cytokine biology, but does **not** enumerate the dengue-specific cytokine cascade (TNF-α/IFN-γ/IL-6/IL-8/IL-10/VEGF, complement C3a/C5a, mast-cell/glycocalyx mechanisms) or use the phrase "cytokine storm" verbatim for dengue. Those mediator-level specifics are included as **universally accepted standard internal-medicine/infectious-disease teaching** and are flagged here for transparency.

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Extended-spectrum beta-lactamases (ESBL)

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — β-Lactamases are bacterial enzymes that hydrolyse the four-membered β-lactam ring and thereby inactivate β-lactam antibiotics; they are the commonest mechanism of β-lactam resistance in gram-negative bacteria. **Extended-spectrum β-lactamases (ESBLs)** are plasmid-encoded β-lactamases — usually evolved by point mutations from earlier penicillinases — that have an *expanded substrate profile* enabling them to degrade the oxyimino (third-generation) cephalosporins (ceftriaxone, cefotaxime, ceftazidime) and the monobactam aztreonam, while remaining **susceptible to β-lactamase inhibitors** (clavulanate, sulbactam, tazobactam) and (characteristically) **not** hydrolysing carbapenems or the cephamycins (cefoxitin). They are predominantly found in *Enterobacterales*, chiefly **Escherichia coli and Klebsiella pneumoniae**, and are a globally disseminated cause of multidrug-resistant infection.

Where ESBLs sit among β-lactamases — classification

Two complementary schemes are used: the **Ambler molecular classification** (based on amino-acid sequence/active site) and the **Bush–Jacoby functional classification** (based on substrate and inhibitor profile). ESBLs are predominantly **Ambler class A, Bush–Jacoby group 2be**.

Ambler class (active site)	Bush–Jacoby group	Enzyme examples	Hydrolyses	Inhibited by clavulanate?
A (serine)	2b / **2be (ESBL)** / 2f	Early TEM-1, SHV-1 penicillinases → **ESBLs: TEM-, SHV-, CTX-M-types**; KPC carbapenemase (2f)	Penicillins, oxyimino-cephalosporins, aztreonam (ESBL); + carbapenems (KPC)	**Yes** (ESBL); KPC variably
B (metallo-, Zn^{2+})	3	**NDM**, VIM, IMP (metallo-carbapenemases)	Penicillins, cephalosporins, **carbapenems** (not aztreonam)	**No** (and not avibactam)
C (serine)	1	**AmpC** (chromosomal in *Enterobacter*; also plasmid)	Penicillins, cephalosporins **including cefoxitin**	**No**
D (serine)	2d	**OXA**-type (incl. OXA-ESBLs; **OXA-48** carbapenemase)	Oxacillin/cloxacillin; some extended cephalosporins; OXA-48 → carbapenems	Variable / poorly

- **Phenotypic / practical classification** the candidate must also state: ESBLs are distinguished from the two great mimics — **AmpC cephalosporinases** (class C; not inhibited by clavulanate, *do* hydrolyse cefoxitin) and **carbapenemases** (KPC, NDM, OXA-48; hydrolyse carbapenems) — because the treatment differs sharply.
- **ESBL families:** the earliest were TEM- and SHV-derived; the now globally **predominant family is CTX-M** (e.g. CTX-M-15), which preferentially hydrolyses cefotaxime/ceftriaxone and drives community-onset ESBL *E. coli*.

Defining hydrolytic profile of ESBLs (substrate "fingerprint")

- **Degraded (resistant):** all penicillins; early- and extended-spectrum cephalosporins — ceftriaxone, cefotaxime, **ceftazidime**; and the monobactam **aztreonam**. Some ESBLs additionally degrade the fourth-generation cephalosporin **cefepime**, making cefepime unreliable.
- **Usually spared (treatment relevant): carbapenems** (imipenem, meropenem, ertapenem, doripenem) are *not* degraded by ESBLs; cephamycins (cefoxitin) are also stable but are not used clinically for this.
- **Inhibited by:** clavulanate, sulbactam, tazobactam (and the newer diazabicyclooctanes avibactam, relebactam) — this *clavulanate susceptibility* is the basis of laboratory confirmation.
- **Co-resistance:** the ESBL plasmid frequently co-carries genes for **fluoroquinolone and aminoglycoside resistance**, so ESBL isolates are often resistant to ciprofloxacin and gentamicin as well — a key reason the carbapenems become indispensable.

Risk factors for acquiring an ESBL-producing organism

- **Prior antimicrobial exposure** — especially recent **third-generation cephalosporins and fluoroquinolones** (selection pressure favouring resistant strains); prior antibiotic therapy of any kind.
- **Prior infection or colonisation with a resistant pathogen**, and being part of a population with a large resistance reservoir.
- **Prior or prolonged hospitalisation**, particularly **ICU stay**; transfer from or residence in **long-term-care / nursing facilities**.
- **Invasive devices** breaching host barriers — indwelling **urinary catheters**, central venous/IV catheters, surgical drains, nasogastric and endotracheal tubes — a frequent source of health-care-associated gram-negative infection.
- **Cross-transmission** in health-care settings via the **contaminated hands of health-care workers** when hand hygiene/infection-control is inadequate.
- **Other widely accepted host factors:** recurrent or complicated urinary tract infection, recent surgery, haemodialysis, diabetes mellitus, immunosuppression, and **travel to / residence in highly endemic regions** (e.g. the Indian subcontinent for community-acquired CTX-M and for NDM carbapenemases).

Implications on antibiotic choice

- **Carbapenems are the drugs of choice** for serious ESBL infections (bacteraemia, pyelonephritis, intra-abdominal sepsis): they are *the most reliable agents* against ESBL producers. Use **meropenem/imipenem** for severe disease; **ertapenem** is a useful *carbapenem-sparing* once-daily option for stable, non-pseudomonal ESBL infection (preserves antipseudomonal carbapenems).
- **Do NOT rely on third-generation cephalosporins** even if the disk reports "susceptible" — there is an inoculum effect and high failure rate; ESBLs hydrolyse them in vivo.
- **β-Lactam/β-lactamase-inhibitor combinations** (e.g. piperacillin-tazobactam) inhibit ESBLs in vitro, but their role in serious/bacteraemic ESBL infection is *debated* and they are generally inferior to carbapenems — reserve, if at all, for source-controlled, lower-acuity infection.

- **If a carbapenem cannot be used** (allergy, stewardship, carbapenemase co-existence): **ceftazidime-avibactam**, or possibly **ceftolozane-tazobactam** or **imipenem-cilastatin-relebactam** can be considered (avibactam/relebactam additionally cover KPC/AmpC, not metallo-enzymes).
- **Uncomplicated lower UTI (cystitis):** oral **nitrofurantoin** or **fosfomycin** are effective ESBL-active options that spare carbapenems (avoid in pyelonephritis/bacteraemia).
- **Fluoroquinolones and aminoglycosides are unreliable empirically** because of frequent plasmid-linked co-resistance — use only if susceptibility is confirmed; amikacin or **plazomicin** may remain active where gentamicin/tobramycin are not.
- **Salvage / extensively-resistant gram-negatives: cefiderocol** (siderophore cephalosporin) and the polymyxins (colistin) are options for carbapenem-resistant organisms.
- **Stewardship and empirical strategy:** in patients with ESBL risk factors who are septic, start **empirical carbapenem cover**, then **de-escalate** to the narrowest effective agent for the shortest course once cultures/susceptibilities return; restrict cephalosporin/fluoroquinolone over-use, enforce hand hygiene and contact precautions to limit spread.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Gram-negative cell-envelope schematic** showing the resistance site: outer membrane with **porin channel**, **β-lactamase enzyme in the periplasmic space** degrading the β-lactam before it reaches its target, and the inner-membrane **penicillin-binding proteins (PBPs/transpeptidases)**. Labels: *Outer membrane, Porin, Periplasmic space, β-lactamase (ESBL), β-lactam antibiotic, PBP/transpeptidase, Peptidoglycan, Inner (cytoplasmic) membrane, Efflux pump.*
- **Classification tree** of β-lactamases: *β-lactamases → Ambler A (ESBL: TEM/SHV/CTX-M, KPC) / B (metallo – NDM, VIM, IMP) / C (AmpC) / D (OXA, OXA-48)*, with a side box: *"ESBL = hydrolyses 3rd-gen cephalosporins + aztreonam; inhibited by clavulanate; spares carbapenems & cefoxitin."*

Clinical / Diagnostic significance

- **Laboratory detection** rests on the *clavulanate effect*: a **phenotypic confirmatory test** shows a ≥3-doubling-dilution fall in the MIC of cefotaxime or ceftazidime when combined with clavulanate; the **double-disk synergy test** shows enhancement of the cephalosporin inhibition zone towards a co-placed amoxicillin-clavulanate disk. Distinguish from AmpC (no clavulanate synergy, cefoxitin-resistant).
- **Empirical choice is local-data-driven:** know the unit/hospital ESBL prevalence; obtain cultures **before** antibiotics; communicate rapid susceptibility results promptly to guide directed therapy.
- **Infection control:** ESBL producers are an *escalating, transmissible* threat (CDC "Serious" category — ESBL-producing *Enterobacterales*); contact precautions, hand hygiene, device removal and antimicrobial stewardship reduce acquisition and spread.
- **Prognostic impact:** ESBL infection independently delays appropriate therapy, prolongs hospital stay and increases mortality — hence the value of risk-stratified empirical carbapenem cover in the septic at-risk patient.

High-yield exam pointers

- **ESBL = plasmid-mediated, Ambler class A / Bush–Jacoby 2be**, clavulanate-inhibited enzyme that hydrolyses **oxyimino-cephalosporins + aztreonam** but **spares carbapenems and cefoxitin**.
- Commonest hosts: **E. coli and K. pneumoniae** (and other *Enterobacterales*); dominant family now **CTX-M** (CTX-M-15).
- **Three mimics to separate:** ESBL (class A, clavulanate-sensitive), **AmpC** (class C, clavulanate-resistant, cefoxitin-resistant), **carbapenemase** (KPC/NDM/OXA-48).
- **Top risk factors:** prior cephalosporin/fluoroquinolone use, prior hospitalisation/ICU, long-term-care residence, indwelling catheters/devices, prior resistant-organism colonisation, endemic-area exposure.
- **Treatment of choice = carbapenem** (ertapenem for carbapenem-sparing; meropenem for severe); **do not use cephalosporins despite "S"** on the report.
- **Carbapenem-sparing alternatives:** ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam; **cystitis** → nitrofurantoin/fosfomycin.
- **Co-resistance** to fluoroquinolones and aminoglycosides is common → narrows empirical options.
- **Detection:** double-disk synergy / clavulanate MIC reduction test.
- **Control:** stewardship + de-escalation + hand hygiene/contact precautions.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bacterial Resistance to Antimicrobial Agents" (β-lactamases, ESBL substrate profile, AmpC vs ESBL, carbapenemases KPC/NDM/OXA-48, β-lactamase inhibitors, cefiderocol; risk factors and epidemiology of resistance; CDC threat categories) and "Treatment and Prophylaxis of Bacterial Infections" (β-lactam mechanism, empirical vs directed therapy, antimicrobial stewardship).
- **CMDT 2026** — "Common Problems in Infectious Diseases & Antimicrobial Therapy" (ESBL → carbapenem; ceftazidime-avibactam / ceftolozane-tazobactam / imipenem-relebactam alternatives; ESBL *E. coli* co-resistant to cephalosporins, aminoglycosides, fluoroquinolones) and "Anti-infective Treatment: Antibiotic, Antifungal & Antiviral Agents" (carbapenems most reliable for ESBL; extended-spectrum penicillins; fosfomycin for UTI).

Coverage note: The Harrison/CMDT corpus describes ESBLs, AmpC, carbapenemases, the inhibitors and the management hierarchy in full, and supplies the risk-factor set (prior antibiotics, prior hospitalisation, prior resistant infection, invasive devices, cross-transmission). The **formal scheme names** (Ambler classes A–D; Bush–Jacoby group 2be), the **enzyme-family names** (TEM/SHV/CTX-M), and the **phenotypic confirmatory/double-disk synergy test** are universally accepted standard infectious-disease microbiology added for completeness, though not spelled out verbatim in this Harrison/CMDT corpus; all such points are stated accurately.

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Septic shock

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Shock is the clinical condition of organ dysfunction resulting from an **imbalance between cellular oxygen supply and demand**, producing cellular and tissue hypoxia; it is a life-threatening state and a common reason for ICU admission. Organ dysfunction in early shock is often **reversible** with restoration of oxygen delivery, but untreated shock transitions to an **irreversible** phase with multisystem organ failure and death. **Septic shock** is the commonest cause of distributive shock and is defined (Sepsis-3, 2016) as the subset of sepsis in which **profound circulatory, cellular, and metabolic abnormalities** increase mortality risk beyond sepsis alone — operationally, a septic patient requiring **vasopressors to maintain MAP ≥65 mmHg** and with **serum lactate >2 mmol/L despite adequate fluid resuscitation**.

Determinants of oxygen delivery and classification of shock

- Oxygen delivery: $\mathbf{DO_2 = CO \times CaO_2}$, where $\mathbf{CO = HR \times SV}$ and $\mathbf{CaO_2 = (Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)}$; stroke volume $\mathbf{SV \propto (Preload \times Contractility) / SVR}$.
- Any disturbance of HR, preload, contractility, SVR, SaO_2 or haemoglobin can reduce DO_2 and cause shock. Shock can also arise from **increased consumption** or **impaired utilisation** (e.g., *cyanide poisoning* uncouples oxidative phosphorylation).
- Four major physiologic types, each with a distinct haemodynamic profile:

Type	Primary derangement	CVP	PCWP	Cardiac output	SVR	Examples
Distributive	↓ SVR (vasodilation)	↓	↓	↑	↓	**Septic shock**, pancreatitis, severe burns, anaphylaxis, neurogenic, adrenal crisis
Cardiogenic	↓ CO (pump failure)	↑	↑	↓	↑	MI, myocarditis, arrhythmia, acute valvular failure
Obstructive	↓ CO (mechanical obstruction)	↑	↓/↑	↓	↑	Tension pneumothorax, tamponade, massive PE, aortic dissection
Hypovolemic	↓ preload	↓	↓	↓	↑	Haemorrhage (trauma, GI bleed), GI/renal/skin fluid losses

- **Mixed shock** is common: e.g., distributive septic shock with superimposed sepsis-induced cardiomyopathy adds a cardiogenic component. **Sepsis is the most common cause of distributive shock** and predominates in the ICU.

Stages of shock

- **Compensated (pre-shock):** physiologic responses (tachycardia, rising CO in early sepsis; ↑SVR and ↑HR in haemorrhage) maintain perfusion; no overt organ dysfunction, perhaps mild lactate or creatinine rise.
- **Decompensated shock:** compensatory mechanisms overwhelmed → frank organ dysfunction (encephalopathy, oliguria). Still reversible with timely restoration of perfusion.

- **Irreversible shock:** permanent organ damage progressing to multisystem organ dysfunction and death.

Pathophysiology of septic shock

- **Trigger: Pathogen-associated molecular patterns (PAMPs)** — bacterial LPS, cell-wall components, pathogen nucleic acids — and host **damage-associated molecular patterns (DAMPs)** — histones, HMGB1, S100 proteins, extracellular DNA, ATP — are sensed by **pattern recognition receptors (PRRs)**: toll-like receptors (TLRs), C-type lectin receptors, RAGE, RIG-I-like and NOD-like receptors.
- **Dysregulated host response:** PRR activation on neutrophils, monocytes and macrophages triggers release of **pro-inflammatory cytokines/chemokines** (IL-1β, IL-6, TNF-α), up-regulates vascular adhesion molecules and drives **emergency granulopoiesis**. Neutrophils release **neutrophil extracellular traps (NETs)**. Concurrent lymphoid exhaustion/apoptosis and myeloid-derived suppressor cells cause **immunosuppression**, predisposing survivors to secondary infection.
- **Endothelial activation:** breakdown of the endothelial **glycocalyx**, ↑ICAM/VCAM-1 expression, loss of VE-cadherin and tight junctions, and endothelial apoptosis cause **capillary leak**, interstitial oedema and increased oxygen-diffusion distance.
- **Coagulopathy:** ↑tissue factor triggers the extrinsic cascade; vWF and platelet aggregates plus NETs form **fibrin-rich microthrombi**. Anticoagulants (antithrombin, tissue factor pathway inhibitor, activated protein C) are depleted and fibrinolysis is impaired (↑PAI-1) → microvascular thrombosis; consumption of factors and platelets causes **DIC** and bleeding. The complement cascade is activated (C3a, C5a anaphylatoxins; **C5b-9 membrane attack complex**) amplifying injury.
- **Circulatory failure:** systemic **arteriolar vasodilation** (partly excess **nitric oxide**) lowers SVR; venodilation and capillary leak reduce venous return and preload; hypotension results. Up to half of patients develop **sepsis-induced cardiomyopathy** (↓LVEF, ↑end-diastolic volume index, RV impairment).
- **Cellular injury:** inadequate oxygen delivery plus direct injury from ROS/reactive nitrogen species and **mitochondrial/metabolic dysfunction** (cytopathic hypoxia) impair ATP generation and ion homeostasis even when oxygen delivery is restored → multiorgan injury. Anaerobic metabolism converts pyruvate to **lactate** (lactic acidosis), the biochemical hallmark.

Recognition and diagnostic criteria

- **Sepsis-3 (current):** sepsis = **life-threatening organ dysfunction from a dysregulated host response to infection**, operationalised as a rise of **≥2 in SOFA score**. **SOFA** scores six systems — neurologic (GCS), cardiovascular (MAP/vasopressors), respiratory (PaO_2/FiO_2), hepatic (bilirubin), renal (creatinine), coagulation (platelets).
- **Septic shock:** vasopressor requirement to keep **MAP ≥65 mmHg** plus **lactate >2 mmol/L** despite fluid resuscitation; mortality up to **40%**.
- **qSOFA** (rapid bedside screen): RR ≥22/min, altered mentation (GCS <15), SBP ≤100 mmHg — score ≥2 (with suspected infection) flags high mortality risk; more specific but less sensitive than SIRS.

- *Historical:* SIRS criteria (temp <36/>38 °C, HR >90, RR >20 or $PaCO_2$ <32, WBC <4000/>12000 or >10% bands); Sepsis-1 (1992), Sepsis-2 (2003) preceded Sepsis-3.
- Initial workup: CBC with differential, basic metabolic panel, LFTs, **serum lactate**, coagulation panel, urinalysis; **cultures of blood and other sites before antibiotics**; targeted imaging (X-ray/CT/USG) for source. Exclude **sepsis mimics** (heart failure, mesenteric ischaemia, adrenal insufficiency, hypovolaemia) — ~25% of presumed sepsis are mimics.

Management of septic shock (Surviving Sepsis Campaign 2021)

- **Early antibiotics — most important survival lever:** immediate empiric **broad-spectrum antimicrobials within 1 h of shock recognition** (after cultures, but do not delay for them). Every 1-h delay adds an estimated **7–8% mortality**. De-escalate on culture data; practise stewardship and short courses.
  - Site-directed empiric choices: **ceftriaxone/cefotaxime** if *Pseudomonas* unlikely; **cefepime, piperacillin-tazobactam, or a carbapenem (meropenem/imipenem)** if *Pseudomonas* likely; add **vancomycin or linezolid** for MRSA risk; **echinocandin** if fungal risk (recent abdominal surgery, TPN, *Candida* colonisation).
- **Fluid resuscitation: balanced crystalloid (lactated Ringer's)** preferred over 0.9% saline; initial bolus ~**30 mL/kg over 5–10 min**. Albumin if large crystalloid volumes already given; **avoid hydroxyethyl/pentastarch** (kidney injury, death). Guide further fluids by **dynamic measures** (capillary refill time, passive leg raise, point-of-care ultrasound/IVC, SV variation) — *not* static CVP-targeted protocols.
- **Vasopressors: Norepinephrine is first-line** (α_1 vasoconstriction + β_1 inotropy/chronotropy) to target **MAP ≥65 mmHg**; **add vasopressin as second agent**, then **epinephrine third**. Place an arterial line for continuous BP. **Dopamine is not first-line** (arrhythmia; increased mortality in cardiogenic subgroup).
- **Corticosteroids: IV hydrocortisone 200 mg/day (50 mg q6h)** for ongoing vasopressor requirement.
- **Inotropy:** for sepsis-induced cardiomyopathy with persistent hypoperfusion after volume, **add dobutamine to norepinephrine or switch to epinephrine**; pulmonary artery catheter only for **mixed septic + cardiogenic shock**.
- **Source control:** drain abscesses, debride necrotising soft-tissue infection, decompress obstructed biliary/urinary tract, remove infected catheters — **as rapidly as possible**.
- **Organ support:** lung-protective ventilation (tidal volume **6–8 mL/kg** ideal body weight, plateau pressure **<30 cmH_2O**, SpO_2 **90–96%**; rescue with prone positioning, neuromuscular blockade, VV-ECMO); RRT for standard indications (refractory acidaemia, hyperkalaemia, uraemia, volume overload); transfuse PRBC for **Hb <7 g/dL**; insulin for glucose **>180 mg/dL**; stress-ulcer prophylaxis and early enteral nutrition (within 48 h) once shock is controlled.

Organ-specific complications and supportive targets

System	Frequency	Key management
Neurologic (encephalopathy)	~54%	Treat cause; correct metabolic/electrolyte derangements; limit neurotoxic sedatives (*cefepime, opioids, benzodiazepines*)
Cardiovascular (shock)	~25% (half with myocardial dysfunction)	Balanced crystalloid; norepinephrine → vasopressin → epinephrine; hydrocortisone; dobutamine for low LVEF
Respiratory (ARDS)	~7%	SpO_2 90–96%; lung-protective ventilation; rescue therapies for refractory hypoxia
Renal (AKI)	up to ~67%	Maintain perfusion, avoid nephrotoxins; RRT/CRRT for standard indications
Hepatic (liver dysfunction)	~50% of septic shock	Avoid hypotension/hepatotoxins; USG if ↑bilirubin
Haematologic (DIC)	up to ~35% of septic shock	Cryoprecipitate (fibrinogen <150 mg/dL), platelets ($\leq 50\times10^9$/L + bleeding), FFP for bleeding with prolonged PT/INR

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Oxygen-delivery / shock cascade flowchart:** Label — $DO_2 = CO \times CaO_2$; $CO = HR \times SV$; $SV \propto (Preload \times Contractility)/SVR$; $CaO_2 = (Hb\times1.34\times SaO_2)+(0.003\times PaO_2)$; branch to the four shock types (Distributive / Cardiogenic / Obstructive / Hypovolemic); endpoint *anaerobic metabolism → ↑lactate → cellular injury*.
- **Septic-shock pathogenesis schematic:** Label — *Pathogen → PAMPs/DAMPs → PRRs (TLR)*; *Cytokines (IL-1β, IL-6, TNF-α)*; *Neutrophil + NETs*; *Endothelial activation → glycocalyx breakdown → capillary leak/oedema*; *Tissue factor → microthrombi → DIC*; *Complement C3a/C5a, C5b-9 (MAC)*; *NO-mediated vasodilation → ↓SVR → hypotension*; *Mitochondrial dysfunction → tissue hypoxia*.

Clinical / Diagnostic significance

- **Lactate** is central to diagnosis, risk stratification and monitoring; serial lactate (or capillary-refill-guided) resuscitation tracks response, though a major trial found capillary-refill-targeted resuscitation non-inferior to lactate-targeted for 28-day mortality.
- **Shock index (HR/SBP;** normal 0.5–0.7, abnormal >0.9) flags occult hypoperfusion and transfusion need.
- "**Windows**" of organ perfusion — CNS (confusion), kidney (oliguria <0.5 mL/kg/h), skin (mottling, prolonged capillary refill, cold clammy skin) — allow bedside recognition before labs return.
- POCUS/echocardiography differentiates shock type and detects sepsis-induced cardiomyopathy and mixed shock.

- Restrictive vs liberal fluid strategy and routine low-dose vasopressin-plus-norepinephrine showed no 90-day/28-day mortality difference — argues against rigid protocols.

High-yield exam pointers

- **Shock = supply–demand O_2 imbalance → tissue hypoxia**, reversible early, irreversible late.
- Four types by haemodynamics: **Distributive (↓SVR, ↑CO)** vs the three low-CO types (↑SVR); memorise the CVP/PCWP/CO/SVR table.
- **Septic shock = sepsis + vasopressor need for MAP ≥65 + lactate >2 despite fluids**; mortality up to 40%.
- Pathogenesis triad: **PAMPs/DAMPs–PRR inflammation → endothelial/glycocalyx injury & capillary leak → coagulopathy/microthrombi (DIC)**, plus NO-driven vasodilation and mitochondrial dysfunction.
- **Antibiotics within 1 h** of shock recognition — 7–8% added mortality per hour's delay.
- **Crystalloid (balanced) ~30 mL/kg**; guide further fluids by dynamic, not static (CVP), measures; avoid starches.
- Vasopressor ladder: **norepinephrine → vasopressin → epinephrine**; **hydrocortisone 200 mg/day** for refractory shock; **dobutamine/epinephrine** for sepsis-induced cardiomyopathy.
- Don't forget **source control** and **culture before antibiotics**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 314 "Approach to the Patient with Shock" (definition, oxygen-delivery determinants, classification, stages, vasopressor pharmacology, undifferentiated-shock management) and Ch 315 "Sepsis and Septic Shock" (Sepsis-3 definitions, pathogenesis, Surviving Sepsis Campaign management, organ-specific complications). Coverage note: All major specifics (hemodynamic profiles, Sepsis-3/qSOFA/SOFA criteria, drug doses, fluid volumes, complication frequencies) are sourced from these two chapters; the Sepsis-1 SIRS/Sepsis-2 historical criteria and shock-index cut-offs are also taken verbatim from Ch 314/315.

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Multidrug-resistant tuberculosis (MDR-TB)

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Multidrug-resistant tuberculosis (MDR-TB) is disease caused by a strain of *Mycobacterium tuberculosis* resistant *at least* to **isoniazid (H) and rifampin (R)** — the two most efficacious first-line bactericidal drugs. It represents one end of a spectrum that ranges from rifampin-resistant (RR) through pre-XDR to extensively drug-resistant (XDR) TB. Because the two most potent drugs are lost and co-resistance to other first-line agents (e.g., ethambutol) is common, MDR-TB requires longer, more toxic, costlier and individualised regimens. Drug resistance almost invariably follows effective **monotherapy** (provider error, poor adherence, malabsorption, or poor-quality/crushed drugs).

Definitions & resistance spectrum

Category	Resistance pattern (Harrison 22e)
RR-TB	Resistant to rifampin (± other drugs); rifampin resistance is an excellent *proxy* for MDR-TB
MDR-TB	Resistant at least to **isoniazid AND rifampin**
Pre-XDR-TB	MDR/RR-TB strain *additionally* resistant to **any fluoroquinolone**
XDR-TB	MDR-TB + resistance to **any fluoroquinolone AND at least one additional Group A drug** (i.e., bedaquiline or linezolid)

- **Primary resistance** = patient infected from the outset by a resistant strain; **acquired resistance** = develops in the infecting strain during inadequate treatment.
- *Mono-resistance to rifampin is rare and is managed as MDR-TB.*

Epidemiology & risk factors

- Of an estimated **10.8 million** new TB cases in 2023, ~**400,000** were RR/MDR-TB — **3.2% of new** and **16% of previously treated** cases. Only ~189,000 were enrolled on treatment, reflecting limited culture/DST capacity.
- Geography: **>50% of all MDR/RR-TB occurs in India (27%), Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%)**; the former Soviet states have the highest *proportion* among new cases (up to one-third).
- **Risk factors:** presenting from an area where ≥5% of incident cases are MDR, **prior TB treatment**, treatment default/failure/relapse, and contact with a known MDR case.
- The **vast majority of XDR-TB remains undiagnosed** because reliable DST and laboratory capacity are lacking in low-income settings.

Molecular basis of drug resistance

Resistance is due to **spontaneous chromosomal mutations** (no plasmid transfer); knowing the target genes underpins rapid molecular DST.

Drug	Gene(s)	Encoded target / note
Isoniazid	*katG*, *inhA* (also *kasA*, *ndh*)	Catalase-peroxidase; enoyl-ACP (keto-enoyl) reductase
Rifampin	*rpoB*	β-subunit of RNA polymerase (core region; mostly missense)
Pyrazinamide	*pncA*	Pyrazinamidase (activates prodrug); mutated in 72–98%
Ethambutol	*embB* (codon 306 in 50–70%)	Arabinosyltransferase
Fluoroquinolones	*gyrA*, *gyrB*	DNA gyrase
Bedaquiline	*atpE*; *Rv0678/mmpR*, *pepQ*	ATP synthase subunit c; efflux-pump repressor → *cross-resistance with clofazimine*
Linezolid	23S rRNA, *rplC* (L3), *rplD* (L4)	50S ribosomal subunit

Diagnosis — rapid drug-susceptibility testing (DST)

- **Universal DST is the WHO standard of care**: every initial isolate should be tested at least to **rifampin** (proxy for MDR); expanded testing to **isoniazid, fluoroquinolones and key second-line drugs is mandatory once RR-TB is found**.
- **Rapid molecular tests (preferred first test):**
  - **Xpert MTB/RIF & Xpert MTB/RIF Ultra** — detect *M. tuberculosis* and **rpoB (rifampin resistance)** simultaneously.
  - **Truenat MTB-Rif Dx** — portable, battery-operated; rifampin resistance sensitivity ~**84%**, specificity ~**97%**.
  - **Line probe assays (LPAs)** — DNA-strip tests detecting *rpoB*, *katG*, *inhA*; **second-line LPAs** are the recommended initial test for **fluoroquinolone / injectable** resistance in confirmed RR/MDR-TB.
- **Phenotypic culture-based DST** (MGIT liquid ~3 weeks; solid Löwenstein-Jensen ≥8 weeks) is still needed for drugs/mutations not covered by molecular tests and to monitor emerging resistance.
- **Whole-genome sequencing (WGS)** and **targeted next-generation sequencing (tNGS)** give comprehensive resistance profiles; tNGS can be run directly on sputum.

WHO drug grouping (for longer regimens) & treatment regimens

WHO priority grouping (Table 183-3):

Group	Drugs	Rule
A (use all three)	Levofloxacin/moxifloxacin; **bedaquiline**; **linezolid**	All three included; ≥3 retained if bedaquiline stopped
B (≥1 included)	Clofazimine; cycloserine/terizidone	Add a 2nd if a Group A drug cannot be used

Group	Drugs	Rule
C (complete the regimen)	Ethambutol, delamanid, pyrazinamide, imipenem-cilastatin/meropenem, amikacin (or streptomycin), ethionamide/prothionamide, PAS	Used when A/B insufficient

- **Kanamycin and capreomycin are NO LONGER recommended** (worse failure/relapse); injectables are now largely avoided. All-oral regimens are preferred.

Recommended all-oral regimens (2022–2024 WHO):

Regimen	Composition & duration	Use
BPaLM *(preferred)*	**B**edaquiline + **Pa** pretomanid + **L**inezolid 600 mg + **M**oxifloxacin × **6 months**	MDR/RR or pre-XDR, age **≥14 y**, any HIV status; *drop Mfx if documented fluoroquinolone resistance* (= BPaL)
BDLLfxCfz	Bedaquiline + delamanid + linezolid 600 + levofloxacin + clofazimine × **6 months**	Non-inferior alternative; usable in **children, adolescents, pregnant/breast-feeding** women
9-month all-oral	**BLMZ**, or BLLfxCfzZ, or BDLLfxZ	No fluoroquinolone resistance & no prior exposure to B/D/L
Longer individualised	≥3 Group A + ≥1 Group B (add C as needed); **≥18–20 months** (15–17 months after culture conversion)	Complex patterns including **XDR-TB**

- **BPaLM** achieves treatment success ~**90%** (TB-PRACTECAL, Nix-TB, ZeNix). It is **avoided in disseminated, CNS and osteoarticular TB and in pregnancy/breast-feeding** (incomplete pretomanid safety data).
- Landmark trials: **STREAM stage-1** (9-month "Bangladesh" regimen), **Nix-TB/ZeNix** (BPaL, linezolid dose-finding), **TB-PRACTECAL** (24-week BPaLM non-inferior with fewer serious adverse events), endTB and BEAT-TB.
- **Surgery** (lobectomy/wedge resection) may be added for localised disease with adequate pulmonary reserve.

Monitoring, key drug toxicities & special situations

- **QT-prolonging drugs — bedaquiline, delamanid, clofazimine, fluoroquinolones:** baseline + serial **ECG**; do **not** use if QTc **>500 ms** or history of ventricular arrhythmia.
- **Bedaquiline:** 400 mg/day × 2 weeks then 200 mg thrice-weekly; FDA **black-box warning** (QT prolongation; excess mortality 11.4% vs 2.5% in one trial); CYP3A4-metabolised — rifampin/efavirenz lower its levels.
- **Linezolid:** 600 mg once daily; optic & peripheral neuropathy, **myelosuppression/pancytopenia**, lactic acidosis, serotonin syndrome (weak MAO inhibitor).
- **Clofazimine:** reversible orange-brown skin/secretion discoloration; very long t½ (~70 days). **Cycloserine:** seizures, psychosis, depression. **Amikacin** (if used): serial **audiometry**.
- **HIV co-infection:** integrase inhibitor **dolutegravir/raltegravir at double dose** (not bictegravir/cabotegravir/elvitegravir) or efavirenz; advanced immunosuppression (CD4 <100/µL) raises failure/relapse risk.

- **Programmatic essentials: DOT/patient support**, informed consent, monthly bacteriologic monitoring, active drug-safety monitoring, infection-control measures.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Concentric/Venn classification of drug resistance:** outermost ring "**RR-TB (rifampin-R)**" → inner "**MDR-TB (H + R resistant)**" → "**Pre-XDR (MDR + any fluoroquinolone-R)**" → core "**XDR (+ bedaquiline or linezolid-R)**". Label each with its defining drug(s).
- **Diagnostic-to-treatment algorithm:** *Sputum* → **Xpert MTB/RIF Ultra** → *Rifampin resistance detected (RR-TB)* → **second-line LPA / phenotypic DST (fluoroquinolone)** → branch to "**BPaLM (6 mo)**", "**9-month all-oral**", or "**Longer ≥18-mo individualised (XDR)**". Labels: *Group A / B / C drugs*, *DST*, *culture conversion*.

Clinical / Diagnostic significance

- A single **rifampin-resistance** result on Xpert should trigger a full second-line DST and an MDR regimen — never treat presumptively as drug-susceptible.
- Empirical MDR therapy is justified in a high-likelihood patient (failure/default, MDR contact) while confirmatory DST is awaited.
- Avoid repeated empirical **fluoroquinolone** courses for "community-acquired pneumonia" — they delay TB diagnosis and **breed fluoroquinolone resistance**.
- Prevention of resistance = ≥2 quality-assured bactericidal drugs to which the strain is susceptible, **fixed-dose combinations**, supervised therapy, and completion of the full course.

High-yield exam pointers

- **MDR = resistant to at least H + R**; XDR adds fluoroquinolone + bedaquiline/linezolid resistance.
- **Rifampin resistance (rpoB) is the molecular proxy for MDR** — basis of Xpert MTB/RIF.
- Isoniazid resistance: **katG / inhA**; pyrazinamide: **pncA**; ethambutol: **embB306**; fluoroquinolone: **gyrA**; bedaquiline: **atpE / Rv0678** (cross-resistant to clofazimine).
- **Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid** (memorise — most heavily weighted).
- **BPaLM × 6 months is now the preferred MDR/RR regimen** (age ≥14 y); BPaL if fluoroquinolone-resistant.
- **Kanamycin and capreomycin are no longer recommended.**
- Mandatory **ECG** monitoring for QT-prolonging anti-TB drugs; linezolid → cytopenias & neuropathy; bedaquiline → black-box QT/mortality warning.
- India carries **27%** of the world's MDR/RR-TB burden.

SOURCE & COVERAGE

Harrison 22e — Ch 183 "Tuberculosis" (epidemiology, definitions, diagnosis/DST, WHO drug groups & regimens, monitoring) + Ch 186 "Antimycobacterial Agents" (drug mechanisms, resistance genes, doses, MDR definition, BPaLM/trials). Coverage note: All specifics (definitions, gene names, regimen compositions, doses, QT cut-off, epidemiology) are drawn from these two chapters; RNTCP/NTEP (India)–specific programmatic nomenclature is not in Harrison and is therefore not quoted.

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Dengue fever with complications

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Dengue is an acute arboviral infection caused by any of four dengue viruses, **DENV-1-4**, transmitted predominantly by *Aedes aegypti* and, less efficiently, *Aedes albopictus*. Clinical disease ranges from asymptomatic infection or classical "break-bone fever" to **severe dengue**, formerly called dengue hemorrhagic fever/dengue shock syndrome. Complicated dengue is defined clinically by **plasma leakage causing shock or respiratory distress**, **severe bleeding**, or **severe organ dysfunction**.

Etiology, transmission and pathogenesis

- Dengue viruses are **flaviviruses** with four antigenically distinct serotypes; infection with one serotype gives durable homologous protection but not reliable long-term protection against the other serotypes.
- Transmission is mainly **human-mosquito-human**. The vector breeds close to human habitation in relatively fresh water in jars, vases, discarded containers, coconut husks, old tires and similar collections; biting is typically daytime.
- Rare non-vector routes include needlestick or mucocutaneous healthcare exposure, vertical transmission, blood products, bone marrow transplantation and solid-organ transplantation.
- Most primary infections are subclinical. Symptomatic patients develop a **febrile phase**, a possible **critical/plasma-leak phase** around defervescence, and a **recovery phase**.
- Severe disease is promoted by host and viral factors, especially **immune-mediated enhancement** during heterotypic reinfection. Severe dengue is associated with vascular permeability; Harrison notes a key role for **DENV NS1 protein** in the vascular-leak phenomenon.
- Risk is higher with secondary infection, some viral variants such as Southeast Asian DENV-2, serotype 2 disease in CMDT, diabetes/obesity, older age and comorbid cardiovascular, pulmonary, renal or cerebrovascular disease.

Clinical phases and warning signs

Phase	Usual timing and features	Exam emphasis
Febrile phase	Incubation is about **4-7 days** in Harrison and usually **7-10 days** in CMDT. Abrupt high fever, chills, frontal headache, retro-orbital pain, severe myalgia/back pain, arthralgia, anorexia, nausea/vomiting and cutaneous hyperesthesia.	May show facial flushing, conjunctival redness, pharyngeal erythema, lymphadenopathy, hepatomegaly, transient macular rash, epistaxis or petechiae.
Critical phase	Often as fever declines, typically around days **3-5**; only a subset enters this phase.	Look actively for plasma leak, hemoconcentration, falling platelets, narrow pulse pressure, restlessness, lethargy and shock.
Recovery phase	Reabsorption of extravascular fluid as leak resolves; BP improves and diuresis occurs.	Reduce fluids to avoid overload; patchy pruritic erythematous rash and desquamation may occur; fatigue/depression may persist.

- **Warning signs requiring admission/close observation**: severe abdominal pain, persistent vomiting, clinical fluid accumulation/serosal effusion, mucosal or GI bleeding, lethargy or restlessness, increasing liver size/hepatomegaly, rising hematocrit with thrombocytopenia, postural symptoms or narrowing pulse pressure.
- **Classical uncomplicated dengue** may show a saddle-back fever, trunk-to-extremity maculopapular rash near defervescence, scattered petechiae and a positive tourniquet test.
- **Tourniquet test**: 10 or more new petechiae in 1 square inch after 5 minutes of BP cuff inflation midway between systolic and diastolic pressure suggests microvascular fragility; it is more associated with severe dengue but is not by itself a marker of major bleeding.

Classification and complications

WHO-style category	Key clinical meaning	Typical action
Dengue without warning signs	Fever with dengue symptoms, no leak/bleeding/organ-risk features.	Outpatient care only if reliable hydration, follow-up and warning-sign education are assured.
Dengue with warning signs	Dengue plus warning signs suggesting impending critical phase.	Admit/observe; serial vitals, urine output, hematocrit, platelets and clinical fluid status.
Severe dengue	Presumptive or confirmed dengue plus severe plasma leakage causing shock/respiratory distress, severe bleeding, or severe organ dysfunction.	Emergency triage, monitored setting/ICU, judicious IV fluids, blood products if bleeding, organ support.

- **Vascular leak/shock**: intravascular volume depletion, hypoalbuminemia, pleural effusion, ascites, narrow pulse pressure, cyanosis, hypothermia, altered consciousness, metabolic acidosis and circulatory collapse. Shock usually lasts **2-3 days** if treated through the critical period.
- **Bleeding**: petechiae, ecchymoses, epistaxis, palatal/gingival bleeding, GI bleeding and severe hemorrhage; DIC may complicate shock and progressive organ impairment.

- **Organ dysfunction**: hepatitis and fulminant hepatitis, encephalitis or altered mental status/seizures, myocarditis/arrhythmias, acute kidney injury, ocular disease including iritis, retinal hemorrhage and maculopathy.
- **Other complications**: pneumonia, bone marrow failure, bacterial superinfection, orchitis, oophoritis, oral bleeding/gingivitis, phrenic neuropathy, Guillain-Barre syndrome, transverse myelitis, cerebral vasculitis, subdural hematoma and acute disseminated encephalomyelitis.
- **Pregnancy**: infection near term risks hemorrhage in mother and infant; severe dengue increases obstetric complications, cesarean delivery, fetal distress and maternal morbidity.

Investigations and diagnosis

- Diagnosis is clinical in an epidemic/endemic setting but should be **laboratory confirmed** because dengue mimics malaria, influenza, chikungunya, leptospirosis, scrub typhus, typhoid, rickettsial infections, meningococcemia, Zika, yellow fever and other viral hemorrhagic fevers.
- **Early illness, first 5 days**: dengue RT-PCR/nucleic acid amplification or **NS1 antigen** detection by ELISA/rapid test. Harrison emphasizes antigen detection and nucleic acid amplification early.
- **After febrile phase/recovery**: IgM ELISA, paired serology or seroconversion. Early, rapidly rising **IgG from about day 4** suggests secondary infection rather than primary infection.
- Interpret serology cautiously because flavivirus cross-reactivity occurs after infection with or vaccination for antigenically related viruses such as yellow fever, Zika and Japanese encephalitis.
- Baseline and serial tests: CBC with hematocrit and platelet count, AST/ALT, bilirubin if jaundice, albumin, electrolytes, urea/creatinine, glucose, PT/INR/aPTT and fibrinogen if bleeding/DIC is suspected, ABG/lactate in shock, urinalysis and pregnancy test where relevant.
- Bedside severity assessment: pulse pressure, postural BP, capillary refill, temperature, mental status, urine output, hepatomegaly and bleeding. Ultrasound or lateral decubitus CXR can detect pleural effusion/ascites before they are clinically obvious.

Management of dengue with complications

- There is **no proven specific antiviral therapy** for dengue. Chloroquine, statins and balapiravir have not shown clear benefit; management is supportive and time-critical.
- **Triage** every suspected case for warning signs and severe dengue. Admit patients with warning signs, comorbid illness, pregnancy, poor oral intake, bleeding, rising hematocrit, rapidly falling platelets or unreliable follow-up. Severe dengue needs monitored care/ICU.
- **Fever and pain**: use acetaminophen/paracetamol. Avoid aspirin and preferably avoid NSAIDs such as ibuprofen because of gastritis, platelet dysfunction and bleeding risk.
- **Fluids**: encourage oral fluids when stable; give early IV isotonic crystalloid when warning signs, hemoconcentration, poor intake or shock are present. Titrate to pulse pressure, BP, capillary refill, mental status, urine output, hematocrit trend, bleeding and signs of fluid overload.
- **Shock**: treat as plasma-leak hypovolemia. Restore intravascular volume promptly but avoid blind over-resuscitation. If shock persists after appropriate volume replacement, use blood products for hemorrhage and vasopressors for ongoing circulatory failure in monitored care.
- **Bleeding and thrombocytopenia**: platelet count alone does not predict clinically important bleeding. Consider platelet transfusion for active bleeding or severe thrombocytopenia

<10,000/mcL; routine prophylactic platelet transfusion in non-bleeding dengue is not useful and may delay platelet recovery.

- **Recovery phase**: as vascular leak resolves, effusions are reabsorbed and diuresis begins. Reduce or stop IV fluids promptly to prevent pulmonary edema and respiratory distress.
- Provide organ-specific support: oxygen/ventilation for respiratory distress or ARDS, renal monitoring and dialysis if AKI is severe, correction of hypoglycemia/electrolytes/acidosis, management of encephalitis/seizures, and treatment of bacterial superinfection when clinically suspected.

Prevention and prognosis

- Prevention depends on **Aedes control**: remove stagnant water and discarded containers, cover water storage, use larvicidal/public-health measures, window screening, long sleeves, repellents and long-lasting insecticides. Emphasize early morning and late afternoon exposure risk.
- Screen blood transfusions for dengue in endemic settings where feasible; defer donation by acutely febrile or recently infected persons.
- **Vaccines**: Dengvaxia/CYD-TDV is a live attenuated tetravalent vaccine whose use is limited to persons with prior dengue infection because seronegative vaccinees have increased risk of severe dengue at first natural infection. TAK-003 has shown efficacy against symptomatic and hospitalized dengue in trials, with ongoing serotype-specific and policy considerations.
- Prognosis is excellent in uncomplicated dengue. Mortality in severe dengue falls sharply with early recognition, monitored fluids and bleeding control; Harrison notes case fatality can be as low as about **1%** in experienced tropical centers, while CMDT cites about **2.5%** of severe cases overall.
- Poor prognostic markers: shock, AKI in dengue shock syndrome, acute hepatitis/fulminant hepatitis, DIC, severe bleeding, persistent altered consciousness, metabolic acidosis, pregnancy near term, older age and major comorbid illness.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Natural history of dengue**: x-axis days 0-10; label febrile phase, defervescence, critical/plasma-leak phase, recovery phase, fever curve, platelet fall, hematocrit rise, shock window, fluid reabsorption/diuresis.
- **Severe dengue triad**: central "Severe dengue" box with three arms labelled plasma leakage -> shock/respiratory distress, severe bleeding -> GI/mucosal/DIC, severe organ dysfunction -> liver/CNS/heart/kidney/eye.

Clinical / Diagnostic significance

- Dengue is a must-consider diagnosis in acute fever with severe myalgia, retro-orbital pain, rash, leukopenia and thrombocytopenia after residence in or travel to an endemic area.
- The life-saving clinical point is **not the platelet count alone** but recognition of the critical phase: defervescence plus rising hematocrit, falling platelets, abdominal pain, vomiting, restlessness/lethargy, effusions or narrow pulse pressure.

- A falling hematocrit in an unstable patient suggests bleeding; a rising hematocrit with worsening perfusion suggests plasma leakage needing fluids.
- Differentiate from malaria, scrub typhus, leptospirosis and enteric fever in India; coinfection can occur, so a positive dengue test should not end evaluation if the clinical course is atypical.
- Avoid iatrogenic harm: NSAIDs/aspirin, unnecessary platelet transfusion and continued IV fluids during recovery can worsen outcomes.

High-yield exam pointers

- Write the **three severe dengue criteria**: severe plasma leakage, severe bleeding, severe organ dysfunction.
- Mention **warning signs at defervescence**; this is the usual time of deterioration.
- Pathogenesis keyword: **heterotypic secondary infection/antibody-dependent enhancement** plus **NS1-mediated vascular leak**.
- Investigations: **NS1/RT-PCR early**, **IgM/IgG later**, serial CBC hematocrit and platelets, LFT, albumin, renal function, coagulation profile, ultrasound/CXR for effusions.
- Management is **supportive, fluid-titrated and monitored**; no routine antiviral.
- Use **acetaminophen**, avoid **aspirin/NSAIDs**.
- Do **not** transfuse platelets just because the count is low; consider if bleeding or **<10,000/mcL**.
- In recovery, stop/reduce fluids because reabsorption of leaked fluid can cause pulmonary edema.
- Prevention answer must include **Aedes source reduction**, personal protection, blood safety and vaccine caveats.

> **SOURCE & COVERAGE**
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> Harrison 22e — "Arthropod-Borne and Rodent-Borne Virus Infections"; CMDT 2026 — "Viral & Rickettsial Infections"; Critical Care — "Resuscitation From Circulatory Shock".

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Dengue fever

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Dengue is an acute, self-limiting yet potentially fatal *arthropod-borne flaviviral* illness caused by four antigenically distinct serotypes (**DENV-1, -2, -3, -4**; genus *Orthoflavivirus*, family *Flaviviridae*) transmitted chiefly by the day-biting *Aedes aegypti* (and *Ae. albopictus*) mosquito. It is the most prevalent arboviral disease of humans (~400 million infections/year, ~100 million clinically apparent), endemic in >100 countries, with Asia bearing ~70% of the global burden. The clinical spectrum ranges from asymptomatic infection and undifferentiated **"break-bone fever"** through a plasma-leakage **critical phase** to **severe dengue** (dengue haemorrhagic fever / dengue shock syndrome), the latter driven largely by **immune-mediated (antibody-dependent) enhancement** on secondary heterotypic infection.

Etiology, Vector and Epidemiology

- **Agent:** single-stranded positive-sense RNA orthoflavivirus, ~40–60 nm enveloped virion; four serotypes that cross-react serologically but confer only *transient* cross-protection. Lifelong immunity is serotype-specific — **infection with one serotype does NOT protect against the other three**.
- **Vector:** *Aedes aegypti* (principal) and *Ae. albopictus* (Asian tiger mosquito); anthropophilic, breed in fresh water in domestic containers (jars, tyres, coconut husks), **bite during daylight** (early morning, late afternoon).
- **Reservoir/cycle:** humans are the main amplifying host in the urban cycle; nonhuman primates maintain a sylvatic cycle.
- **Transmission:** principally human→mosquito→human; rarely needlestick/mucocutaneous, vertical (peripartum), and via blood transfusion or organ/marrow transplant.
- **Distribution:** year-round transmission between latitudes ~25°N and 25°S; spread driven by urbanisation, travel and climate. Along with malaria, dengue is one of the two commonest vector-borne diseases and the second commonest cause of febrile illness in returning travellers.

Pathogenesis — Antibody-Dependent Enhancement and Plasma Leakage

- **Primary infection** is usually subclinical or causes uncomplicated febrile dengue; it generates serotype-specific neutralising antibody (protective) plus *cross-reactive, non-neutralising* antibody whose protection wanes over weeks to months.
- **Antibody-dependent enhancement (ADE):** on **secondary infection with a different (heterotypic) serotype**, pre-existing non-neutralising antibody binds virus and, via Fc receptors, *enhances* uptake into mononuclear phagocytes → higher viral load and an amplified, dysregulated cytokine response → the central lesion of **increased vascular permeability and plasma leakage**.
- **NS1 (non-structural protein 1)** has a key, recently recognised role in driving the endothelial vascular-leak phenomenon of severe dengue.
- **Net effect:** capillary leak → intravascular volume depletion, haemoconcentration, hypoalbuminaemia, serosal effusions; with thrombocytopenia, coagulopathy and (in severe disease) DIC contributing to haemorrhage and shock.

- **Risk factors for progression to severe dengue:** enhancing non-neutralising antibody (secondary heterotypic infection — *the* major determinant), age (susceptibility falls markedly after 12 years), female sex, particular serotype sequences (DENV-1 then DENV-2 is especially severe), virulent Southeast-Asian DENV-2 variants; and per CMDT, suboptimally controlled type-2 diabetes, obesity, and comorbidity (cardiovascular/renal/pulmonary disease, older age).

Clinical Course and WHO Classification

After an **incubation of ~4–14 days** (typically 4–7 days), symptomatic illness evolves through **three phases**:

- **Febrile phase (days 1–~5):** abrupt high-grade fever, frontal headache, **retro-orbital pain**, severe myalgia/arthralgia ("break-bone fever"), facial flushing, transient macular rash, conjunctival injection, pharyngeal erythema, lymphadenopathy, hepatomegaly; a **positive tourniquet test** and petechiae may appear.
- **Critical / plasma-leakage phase (around defervescence, days 3–5, lasting 24–48 h):** the window for **plasma leakage** — pleural effusion, ascites, rising haematocrit with falling platelet count, hypoalbuminaemia, and, if a critical volume is lost, **shock**. Warning signs herald this phase.
- **Recovery phase:** reabsorption of extravascular fluid, haemodynamic stabilisation, diuresis; a confluent pruritic rash with islands of sparing may desquamate; prolonged fatigue/depression in convalescence.

Feature	WHO 1997 classification	WHO 2009 (revised) classification
Categories	Dengue fever (DF); Dengue haemorrhagic fever (DHF) graded **I–IV**; Dengue shock syndrome (DSS)	**Dengue without warning signs**; **Dengue with warning signs**; **Severe dengue**
DHF/severe defined by	Fever + thrombocytopenia + haemorrhage + plasma leakage (DHF); circulatory failure = DSS	Plasma leakage (shock / respiratory distress), severe bleeding, or severe organ involvement
DHF grades	**I**: fever + constitutional + positive tourniquet test only; **II**: grade I + spontaneous bleeding; **III**: circulatory failure (weak rapid pulse, narrow pulse pressure ≤20 mmHg, hypotension) = DSS; **IV**: profound shock, unrecordable BP/pulse = DSS	Stratifies management by warning signs (see below)

- **Warning signs (2009 WHO):** abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation (ascites/pleural effusion), mucosal bleeding, lethargy/restlessness, tender hepatomegaly (>2 cm), and a rising haematocrit with rapid fall in platelet count.
- **Severe dengue (Harrison/2009 criteria):** definite/presumptive dengue **plus** (1) plasma leakage causing **shock or respiratory distress**, **or** (2) severe bleeding, **or** (3) severe organ dysfunction (e.g. transaminases markedly raised, impaired consciousness, myocarditis).
- **Organ involvement:** hepatitis, encephalitis/encephalopathy, myocarditis, acute kidney injury (AKI in shock syndrome carries high mortality), retinal haemorrhage/maculopathy.

Diagnosis and Investigations

- **Non-specific haematology: leukopenia** (with neutropenia), **thrombocytopenia**, and rising **haematocrit** (haemoconcentration = marker of plasma-leak severity); modestly elevated AST/ALT; normal ESR in most.
- **Phase-dependent virological/serological testing:**

Test	Useful window	Comment
NS1 antigen (ELISA / rapid test)	Days 1–~5 (febrile)	Early diagnosis; often combined with IgM at point of care
RT-PCR / viral isolation	First ~5 days	Confirms infection, allows serotyping
IgM ELISA	From ~day 4–5 onward	Indicates acute/recent infection
IgG ELISA / paired serology	Convalescence	**Early, rapidly rising IgG (~day 4) suggests a secondary infection** (primary = late, low-titre IgG)

- **Tourniquet (Hess) test:** ≥10 new petechiae per square inch on the forearm after BP-cuff inflation midway between systolic and diastolic for 5 min — a bedside index of capillary fragility; more often positive in severe dengue.
- **Imaging:** lateral-decubitus CXR / ultrasound detects pleural effusion and ascites before they are clinically obvious.
- **Caveat:** serologic **cross-reactivity** with other flaviviruses (Zika, yellow fever, Japanese encephalitis, prior vaccination) confounds IgG/IgM interpretation.
- **Differential diagnosis:** malaria, chikungunya (more chronic arthritis), Zika, leptospirosis, rickettsial/scrub typhus, typhoid, influenza, other viral haemorrhagic fevers.

Management

- **No specific antiviral exists — care is supportive**, hinging on meticulous fluid management and serial monitoring (vitals, urine output, **haematocrit**, platelets, albumin, AST/ALT).
- **Antipyretic/analgesic: acetaminophen (paracetamol)**; **avoid aspirin and NSAIDs** (gastritis/bleeding risk, platelet effects).
- **Fluids:** judicious **isotonic crystalloid** titrated to clinical parameters; escalate to **colloid** and **blood products** in shock per WHO algorithmic protocols. In the recovery phase, anticipate **fluid reabsorption** and avoid overload/pulmonary oedema.
- **Severe dengue / DSS:** hospitalise, rapid triage, early IV fluids **before** overt shock; vasopressors and blood/component replacement for refractory shock or bleeding; manage AKI, hepatic and CNS complications.
- **Platelets:** counts do **not** reliably predict bleeding; **platelet transfusion only for severe thrombocytopenia (<10,000/µL) or active bleeding** — prophylactic transfusion gives no proven benefit and may delay count recovery.
- **Prognosis:** overall mortality of severe disease ~2.5% and falling with early recognition; at experienced tropical centres CFR may be as low as ~1%. Thrombocytopenia, acute hepatitis and AKI in DSS predict poor outcome.

Prevention and Vaccines

- **Vector control** is the cornerstone: source reduction (eliminate breeding sites), screening, insecticides/repellents (especially early morning and late afternoon), and novel strategies (*Wolbachia*-infected or genetically modified *Aedes*). Screen blood donations in endemic areas.
- **CYD-TDV (Dengvaxia):** recombinant **live-attenuated tetravalent** vaccine on the **yellow-fever 17D backbone**; 0/6/12-month schedule; ~56% overall efficacy. **Increases risk of severe dengue in seronegative recipients** ("first serologic hit") → WHO recommends use **only in the previously dengue-seropositive**, with pre-vaccination screening; indicated ~9–45 years; not for pregnant/immunosuppressed persons.
- **TAK-003 (Qdenga):** live tetravalent, **two doses 3 months apart**; ~62% efficacy against symptomatic and ~83.6% against hospitalised dengue; protective against all four serotypes in seropositive children and DENV-1/-2 in seronegatives (weaker for DENV-3); approved in several European countries.
- **Newer candidates: Butantan-DV** (single-dose tetravalent — prevents DENV-1/-2) and **TV003/TV005** (single-dose) in late-phase evaluation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Triphasic course of dengue (timeline graph).** X-axis = days of illness (1–10); plot three overlapping curves and label: **"Febrile phase"**, **"Critical / plasma-leakage phase"**, **"Recovery phase"**; **Temperature** curve (high then defervescence at day ~3–5, optional "saddle-back" rise); **Platelet count** (falling, nadir in critical phase); **Haematocrit** (rising in critical phase, falling in recovery); mark the **"Warning-signs / leakage window"** at defervescence, and label complications — **shock, effusions, bleeding**.
- **Antibody-dependent enhancement (ADE) schematic.** Labels: **Primary DENV infection → serotype-specific neutralising antibody (protective)** vs **cross-reactive non-neutralising antibody (waning)**; **Secondary heterotypic DENV → antibody–virus complex → Fc-receptor uptake into macrophages → increased viral load + cytokine surge → NS1-mediated capillary leak → plasma leakage / DHF–DSS**.

Clinical / Diagnostic significance

- **Defervescence is the danger period**, not the end of illness — the critical plasma-leak phase begins as fever falls; serial haematocrit + platelet trends are the key bedside guide.
- A **rising haematocrit with falling platelets** is the earliest objective signal of significant plasma leakage and impending shock.
- **NS1 antigen** enables diagnosis in the first few febrile days (before antibodies appear); combine with IgM for higher yield.
- **Secondary heterotypic infection** is the principal driver of severe disease — a vital concept for hyperendemic regions and for the seronegative-vaccination hazard.
- Recognising **narrow pulse pressure (≤20 mmHg)** as early DSS allows fluid resuscitation before profound shock.
- Avoiding NSAIDs/aspirin and prophylactic platelet transfusion reflects evidence-based, harm-avoiding dengue care.

High-yield exam pointers

- Four serotypes **DENV-1–4**; immunity is **serotype-specific**; flavivirus; vector ***Aedes aegypti*, a day-biter**.
- Triphasic illness: **febrile → critical (plasma leak at defervescence) → recovery**.
- **WHO 2009:** dengue *without* warning signs / *with* warning signs / **severe dengue**; **WHO 1997:** DF, **DHF grades I–IV**, DSS.
- **Severe dengue** = dengue + plasma leakage (shock/respiratory distress) OR severe bleeding OR severe organ dysfunction.
- **Antibody-dependent enhancement** on **secondary heterotypic infection**; **NS1** drives vascular leak.
- Labs: **leukopenia, thrombocytopenia, rising haematocrit**, raised transaminases; **NS1 → RT-PCR → IgM → IgG**; **early high IgG = secondary infection**.
- **Tourniquet test** = ≥10 petechiae/inch^2 after 5-min cuff.
- Treatment: **supportive + fluids + paracetamol**; **avoid NSAIDs/aspirin**; platelets only if **<10,000/µL or bleeding**.
- Vaccines: **Dengvaxia (CYD-TDV)** — seropositive only, risk in seronegatives; **Qdenga (TAK-003)** — two-dose tetravalent.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Arthropod-Borne and Rodent-Borne Virus Infections" (Flavivirids: Dengue and Severe Dengue; Viral Haemorrhagic Fever section) — pathogenesis, antibody-dependent enhancement, NS1, three-phase course, tourniquet-test definition, severe-dengue criteria, vaccines (CYD-TDV/Dengvaxia, TAK-003/Qdenga, Butantan-DV, TV003/TV005).
- **CMDT 2026** — "Viral & Rickettsial Infections: Dengue" — epidemiology, clinical findings, laboratory diagnosis (NS1/IgM/IgG/PCR), WHO 1997 vs 2009 classification, supportive management, platelet-transfusion threshold, prevention and vaccines.
- **Coverage note:** The explicit **DHF grading I–IV** table is the standard **WHO 1997** classification — universally accepted internal medicine but cited by name rather than tabulated verbatim in Harrison 22e (which adopts the 2009 scheme) / CMDT 2026; the consolidated **2009 warning-signs list** is standard WHO and partially enumerated in CMDT. Incubation period is given as ~4–7 days (Harrison) and 7–10 days (CMDT); both are within the accepted 4–14-day range.

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HIV infection — diagnosis and laboratory monitoring

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Diagnosis of HIV infection rests on demonstrating either **antibodies to HIV and/or the p24 antigen** (serologic/screening tests) or **direct detection of the virus or its components** (nucleic acid/antigen tests). Laboratory monitoring then quantifies the **degree of immune damage** (CD4+ T-cell count) and the **magnitude of viral replication** (plasma HIV RNA). Together these tools establish the diagnosis, stage the disease, time opportunistic-infection (OI) prophylaxis, and gauge the response to antiretroviral therapy (ART). The CDC recommends that HIV screening be offered as a routine part of health care.

The diagnostic window & basis of testing

- Antibodies to HIV generally appear in the circulation **3–12 weeks** after infection; with modern fourth-generation tests, antibody/antigen is detectable in ~99% within **6 weeks**, median ~2 weeks.
- The **window period** (interval from infection to detectability) has shortened progressively with assay generation: **22 days** with antibody testing → **16 days** with p24 antigen testing → **12 days** with nucleic acid testing (NAT).
- Standard screening detects **antibody and/or p24 antigen**; direct tests detect HIV RNA, proviral DNA, or p24 antigen.
- The screening enzyme immunoassay (**ELISA/EIA**) has sensitivity **>99.5%** but imperfect specificity; in low-risk populations (e.g., volunteer blood donors) as few as ~10% of EIA-positives are truly infected, so every reactive screen needs confirmation.

Screening & confirmatory tests — the CDC algorithm

- **Step 1 (initial/screening):** a **fourth-generation HIV-1/2 antigen-antibody combination immunoassay** — detects antibodies to HIV-1 and HIV-2 *plus* HIV-1 **p24 antigen** (closes much of the early window). Scored highly-reactive, non-reactive, or indeterminate.
- **Step 2 (confirmation/differentiation):** a reactive screen → **HIV-1/HIV-2 antibody differentiation immunoassay** (e.g., *Bio-Rad Geenius*), which both confirms and distinguishes HIV-1 from HIV-2.
- **Step 3 (NAT for discordant results):** if the differentiation assay is **negative or indeterminate** → **HIV-1 RNA (NAT)**. A **positive NAT with negative antibody** = **acute HIV-1 infection**; a negative NAT in this setting indicates a **false-positive** screen.
- The **Western blot is no longer used** for confirmation. A positive fourth-generation assay confirmed by a second HIV-1– or HIV-2–specific immunoassay *or* a plasma HIV RNA level is adequate for diagnosis.
- **Point-of-care/rapid tests** (blood or oral fluid) give results in 10–20 min, need minimal training, and have sensitivity/specificity >99% for chronic infection (lower in acute infection); a reactive rapid test must be confirmed by the standard algorithm. A home oral-swab test (*OraQuick*) is FDA-approved.

Test	What it detects	Role in algorithm
4th-gen Ag/Ab combination immunoassay	HIV-1 & HIV-2 antibody + HIV-1 p24 antigen	**Initial screen** (sensitivity >99.5%)
HIV-1/HIV-2 antibody differentiation immunoassay (Geenius)	Distinguishes HIV-1 vs HIV-2 antibody	**Confirmation** after reactive screen
HIV-1 RNA (NAT)	Plasma viral RNA	Resolves screen+ / differentiation– → **acute HIV**
Rapid antibody test (blood/oral fluid)	HIV-1/HIV-2 antibody	Field/POC screen; confirm if reactive

Direct detection of virus & its components

- **p24 antigen capture assay** — EIA detecting HIV core protein p24; ~30% of untreated patients have detectable free p24, rising to ~50% after weak-acid dissociation of antigen-antibody complexes (down to ~15 pg/mL). High early (pre-seroconversion) levels make it useful in suspected **acute HIV syndrome**; now incorporated into the 4th-generation screen.
- **Nucleic acid amplification tests (quantitative HIV RNA)** — provide both diagnosis (in misleading-serology settings) and prognosis/treatment monitoring:

Assay	Method	Lower reliable limit
RT-PCR	Reverse transcription + PCR amplification of HIV-1 RNA	**20 copies/mL**
bDNA (branched DNA)	Signal amplification of particle-associated RNA	**50 copies/mL**
NASBA	Isothermal amplification	**80 copies/mL**
TMA	Transcription-mediated amplification (T7 polymerase)	**100 copies/mL**

- **DNA PCR** amplifies **proviral DNA** from peripheral blood mononuclear cells (sensitive to 1 copy/10,000–100,000 cells) — valuable for **neonatal diagnosis** (maternal antibody crosses placenta, making serology unreliable) and in **hypogammaglobulinemia/advanced disease**.
- **"Gold standard" for diagnosis = a positive EIA together with a positive HIV RNA assay.** Because high sensitivity costs specificity, NAT should be used for diagnosis only when standard serology fails to give a definitive answer.

Special / difficult diagnostic situations

- **False-positive EIA** — anti-class II (HLA) antibodies (post-pregnancy, transfusion, transplant), autoantibodies (collagen-vascular/autoimmune disease), hepatic disease, recent **influenza vaccination**, acute viral infections, and prior HIV-vaccine receipt; confirm with a specific immunoassay or HIV RNA.
- **Acute (primary) HIV** — antibody may be absent; rely on **p24 antigen** and/or **HIV RNA** (RNA is typically very high). Caution: low-level viremia **<1000 copies/mL** with negative serology may be a false-positive RNA.

- **Recent vs established infection** — a "**detuned**" (less-sensitive) EIA scores positive only in established infection, helping date seroconversion for surveillance.
- **Reversion to negative EIA** can occur in patients treated very early; it does not mean cure.

Laboratory monitoring — CD4+ T-cell count

- The **CD4+ T-cell count is the best single indicator of immediate immunologic competence** and the basis for staging and OI prophylaxis.
- **Thresholds:** CD4 **<200/µL** → high risk of *Pneumocystis jirovecii* pneumonia → **start PCP prophylaxis**; CD4 **<50/µL** → risk of **CMV, Mycobacterium avium complex (MAC), and Toxoplasma** → **MAC primary prophylaxis** (unless ART is started immediately).
- **CDC staging (age ≥6 yr to adult):** Stage 1 = CD4 **≥500/µL** (≥26%); Stage 2 = **200–499/µL** (14–25%); Stage 3 (AIDS) = **<200/µL** (<14%) *or* an AIDS-defining OI. **CD4% of 15 ≈ CD4 count of 200/µL.**
- **Frequency:** at diagnosis, then **every 3–6 months** for the first 2 years; more often if declining. After ≥2 years on ART with HIV RNA persistently <50 copies/mL and CD4 300–500/µL → annually; if CD4 **>500/µL** monitoring is **optional**.
- **CD4 can mislead:** falsely high in **HTLV-1 co-infection**; use the **CD4 percentage** in hypersplenism, post-splenectomy, or marrow-suppressing therapy (e.g., IFN-α). Counts also fall transiently with intercurrent illness/vaccination and show diurnal/inter-laboratory variation — *trend matters more than a single value*.

Laboratory monitoring — HIV RNA, resistance & tropism

- **Plasma HIV RNA (viral load)** is the most accurate indicator of viral replication and the **response to ART**. Measure at diagnosis; after starting ART, monitor about **every 4 weeks** until a new steady state, then **every 3–6 months**.
- **Goal of effective ART:** HIV RNA falls to **<50 copies/mL within ~6 months**. Commercial assays reliably detect to ~20–50 copies/mL; avoid the term "undetectable" (virus is not zero). Never base decisions on a single value, as RNA fluctuates with immune activation, intercurrent infection, or immunization.
- **HIV drug-resistance testing** — **genotypic** (sequence vs known resistance profiles) or **phenotypic** (growth of patient virus across drug concentrations). Recommended **at initial diagnosis** and at **ART initiation**, and in **virologic failure**; requires HIV-1 RNA **>500–1000 copies/mL** for an accurate result.
- **Co-receptor tropism assay** (e.g., *Trofile*) before using the CCR5 antagonist **maraviroc**, which works only against **CCR5-tropic** virus (early disease tends CCR5-tropic, shifting to CXCR4 later).
- **Other markers** — hs-**CRP**, **IL-6**, **D-dimer**, and **sCD14** correlate with all-cause mortality but are not used routinely.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CDC diagnostic algorithm (flowchart):** Box 1 "**HIV-1/2 antigen/antibody combination immunoassay**" → if **non-reactive** = "Negative (consider acute HIV → NAT if recent exposure)"; if **reactive** → Box 2 "**HIV-1/HIV-2 antibody differentiation immunoassay**" with three outputs — "**HIV-1 antibodies +**", "**HIV-2 antibodies +**", "**indeterminate/negative**"; the indeterminate/negative arm → Box 3 "**HIV-1 NAT**" → "**NAT + = acute HIV-1 infection**" / "**NAT – = HIV negative (false-positive screen)**". Label arrows +/–.
- **CD4 vs opportunistic-disease graph:** Y-axis "**CD4 count (cells/µL)**" with marked lines at **500, 200, 50**; plot disease onset bands — *herpes zoster / oral candidiasis* (~300–500), **PCP / Kaposi sarcoma** (≤200), **CMV retinitis / MAC / CNS lymphoma / cryptococcosis** (≤50). Title: *Relationship between CD4 count and opportunistic infections.*

Clinical / Diagnostic significance

- A **single reactive screen never diagnoses HIV** — the differentiation assay (± NAT) is mandatory; this avoids labelling false-positives.
- The **fourth-generation Ag/Ab test + NAT** strategy diagnoses **acute HIV** that older antibody-only tests miss — critical for interrupting onward transmission.
- **CD4 count drives prophylaxis** (<200 → PCP; <50 → MAC/Toxo/CMV) and defines **AIDS** (Stage 3).
- **Viral load** confirms ART efficacy (target <50 copies/mL) and, with persistent suppression, supports **U=U** (untransmittable) and reduced monitoring frequency.
- **Resistance + tropism testing** individualises the regimen and is prerequisite for CCR5 antagonists.

High-yield exam pointers

- **Initial test = 4th-generation HIV-1/2 antigen/antibody combination immunoassay** (antibody + **p24 antigen**); EIA sensitivity **>99.5%**.
- **Confirmation = HIV-1/HIV-2 antibody differentiation immunoassay (Geenius); Western blot is obsolete.**
- **Discordant (screen+, differentiation–) → HIV-1 NAT; NAT+ antibody– = acute HIV.**
- **Window period:** antibody 22 d → p24 antigen 16 d → NAT 12 d.
- **Gold standard for diagnosis = positive EIA + positive HIV RNA.**
- **CD4 <200/µL → PCP prophylaxis; <50/µL → MAC prophylaxis; CD4% 15 ≈ 200/µL.**
- **CDC Stage 3 (AIDS):** CD4 <200/µL (or <14%) or an AIDS-defining illness.
- **Viral load <50 copies/mL by 6 months = effective ART;** monitor every 3–6 months; never act on a single value.
- **Resistance testing needs HIV RNA >500–1000 copies/mL;** tropism (Trofile) before **maraviroc**.
- **DNA PCR** for **neonatal** diagnosis (passive maternal antibody confounds serology).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (diagnosis algorithm, window periods, p24 antigen and HIV RNA/DNA assays, CD4 and viral-load monitoring, resistance and tropism testing, CDC staging Tables 208-1/208-2/208-8).
- **CMDT 2026** — "HIV Infection & AIDS" (current fourth-generation Ag/Ab → differentiation → NAT algorithm, rapid/home tests, Table 36-2 commonly ordered tests, CD4-count interpretation and OI thresholds).

Coverage note: Both sources describe the U.S. CDC laboratory algorithm. The Indian **NACO / WHO "three sequential rapid-test" (Strategy III) diagnostic algorithm** used in resource-limited programmatic settings is standard practice but is not detailed in this corpus and has not been elaborated here.

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Falciparum malaria

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Malaria is a protozoan infection transmitted by the bite of an infected female *Anopheles* mosquito; *Plasmodium falciparum* is the species responsible for nearly all malaria deaths. It is distinguished from the other human plasmodia by its ability to invade red cells of **all ages** (producing very high parasitaemias) and by **cytoadherence and sequestration** of parasitised erythrocytes in vital organs, which underlies the life-threatening complications. Falciparum malaria must never be a clinical diagnosis alone — it requires parasitological confirmation — and severe disease is a medical emergency demanding immediate parenteral **artesunate**.

Pathophysiology relevant to diagnosis and severity

- After hepatic schizogony, merozoites invade RBCs and multiply 6- to 20-fold every **48 h**; symptoms begin once densities reach ~50/μL.
- *P. falciparum*–infected RBCs develop surface "knobs" expressing the variant adhesin **PfEMP1**, which mediates **cytoadherence** to endothelial receptors — **ICAM-1 and endothelial protein C receptor (EPCR)** in the brain, **VAR2CSA/chondroitin sulfate A** in the placenta, and **CD36** in most other organs.
- **Rosetting** (binding to uninfected RBCs) and **agglutination** add to microvascular obstruction → tissue hypoxia and lactic acidosis.
- Because mature forms sequester, **only young ring forms circulate** in peripheral blood; peripheral parasitaemia therefore *underestimates* the true parasite burden — a key diagnostic caveat.

Clinical features and recognition of severe disease

- **Uncomplicated malaria:** non-specific prodrome (malaise, headache, fatigue, myalgia, abdominal discomfort) followed by fever; classic periodic paroxysms are *unusual* in falciparum. Few signs

other than fever, mild anaemia, jaundice and splenomegaly. **Thrombocytopenia is usual** — a normal platelet count should question the diagnosis. There is no rash.

- Generalised **seizures** are specifically associated with falciparum malaria and may herald cerebral malaria.
- **Severe falciparum malaria** is defined by vital-organ dysfunction or parasitaemia >2% in a non-immune patient. Uncomplicated disease, promptly treated, has mortality <0.1%; once severe features appear, mortality rises steeply.

WHO criterion (severe falciparum malaria)	Threshold
Cerebral malaria (unarousable coma)	GCS <11, or Blantyre Coma Score <3; coma >30 min post-convulsion
Severe anaemia	Hb <5 g/dL (Hct <15%) with parasitaemia >10,000/µL
Acidosis	pH <7.25, HCO_3^- <15 mmol/L, base deficit >8, or **lactate ≥5 mmol/L**
Hypoglycaemia	Plasma glucose <2.2 mmol/L (<40 mg/dL)
Acute kidney injury	Creatinine >265 µmol/L (>3 mg/dL)
Pulmonary oedema / ARDS	SpO_2 <92% on air, RR >30, non-cardiogenic oedema
Shock	SBP <80 mmHg (adults) with impaired perfusion
Hyperparasitaemia	>5% non-immune (>10% any patient)
Bleeding/DIC, ≥2 convulsions/24 h, haemoglobinuria, jaundice (bilirubin >3 mg/dL with parasitaemia >100,000/µL), prostration	—

- **Poor-prognosis markers:** hyperlactataemia, acidotic ("respiratory distress") breathing, deep coma, repeated convulsions, anuria, hypoglycaemia, >20% of parasites being pigment-containing trophozoites/schizonts, or pigment in >5% of neutrophils. Concomitant bacteraemia (notably non-typhoidal *Salmonella*) complicates ~6% of children and adults with >20% parasitaemia.

Diagnosis

- **Demonstration of the parasite (gold standard):** thick and thin **Giemsa-stained smears** (Giemsa at pH 7.2; Field's, Wright's or Leishman's acceptable), examined immediately.
  - *Thick film* — unfixed, lyses RBCs and **concentrates parasites 40–100×**; high sensitivity (~0.001% parasitaemia); count asexual parasites per 200 WBC (assume WBC 8000/µL → parasites/µL = count × 40).
  - *Thin film* — methanol-fixed; allows **species identification** and quantification (parasitised RBC per 1000 RBC); in severe disease, assess proportion of mature forms and pigment-laden neutrophils.
  - Falciparum hallmarks: predominance of small **ring forms**, multiply-infected cells, appliqué/accolé forms, **banana-shaped gametocytes**, **Maurer's clefts**, and high parasite density.

- A single negative smear does not exclude malaria — **repeat 12-hourly over 2–3 days** before excluding the diagnosis.

- **Rapid diagnostic tests (RDTs):** immunochromatographic detection of **PfHRP2** (falciparum-specific), **parasite LDH (pLDH)** or **aldolase**.
  - Useful where reliable microscopy is unavailable; some carry a pan-malaria/vivax band to distinguish species.
  - Limitations: do **not quantify** parasitaemia; PfHRP2 **stays positive for weeks** after cure (a problem in high transmission, but an advantage when diagnosing severe malaria in a partly treated patient with negative film); false negatives from **pfhrp2/3 gene deletions** (notably the Horn of Africa).
- **PCR/molecular:** most sensitive for low-density and mixed infections and for speciation; used in reference labs — too sensitive for routine primary diagnosis in endemic areas. **Serology has no role** in acute illness.
- **Supportive laboratory findings:** normochromic normocytic anaemia, thrombocytopenia, normal/low WBC; in severe disease — metabolic acidosis, hypoglycaemia, hyponatraemia, elevated lactate, urea, creatinine, bilirubin and transaminases.

Treatment of uncomplicated falciparum malaria

- **WHO first-line = Artemisinin-based Combination Therapy (ACT)** — a fast-acting artemisinin derivative (artesunate/artemether/dihydroartemisinin) plus a slowly eliminated partner drug, given for **3 days**. Six WHO-recommended ACTs:

ACT regimen	Note
Artemether-lumefantrine (Coartem)	Most widely used; preferred in 1st-trimester pregnancy; take with fat/food (1.5/9 mg/kg bd × 3 days)
Artesunate-amodiaquine	First-line in much of Africa
Artesunate-mefloquine	SE Asia, South America
Dihydroartemisinin-piperaquine	Longest post-treatment prophylaxis (piperaquine t½ ~3 wk)
Artesunate-sulfadoxine-pyrimethamine	First-line in some countries
Artesunate-pyronaridine	Most recently approved

- Add a **single low dose of primaquine 0.25 mg base/kg** as a *gametocytocide* (to block transmission) in low-transmission/elimination settings — safe even in G6PD deficiency; **not** in pregnancy/infants.
- **Atovaquone-proguanil** (20/8 mg/kg/day × 3 days, with food) is an effective alternative for imported/traveller malaria.
- **Second-line / no ACT available:** oral **quinine 10 mg salt/kg tds × 7 days plus doxycycline** (3 mg/kg/day; avoid <8 yr and pregnancy) **or clindamycin** (10 mg/kg bd).
- Watch for vomiting within 1 h of an oral dose → repeat the dose; treat fever with paracetamol to reduce vomiting. Confirm parasite clearance with daily counts; failure to clear by day 7 → switch to a different ACT.

Treatment of severe falciparum malaria

- **IV artesunate is the drug of choice everywhere** — large RCTs showed mortality reduction of **35% in Asian adults/children (SEAQUAMAT)** and **22.5% in African children (AQUAMAT)** versus quinine. It is FDA-approved, simple, safe, needs no dose adjustment for hepatic/renal failure, and is given in pregnancy in all trimesters.
  - **Dose: 2.4 mg/kg IV at 0, 12 and 24 h, then once daily**; children <20 kg get **3 mg/kg per dose**. Continue parenteral therapy ≥24 h, then complete a **full 3-day oral ACT** once the patient can swallow (avoid mefloquine follow-on — post-malaria neurological syndrome).
  - **Pre-referral rectal artesunate** reduces mortality in rural children who cannot reach parenteral care.
- **Alternatives if artesunate unavailable:** IM **artemether** 3.2 mg/kg stat then 1.6 mg/kg/day; or **quinine dihydrochloride** 20 mg salt/kg loading over 4 h, then 10 mg salt/kg over 2–8 h every 8 h (rate-controlled infusion; risk of hypotension and hypoglycaemia; cardiac monitoring; reduce maintenance dose by 30–50% if renal failure persists >48 h — never the loading dose). In confirmed artemisinin-resistance areas, give **artesunate + quinine together**.
- **Supportive / intensive care** (severe malaria = ICU-level care):
  - **Fluids:** cautious — the line between under- and over-hydration is thin; **fluid boluses are dangerous** in severe malaria (unlike sepsis) and precipitate pulmonary oedema.
  - **Hypoglycaemia:** monitor glucose 4–6 hourly; treat with 20% dextrose 2 mL/kg over 10 min then 10% dextrose infusion; keep glucose >4 mmol/L.
  - **Seizures:** IV/rectal benzodiazepines; **levetiracetam** is the preferred anticonvulsant; avoid prophylactic high-dose phenobarbital (20 mg/kg) without ventilatory support (respiratory arrest).
  - **Anaemia:** transfuse if **Hct <20%** (threshold ~15% in high-transmission settings); fresh whole blood/packed cells slowly.
  - **AKI / severe acidosis:** early **haemofiltration or haemodialysis** (superior to peritoneal dialysis).
  - **Sepsis cover:** add broad-spectrum antibiotics (covering non-typhoidal *Salmonella*) in children and in adults with >20% parasitaemia or unexplained deterioration; take blood cultures.
  - **Exchange transfusion** is sometimes used for very high parasitaemia (>5–10%) but benefit is unproven.
  - **Ineffective/harmful adjuncts (do NOT use):** corticosteroids, mannitol, heparin, dextran, urea, desferrioxamine, anti-TNF-α, large fluid/albumin boluses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Peripheral smear of *P. falciparum* (thin film):** label — *delicate ring/trophozoite, appliqué (accolé) form, double-chromatin ring, multiply-infected RBC, Maurer's clefts, banana-shaped (crescentic) gametocyte, pigment in neutrophil.*
- **Pathogenesis of sequestration:** label — *infected RBC with knobs, PfEMP1 adhesin, endothelial receptors (ICAM-1/EPCR in brain, CD36, VAR2CSA in placenta), cytoadherence to venular endothelium, rosetting with uninfected RBCs, microvascular obstruction → coma/lactic acidosis.*

Clinical / Diagnostic significance

- **Speed saves lives:** start parenteral artesunate immediately in any patient with severe features; do not wait for full work-up.
- Cerebral malaria is a diffuse symmetrical encephalopathy (no focal signs, no meningism); retinal whitening and pale-centred haemorrhages on fundoscopy support the diagnosis. Death rates ~20% (adults) and ~15% (children) even with treatment.
- **Blackwater fever** — massive intravascular haemolysis with haemoglobinuria — and **delayed post-artesunate haemolysis** (1–3 weeks after clearing hyperparasitaemia, from synchronous loss of "pitted" once-parasitised cells) require monitoring of Hb after discharge.
- Pregnancy: falciparum causes placental sequestration, low birth weight and severe maternal disease (hypoglycaemia, pulmonary oedema) — treat with IV artesunate in all trimesters.
- Resistance surveillance uses molecular markers: **pfkelch13** (artemisinin), **pfcrt** (chloroquine), **pfmdr1** (mefloquine), **pfpm2** amplification (piperaquine).

High-yield exam pointers

- Falciparum invades RBCs of **all ages** → high parasitaemia; sequestration means **only rings** seen peripherally — count underestimates true burden.
- **Thick film** = most sensitive (concentrates 40–100×, detect & quantify); **thin film** = species ID; **Giemsa at pH 7.2** is the preferred stain.
- **RDTs** detect **PfHRP2 / pLDH / aldolase**; PfHRP2 stays positive weeks after cure; beware **pfhrp2/3 deletions** causing false negatives.
- Severe disease defined by WHO criteria — memorise coma (GCS <11/Blantyre <3), lactate ≥5, glucose <2.2 mmol/L, creatinine >3 mg/dL, Hb <5 g/dL, parasitaemia >5–10%.
- **IV artesunate 2.4 mg/kg at 0, 12, 24 h then daily** is first-line for severe malaria everywhere (SEAQUAMAT 35%, AQUAMAT 22.5% mortality reduction vs quinine).
- **Avoid fluid boluses** in severe malaria; manage hypoglycaemia, seizures (levetiracetam), AKI (early dialysis) and add antibiotics for possible bacteraemia.
- **ACT × 3 days** is first-line for uncomplicated falciparum; add **single-dose primaquine 0.25 mg/kg** as gametocytocide (safe in G6PD deficiency).
- A **normal platelet count argues against** falciparum malaria; malaria causes **no rash**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Malaria"** (Ashley & White): pathophysiology, severe-malaria criteria (Tables 231-2/231-3), diagnostic methods (Table 231-5), treatment regimens (Tables 231-6/231-7), artesunate dosing and supportive care.
- **CMDT 2026 — "Protozoal & Helminthic Infections"** (malaria section, Tables 40-2/40-3): current WHO ACT list, IV artesunate as FDA-approved standard of care, exchange-transfusion caveat, drug-specific notes.

Coverage note: The corpus covers this topic comprehensively; no significant gaps. Trial eponyms (SEAQUAMAT/AQUAMAT) are universally accepted designations for the artesunate-versus-quinine mortality data quoted verbatim from Harrison.

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Brucellosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine. It is known colloquially as *undulant fever* because of the remittent (waxing-and-waning) character of its pyrexia. Although it commonly presents as an acute febrile illness, the clinical manifestations are protean and definitive diagnostic signs may be lacking; thus the clinical impression must usually be confirmed by bacteriologic and/or serologic testing. It remains a major public-health problem in India, the Mediterranean basin, western/central Asia, Africa and Latin America, with an estimated >2 million human cases worldwide annually.

Etiologic agents and microbiology

- Caused by the genus ***Brucella*** — small, gram-negative, unencapsulated, non-sporulating **coccobacilli** that behave *in vivo* as **facultative intracellular parasites**; they grow aerobically on peptone-based medium at 37°C, with growth of some types enhanced by supplementary CO_2.
- **Species and animal reservoir** (host preference drives epidemiology):

Species	Main animal source	Clinical note
B. melitensis	Sheep, goats, camels	Commonest cause of symptomatic human disease; most **acute/aggressive**
B. abortus	Cattle, buffalo	**Insidious** onset; more likely to become **chronic**
B. suis	Swine (also reindeer/caribou, rodents)	Tendency to **focal abscess** formation
B. canis	Dogs	Generally milder, but can cause endocarditis
B. ovis	Sheep (reproductive)	Not clearly implicated in human disease

Species	Main animal source	Clinical note
B. neotomae, *B. ceti*, *B. pinnipedialis*	Desert rodents; marine mammals	Rare/emerging human infections

- **Environmental resistance:** killed by **boiling and pasteurization**, sunlight and moderate heat, but **resistant to freezing and drying** — this aerosol stability facilitates airborne and laboratory transmission. Organisms survive ~2 months in soft cheeses, ≥6 weeks in dry contaminated soil and ≥6 months in damp soil/manure.
- Now genetically related to (and reclassified to include) *Ochrobactrum* spp., which can cause laboratory misidentification with very different clinical management.

Epidemiology and transmission

- A zoonosis whose human occurrence mirrors prevalence in domesticated animals; increasingly recognised in **India, Pakistan, Sri Lanka and China**.
- **Occupational exposure:** farmers, shepherds, goatherds, **veterinarians**, abattoir and meat-processing workers, feral-pig hunters, and **diagnostic laboratory staff** (handling cultures/samples).
- **Food-borne/urban exposure:** consumption of **unpasteurized milk, soft cheeses and ice cream** is the commonest non-occupational route; raw meat/bone marrow rarely.
- **Routes of entry:** ingestion, inhalation, or mucosal/percutaneous contact. Accidental injection or ingestion of **live veterinary vaccine strains** (*B. abortus* S19 and RB51; *B. melitensis* Rev 1) can cause disease.
- **Person-to-person transmission is extremely rare** (occasional reports via tissue/blood). No increased prevalence/severity in HIV or other immunosuppression.
- *B. melitensis* and *B. suis* are recognised potential **bioterrorism agents** — consider in sudden unexplained outbreaks.

Pathogenesis (the "stealth" intracellular pathogen)

- Both **humoral and cell-mediated** immunity are elicited, but antibodies alone cannot eradicate infection; **protective immunity is predominantly TH1/cell-mediated**.
- The **macrophage is the key target cell**. After uptake (smooth strains enter via lipid rafts using smooth LPS), the organism survives intracellularly by:
  - restricting fusion of the **type IV secretion system (VirB)-dependent *Brucella*-containing vacuole** with lysosomes, diverting replication to the **endoplasmic reticulum**;
  - inhibiting apoptosis of infected mononuclear cells and blocking dendritic-cell maturation/antigen presentation;
  - producing **Cu-Zn superoxide dismutase** and acid-stable proteins resisting reactive oxygen intermediates and defensins.
- **Smooth LPS** has an unusual O-chain with low endotoxin activity, aiding evasion of serum killing and pyrogenicity.
- **TNF-α** (early), **IL-12 → IFN-γ** drive macrophage activation and TH1 responses; IL-4/IL-6/IL-10 downregulate protection.

- Initial replication occurs in regional lymph nodes; **haematogenous spread** seeds the reticuloendothelial system, musculoskeletal and genitourinary tissues, producing **granulomas (with/without necrosis)** and abscesses.

Clinical features

- **Fever** is almost invariable, with profuse drenching **night sweats**; untreated, it shows the classic **undulating pattern**, and is accompanied by musculoskeletal symptoms in about **half** of patients. Constitutional features: apathy, fatigue, anorexia, weight loss, myalgia, headache, chills. Incubation 1 week to several months.
- **Three classic presentation patterns:** (1) typhoid-like febrile illness but less severe; (2) **fever + acute monoarthritis of hip or knee in a young child**; (3) long-standing fever with **low-back or hip pain in an older man**.
- **Musculoskeletal (~40%, the most common focal disease):**
  - **Spondylitis/osteomyelitis** — favours **lumbar and low-thoracic vertebrae**; anterosuperior end-plate erosion early, eventual whole-vertebra sclerosis.
  - **Septic arthritis** — knee, hip, **sacroiliac**, shoulder, **sternoclavicular** joints (mono- or poly-arthritic).
- **Other organ involvement:**
  - Respiratory: dry cough in ~25% (chest X-ray often normal); rarely pneumonia/empyema/lung abscess.
  - **Hepatosplenomegaly (~25%)**, lymphadenopathy (10–20%) — mimics glandular-fever syndromes.
  - Genitourinary: **epididymo-orchitis in up to 10% of men** (distinguish from mumps/torsion); prostatitis, salpingitis, pyelonephritis; **increased fetal loss** in pregnancy (no teratogenicity).
  - **Neurobrucellosis:** depression/lethargy; **lymphocytic meningoencephalitis** mimicking neuro-TB; rarely intracerebral abscess, cranial-nerve palsies, mycotic aneurysm.
  - **Endocarditis (~1%)** — most often the **aortic valve** (native or prosthetic); leading cause of death.
  - Metastatic abscesses, with a predilection for the **breast and thyroid**.

Diagnosis

- **Routine labs (non-specific):** WBC usually **normal or low with relative lymphocytosis**; mild anaemia, sometimes thrombocytopenia/DIC; ESR and CRP often normal; mildly raised transaminases/bilirubin. CSF/joint fluid show **lymphocytosis with low glucose**; biopsy may show **non-caseating granulomas without acid-fast bacilli**.
- **Culture (definitive):** isolation from blood, bone marrow, CSF, joint fluid or tissue is positive in **50–70%**; automated systems (e.g., **Bactec**) usually flag within **7 days**. Warn the laboratory — handle under **containment for dangerous pathogens**. May be misidentified as *Agrobacterium*, *Ochrobactrum* or *Psychrobacter (Moraxella) phenylpyruvicus*; **MALDI-TOF MS** identification has historically been unreliable for the genus.

- **PCR / NAAT:** targets the **rrs–rrl (16S–23S) spacer**, outer-membrane protein genes, insertion sequence **IS711** and **BCSP31** — sensitive, rapid, biohazard-free; prolonged post-treatment positivity is of uncertain significance.
- **Serology (often the only positive finding):** IgM appears first, followed by IgG and IgA. The **standard agglutination test (SAT)** is the mainstay.
  - **Diagnostic titres:** in endemic areas, **1:320–1:640 or higher**; in non-endemic areas, **≥1:160** is significant. A rising titre on repeat testing at 2–4 weeks is confirmatory.
  - **Rose Bengal test** used for screening.
  - **Cross-reactions** (false positives) with *Yersinia enterocolitica* O:9, *E. coli* O157, *Francisella tularensis*, *Salmonella* group N, *Stenotrophomonas maltophilia* and *Vibrio cholerae*.
  - **Rough strains (*B. canis*, *B. ovis*) and vaccine strain RB51 give false-negative results** in conventional smooth-antigen tests.

Treatment

- **Principles:** prolonged combination therapy (single agents relapse), exclude/cover tuberculosis (shared drugs — never use rifampin alone), and emphasise **adherence** (poor compliance, not resistance, causes most failures).

Indication	Regimen	Notes
Acute non-focal (gold standard)	**IM streptomycin 0.75–1 g/day × 14–21 days + doxycycline 100 mg BD × 6 weeks**	Relapse 5–10%
WHO alternative (oral)	**Rifampin 600–900 mg/day + doxycycline 100 mg BD × 6 weeks**	Easier; relapse ~10% (>20% in practice)
Aminoglycoside substitute	**Gentamicin 5–6 mg/kg/day × 1–2 weeks** in place of streptomycin	US/UK guidelines; avoid short courses
Children / pregnant women	**High-dose TMP-SMX** (with rifampin) — avoid tetracyclines	Watch rising TMP-SMX resistance
Complicated / focal disease	**Triple therapy** = doxycycline + rifampin + initial aminoglycoside	≥3 months
Neurobrucellosis	Standard regimen + **ceftriaxone**, 3–6 months	—
Endocarditis	≥3 drugs (**aminoglycoside + tetracycline + rifampin** ± ceftriaxone/fluoroquinolone) 4–6 months	**Surgery** usually needed for prosthetic valves

- **Fluoroquinolones** are not recommended first-line (the *Ioannina Recommendations*); poor intravacuolar activity at low pH.
- **Post-exposure prophylaxis:** rifampin + doxycycline (or doxycycline alone) for **3 weeks**; **omit rifampin after RB51 exposure** (RB51 is rifampin-resistant) — substitute TMP-SMX.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Intracellular pathogenesis of *Brucella*:** Inhaled/ingested coccobacillus → uptake by **macrophage** (smooth LPS / lipid raft entry) → **type IV secretion system (VirB)** prevents **phagolysosome fusion** → replication in **endoplasmic-reticulum-derived *Brucella*-containing vacuole** → suppressed apoptosis & antigen presentation → haematogenous spread → **granuloma** in reticuloendothelial/musculoskeletal tissue. Labels: *macrophage, smooth LPS, VirB type IV secretion system, Brucella-containing vacuole, ER, blocked phagolysosome fusion, IFN-γ/TH1, granuloma.*
- **Spinal radiology — Brucella vs TB spondylitis:** two vertebral-column sketches. Labels for *Brucella*: lumbar site, **anterosuperior end-plate erosion**, intact body until late, **whole-body sclerosis on recovery**, small well-localised paravertebral abscess, parrot-beak osteophyte, canal compression rare. Labels for TB: dorsolumbar, early body destruction, **gibbus/anterior wedge**, large psoas/paravertebral abscess, early canal compression.

Clinical / Diagnostic significance

- The single most important **differential is tuberculosis**, especially in spondylitis — radiological discriminators (Table 174-1: site, sequence of disk involvement, body destruction, abscess size, gibbus) guide both therapy and prognosis.
- Triad of **fever + sweats + back/joint pain** with an exposure history (unpasteurized dairy, animal/abattoir contact, endemic-area travel, similar family illness in ~50%) should prompt brucella serology and prolonged blood cultures.
- A SAT titre alone never diagnoses disease — interpret with **exposure history, clinical picture and a rising titre**; remember rough-strain (*B. canis*) infection is **serology-negative**.
- Always alert the microbiology laboratory: brucella is a **biosafety-level-3** pathogen and a frequent cause of laboratory-acquired infection.

High-yield exam pointers

- **Undulant fever**; zoonosis from **unpasteurized dairy / animal contact**; *B. melitensis* commonest and most severe.
- **Gram-negative facultative intracellular coccobacillus**; macrophage is the key host cell; survives via **type IV (VirB) secretion** avoiding phagolysosome fusion.
- Musculoskeletal disease in ~40% — **sacroiliitis, lumbar spondylitis**; child with **monoarthritis of hip/knee**.
- **Endocarditis (~1%, aortic valve) is the leading cause of death**; mortality overall <1%.
- **Gold-standard therapy: streptomycin + doxycycline × 6 weeks**; WHO oral alternative **rifampin + doxycycline**; **TMP-SMX** for children/pregnancy.
- **SAT diagnostic titre** ≥1:160 (non-endemic) or 1:320–1:640 (endemic); cross-reacts with *Yersinia enterocolitica* O:9.
- **Relapse up to 30%** in poorly compliant patients — follow up to **2 years**; weight/well-being beat serology for monitoring.
- **Notifiable disease**; prevention = animal test-and-slaughter, vaccination and **milk pasteurization**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Brucellosis"** (primary source for definition, etiologic agents, epidemiology, pathogenesis, clinical features, diagnosis, Table 174-1 spine radiology, treatment regimens, prognosis and prevention).
- **CMDT 2026** — *Bacterial & Chlamydial Infections* and the *Anti-infective Treatment* chapter (corroboration of streptomycin/doxycycline combination regimens and differential diagnosis of febrile zoonoses).
- *Coverage note:* No dedicated infectious-disease subspecialty text was listed in the spec for this topic; CMDT covers brucellosis only briefly (mainly cross-references). Harrison Ch 174 is comprehensive and fully supports every specific stated above.

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Severe sepsis

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Sepsis is an infectious syndrome causing considerable morbidity, mortality, and long-term sequelae among survivors. Under the historic Sepsis-1/Sepsis-2 framework, **severe sepsis** meant sepsis plus hypoperfusion or end-organ dysfunction (oliguria, acute mental-status change, or lactic acidosis), while **septic shock** was sepsis-induced hypotension persisting despite adequate volume resuscitation. The current **Sepsis-3 (2016)** consensus *eliminated the term "severe sepsis"* and redefined **sepsis** as *life-threatening organ dysfunction caused by a dysregulated host response to infection*, with **septic shock** as the subset showing profound circulatory, cellular, and metabolic abnormalities and markedly higher mortality. Thus, what was formerly called "severe sepsis" is, in present nomenclature, simply **sepsis**.

Evolving definitions — where "severe sepsis" fits

Consensus (year)	Sepsis criterion	"Severe sepsis"	Septic shock
Sepsis-1 (1992)	Suspected infection + ≥2 **SIRS** (temp <36 or >38°C; HR >90; RR >20 or $PaCO_2$ <32; WBC <4000 or >12,000/μL or >10% bands)	Sepsis + hypoperfusion / organ dysfunction (oliguria, altered mentation, lactic acidosis)	Sepsis-induced hypotension (SBP <90 or ↓≥40 from baseline) despite adequate volume resuscitation
Sepsis-2 (2003)	Expanded list of clinical & laboratory criteria beyond SIRS	Retained	As above
Sepsis-3 (2016)	Suspected/confirmed infection + ↑**SOFA ≥2** from baseline	**Term abolished** (folded into "sepsis")	Vasopressor needed for **MAP >65 mmHg** *and* **lactate >2 mmol/L** despite fluid resuscitation

- Epidemiology: ~48.9 million sepsis cases occur globally each year with ~11 million deaths (1 in 5 of all global deaths; 85% in low/middle-income countries). Sepsis affects ~6% of hospitalised US adults, with ~15% overall mortality rising to **up to 40% in septic shock**.

- ~88% are community-onset; ~53% are culture-positive with a roughly even gram-positive/gram-negative split. Commonest primary sites: urinary tract (~49%), respiratory (~33%), intra-abdominal (~14%), skin/soft tissue (~10%). Key organisms: *S. aureus, Streptococcus, Enterococcus* (gram +) and *E. coli, Klebsiella, Pseudomonas* (gram −).

Pathophysiology — the dysregulated host response

The unifying mechanism is an **exuberant, dysregulated immune response** to infection causing systemic vasodilation, capillary leak, microvascular thrombosis, and impaired oxygen delivery/utilisation, culminating in multi-organ injury.

- **Triggers & recognition:** Pathogen components (**PAMPs** — e.g., LPS, cell-wall components, microbial nucleic acids) and host-derived **DAMPs** (histones, **HMGB1**, S100 proteins, oxidised phospholipids, dsDNA, ATP) are sensed by **pattern-recognition receptors (PRRs)** — **TLRs** (10 in humans), C-type lectin receptors, RAGE, RIG-I, and NOD-like receptors.
- **Myeloid responses:** Activated **neutrophils** upregulate adhesion molecules (CD11b) and release **neutrophil extracellular traps (NETs)** — DNA webs studded with cathepsin-G, myeloperoxidase, and neutrophil elastase — which, with platelets and fibrin, form microthrombi. **Emergency granulopoiesis** (driven by IL-6, GM-CSF, G-CSF) releases immature neutrophils and predicts poor outcome. **Monocytes** (classical $CD14^{+}CD16^{-}$, intermediate, non-classical) differentiate into dendritic cells and **M1 (pro-inflammatory) macrophages** releasing IL-1β, IL-6, and TNF-α.
- **Lymphoid responses & immunosuppression: NK cells** amplify inflammation (IFN-γ, granzyme) but also release IL-10. Progressive **lymphocyte apoptosis, exhaustion, and reduced proliferation**, plus myeloid-derived suppressor cells, produce a state of **sepsis-induced immunosuppression** predisposing survivors to secondary infection.
- **Endothelial activation:** PAMPs/DAMPs degrade the endothelial **glycocalyx** and upregulate **ICAMs and VCAM-1**, tissue factor, and PAI-1, while loss of **VE-cadherin** and tight junctions causes capillary leak → interstitial oedema, increased oxygen-diffusion distance, and hypoperfusion. Excess endothelial **nitric oxide (NO)** drives vasodilation.
- **Coagulopathy:** Endothelial/leukocyte **tissue factor** triggers the extrinsic cascade → thrombin → fibrin; **vWF** (Weibel-Palade bodies) aggregates platelets; all three complement pathways activate, releasing **C3a/C5a** anaphylatoxins and assembling the **membrane-attack complex (C5b-9)**. Natural anticoagulants (antithrombin, tissue-factor-pathway inhibitor, activated protein C) fall while antifibrinolytics (PAI, TAFI) rise, producing microvascular thrombosis; consumption of platelets/factors then causes bleeding (**DIC**).
- **Cellular injury:** Hypotension (vasodilation, myocardial depression, hypovolaemia), interstitial oedema, and microcirculatory thrombosis impair oxygen delivery; **ROS and reactive nitrogen species** (peroxynitrite) oxidise proteins/lipids and damage DNA. Even with adequate oxygen, **mitochondrial and metabolic dysfunction** disrupts ATP generation and ion homeostasis.

Clinical recognition, scoring & diagnosis

- Presentation is **non-specific** — fever, tachycardia, lethargy, myalgia — with or without localising features (cough, pyuria, abdominal pain) or signs of organ failure (oliguria, altered mentation). **There is no gold-standard diagnostic test.**

- **SOFA score** grades dysfunction in six systems: neurologic (GCS), cardiovascular (MAP / vasoactive agents), respiratory (PaO_2/FiO_2 or ventilation), hepatic (bilirubin), renal (creatinine), and coagulation (platelets). An increase of **≥2** operationalises Sepsis-3.
- **qSOFA** (RR ≥22, GCS <15, SBP ≤100) ≥2 flags poor outcome — more specific but less sensitive than SIRS.
- Baseline workup: CBC with differential, basic metabolic panel, LFTs, **serum lactate**, coagulation panel, urinalysis, and **cultures of blood and suspected sites before antibiotics**, plus targeted imaging (x-ray/CT/ultrasound) to localise and enable **source control**.
- **Sepsis mimics** (~25% of suspected ICU cases): heart failure/cardiac arrest, non-infective COPD/pneumonitis, mesenteric ischaemia, inflammatory bowel disease, hypovolaemia, autonomic dysfunction, and adrenal insufficiency — mandating continuous re-evaluation.

Management — resuscitation per the 2021 Surviving Sepsis Campaign

Initial priorities: timely blood-pressure and organ support, antimicrobials, and source control; target **ICU admission within 6 h** for the critically ill.

- **Antibiotics:** In bacterial septic shock, every 1-h delay adds an estimated **7–8% mortality** → give **empiric antibiotics within 1 h of shock recognition**. Without shock and with diagnostic uncertainty, a time-limited evaluation is acceptable, giving antibiotics by **3 h** if no alternative diagnosis emerges. Choice is guided by site, community vs health-care exposure, prior resistance, and host factors: third-generation cephalosporin (ceftriaxone/cefotaxime) if *Pseudomonas* unlikely; **cefepime, piperacillin-tazobactam, or a carbapenem** if *Pseudomonas* likely; **two** gram-negative agents if highly resistant organisms are a risk; add **vancomycin or linezolid** for MRSA risk. Add an **echinocandin** only for high fungal risk; **remdesivir/oseltamivir** for SARS-CoV-2/influenza. De-escalate and shorten courses with culture data.
- **Source control:** Drain/debride/decompress (intra-abdominal abscess, bowel perforation, pyelonephritis, cholangitis, necrotising soft-tissue infection) **as rapidly as possible**; remove infected indwelling catheters.
- **Fluids: Balanced crystalloid** (e.g., lactated Ringer's) is preferred over 0.9% saline (which risks hyperchloraemic acidosis); **avoid pentastarch/hydroxyethyl starch** (kidney injury, death). Give a bolus over 5–10 min at **~30 mL/kg** (individualise in ESRD/systolic HF). Guide further fluids by **dynamic assessment** (capillary refill, passive-leg-raise, point-of-care ultrasound), *not* static CVP-based protocolised targets.
- **Vasopressors: Norepinephrine first-line** (MAP target **≥65 mmHg**), add **vasopressin** second, **epinephrine** third. Place an arterial line for continuous monitoring.
- **Inotrope:** For myocardial dysfunction (sepsis-induced cardiomyopathy) with persistent hypoperfusion, add **dobutamine** to norepinephrine or use epinephrine alone.
- **Corticosteroids: IV hydrocortisone 200 mg/day** (50 mg q6h) if ongoing vasopressor requirement.

Organ-specific complications & targeted management

System (frequency)	Key findings	Management essentials
Neurologic (54% — encephalopathy)	Altered consciousness/cognition; seizure, stroke	Treat infection; correct metabolic/electrolyte derangement; **limit neurotoxic drugs** (e.g., cefepime), opiates, benzodiazepines; EEG/MRI/LP as indicated
Cardiovascular (25% shock; ½ with myocardial dysfunction)	Hypotension, skin mottling, prolonged capillary refill, oliguria	Balanced crystalloid ~30 mL/kg; norepinephrine → vasopressin → epinephrine; hydrocortisone 200 mg/d; dobutamine/PAC if mixed cardiogenic picture
Respiratory (7% — ARDS)	Tachypnoea, hypoxia; bilateral infiltrates, PaO_2/FiO_2 <300	Target **SpO_2 90–96%**; HFNC preferred over NIV; **plateau pressure <30 cmH_2O, tidal volume 6–8 mL/kg IBW**; rescue: prone positioning, neuromuscular blockade, VV-ECMO
Renal (up to 67% — AKI)	Oliguria/anuria, ↑creatinine/BUN, acidaemia, hyperkalaemia	Maintain perfusion, avoid nephrotoxins; **RRT for standard indications** (refractory acidaemia, hyperkalaemia, uraemia, volume overload); CRRT preferred in shock; bicarbonate if **pH ≤7.2**
Hepatic/GI (50% liver dysfunction)	RUQ pain, jaundice, asterixis; ↑bilirubin/ALP	Treat infection, avoid hypotension/hepatotoxins; stress-ulcer prophylaxis for high-risk; **enteral feeding within 48 h** once shock controlled; insulin if glucose >180 mg/dL
Haematologic (35% septic shock — DIC)	Thrombocytopenia, ↑fibrin split products, ↓fibrinogen, prolonged PT/INR	**Cryoprecipitate** for fibrinogen <150 mg/dL; **platelets** if $\leq 50\times10^9$/L + bleeding; **FFP** for prolonged PT/INR + bleeding; **PRBC** for Hb <7.0 g/dL

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sepsis pathogenesis schematic** (label clearly): *Pathogen → PAMPs/DAMPs → PRR (TLR)* on **monocyte/neutrophil**; *Tissue factor* on endothelium/leukocytes → *clotting cascade → thrombin → fibrin*; *NETs*; *platelet aggregates + vWF*; *↓antithrombin, ↑PAI-1*; *complement C3a/C5a, MAC (C5b-9)*; *endothelial ICAMs/VCAM-1, glycocalyx degradation, loss of VE-cadherin → interstitial oedema*; *NO-mediated vasodilation*; *mitochondrial/metabolic dysfunction*; *M1 macrophage*; *lymphocyte exhaustion/apoptosis*.
- **Sepsis-3 management algorithm:** *Suspected infection → screen (ΔSOFA ≥2 / qSOFA) → cultures + lactate → empiric antibiotics ≤1 h (shock) → 30 mL/kg balanced crystalloid → dynamic reassessment (PLR/POCUS/capillary refill) → norepinephrine (MAP ≥65) → vasopressin → epinephrine → hydrocortisone 200 mg/d → source control → ICU ≤6 h.*

Clinical / Diagnostic significance

- **Lactate** is both a diagnostic threshold for septic shock (>2 mmol/L) and a resuscitation marker; a randomised trial found capillary-refill-guided resuscitation was non-inferior to lactate-targeted resuscitation for 28-day mortality — relevant in resource-limited settings.
- **Sepsis-induced coagulopathy (SIC)** scoring (platelets, PT, SOFA) detects coagulopathy earlier and more sensitively than overt-DIC criteria.
- Machine-learning **phenotypes (α, β, γ, δ)** carry distinct mortality (2%, 5%, 15%, 32%) and may refine future trial design and prognostication.
- A restrictive-vs-liberal early-fluid trial and protocolised CVP/$ScvO_2$ targets showed **no mortality benefit**, underpinning the modern shift to individualised, dynamic resuscitation.

High-yield exam pointers

- Sepsis-3 **abolished "severe sepsis"**: today it is **sepsis (organ dysfunction, ΔSOFA ≥2)** and **septic shock (vasopressor for MAP >65 + lactate >2 despite fluids)**.
- **Antibiotics within 1 h** of septic-shock recognition; **~7–8% added mortality per hour** of delay.
- **Norepinephrine → vasopressin → epinephrine**; MAP target **≥65 mmHg**.
- **Balanced crystalloid ~30 mL/kg**; avoid starch (HES); guide by dynamic measures, not CVP.
- **Hydrocortisone 200 mg/day** for vasopressor-dependent shock.
- ARDS: **6–8 mL/kg tidal volume, plateau <30 cmH_2O, SpO_2 90–96%**; rescue with prone/NMB/VV-ECMO.
- AKI: RRT for **standard indications only**; bicarbonate if **pH ≤7.2**; PRBC transfuse at **Hb <7 g/dL**.
- Most frequent primary site = **urinary tract**; septic-shock mortality **up to 40%**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 315 "Sepsis and Septic Shock" (Strich & Chertow). **Coverage note:** The exam phrasing "severe sepsis" reflects the older Sepsis-1/Sepsis-2 nomenclature; Harrison 22e follows **Sepsis-3 (2016)**, which eliminated the term — the answer therefore maps "severe sepsis" onto current "sepsis"/"septic shock" definitions. SIRS thresholds and the original severe-sepsis/septic-shock criteria are quoted from the chapter's historical-definitions paragraph. All drug doses, vasopressor sequence, ventilation targets, transfusion triggers, and organ-specific frequencies are taken verbatim from the chapter text and Tables 315-1/315-2.

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Neurological disorders in HIV disease

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Neurologic disease in HIV includes direct effects of HIV on the nervous system, opportunistic infections and neoplasms due to immunosuppression, immune reconstitution inflammatory syndromes, and treatment-related toxicities. Neurologic involvement may occur at any stage, from acute seroconversion meningitis to advanced AIDS with focal brain lesions, dementia, myelopathy, or peripheral neuropathy. The approach in an exam answer is to classify by **anatomic syndrome**, **CD4 count**, and **treatable emergency**.

Classification of neurologic disorders in HIV

- **Primary HIV-related disorders**:
  - **Acute HIV aseptic meningitis / meningoencephalitis** during seroconversion, with fever, headache, photophobia, lymphocytic CSF, and sometimes cranial neuropathies.
  - **HIV-associated neurocognitive disorder (HAND)**: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and **HIV-associated dementia**.
  - **Vacuolar myelopathy**, usually in advanced HIV, resembling subacute combined degeneration with spastic paraparesis and posterior-column signs.
  - **Peripheral neuropathies**: distal symmetric polyneuropathy, inflammatory demyelinating polyneuropathy, mononeuritis multiplex, radiculopathy, and autonomic neuropathy.
- **Opportunistic infections of CNS**:
  - **Toxoplasma encephalitis**, **cryptococcal meningitis**, **tuberculous meningitis**, **progressive multifocal leukoencephalopathy (PML)**, **CMV encephalitis / polyradiculopathy**, VZV vasculopathy, neurosyphilis, and bacterial or fungal abscesses.
- **Neoplasms**:
  - **Primary CNS lymphoma**, systemic lymphoma with CNS spread, and rarely Kaposi-related or other metastatic disease.
- **Immune-mediated / ART-related**:

- **IRIS** unmasking or worsening cryptococcosis, tuberculosis, PML, or toxoplasmosis after ART initiation.
- Drug toxicities: zidovudine myopathy, older nucleoside analogue mitochondrial toxicity, efavirenz neuropsychiatric symptoms, and chemotherapy-related neuropathy.

Primary HIV-related neurologic syndromes

Syndrome	Typical setting	Key clinical features	Diagnosis	Management
Acute aseptic meningitis	Primary HIV infection	Fever, headache, meningism, photophobia, cranial nerve palsy; may accompany rash, pharyngitis, lymphadenopathy	CSF lymphocytic pleocytosis, raised protein, normal or mildly low glucose; exclude HSV, VZV, TB, cryptococcus	Supportive care; initiate ART as per HIV guidelines after evaluation
HAND / HIV-associated dementia	Chronic HIV; more severe with low CD4 and high viral load	Subcortical pattern: psychomotor slowing, impaired attention and executive function, apathy, gait difficulty, poor fine motor speed	Neuropsychological testing; MRI may show cerebral atrophy or white-matter signal change; exclude depression, drugs, OI, B12, thyroid disease	Effective ART with CNS-active regimen when possible; treat comorbidities and rehabilitation
Vacuolar myelopathy	Advanced AIDS	Slowly progressive spastic paraparesis, hyperreflexia, extensor plantars, sensory ataxia, urinary urgency; often with dementia or neuropathy	MRI spinal cord may be normal or show atrophy; B12, copper, HTLV-1, syphilis, compressive myelopathy must be excluded	ART; physiotherapy, antispasticity measures, bladder care
Distal symmetric polyneuropathy	Common in advanced or treated HIV	Burning feet, numbness, allodynia, reduced ankle reflexes; length-dependent sensory loss	Clinical plus nerve conduction if uncertain; screen diabetes, B12 deficiency, alcohol, renal disease, drugs	ART optimization, remove neurotoxic drugs, pregabalin/gabapentin/duloxetine/TCA, foot care

- **HIV-associated dementia** is classically a **subcortical dementia**: slowed thinking, impaired concentration, apathy, personality change, gait imbalance, tremor, and later incontinence.
- It must not be diagnosed until **opportunistic infection, CNS lymphoma, metabolic encephalopathy, depression, substance use, and drug toxicity** have been excluded.
- **Vacuolar myelopathy** is the important spinal cord answer: corticospinal tract and posterior column dysfunction, often without a compressive lesion on imaging.
- **Peripheral neuropathy** is among the commonest neurologic complications of HIV; severe pain and loss of ankle reflexes are high-yield clinical clues.

Opportunistic infections: CD4-linked approach

Disorder	Usual immune setting	Clinical clues	Imaging / CSF clues	Treatment principle
Toxoplasma encephalitis	CD4 usually <100 cells/microL; Toxoplasma IgG positive	Headache, fever, confusion, seizures, focal deficits	Multiple ring-enhancing basal ganglia or corticomedullary lesions with edema; CSF PCR may help	Pyrimethamine + sulfadiazine + leucovorin or TMP-SMX; continue at least 6 weeks, then maintenance until immune recovery
Cryptococcal meningitis	CD4 often <100 cells/microL	Subacute headache, fever, vomiting, altered sensorium; meningism may be mild	High opening pressure; cryptococcal antigen positive; lymphocytic or paucicellular CSF	Amphotericin B plus flucytosine induction, then fluconazole consolidation and maintenance; repeated therapeutic LP for raised pressure
Tuberculous meningitis / tuberculoma	Any stage, common in advanced disease	Chronic fever, headache, basal meningitis, cranial neuropathy, stroke, hydrocephalus	Basal exudates, infarcts, hydrocephalus; CSF lymphocytes, high protein, low glucose; NAAT/culture	Standard anti-TB therapy with corticosteroids; manage hydrocephalus and ART timing carefully
PML (JC virus)	CD4 usually <200 cells/microL	Subacute focal deficits, visual field loss, aphasia, ataxia; usually no fever or mass effect	Non-enhancing or faintly enhancing white-matter lesions without marked edema; CSF JC virus PCR	No specific antiviral of proven value; restore immunity with ART; distinguish from PML-IRIS
CMV encephalitis / polyradiculopathy	CD4 usually <50 cells/microL	Delirium, ventriculoencephalitis, retinitis; cauda equina syndrome with flaccid weakness and urinary retention	CSF neutrophils may occur in polyradiculopathy; CMV PCR supportive	IV ganciclovir, often with foscarnet in severe disease; start or optimize ART

- **CNS toxoplasmosis** is the commonest cause of multiple ring-enhancing brain lesions in advanced AIDS; empirical treatment is reasonable when the clinical-radiologic picture is typical, but failure to improve should prompt biopsy to exclude lymphoma.
- **Cryptococcal meningitis** is a raised intracranial pressure disease: repeated lumbar puncture is therapeutic and lifesaving; corticosteroids are not routine unless another indication exists.
- **PML** gives progressive demyelinating focal neurologic deficits without a bulky enhancing mass; deterioration after ART may represent **PML-IRIS**.
- **CMV polyradiculopathy** is suggested by rapidly progressive flaccid paraparesis, saddle sensory loss, areflexia, and bladder dysfunction in very advanced HIV.

Focal brain lesion in HIV: differential diagnosis

- **Multiple ring-enhancing lesions**:

- Most likely **toxoplasma encephalitis**, especially basal ganglia lesions with edema and positive Toxoplasma IgG.
- Differentials: tuberculoma, fungal abscess, bacterial abscess, metastasis, and lymphoma.

- **Solitary enhancing mass**:
  - Consider **primary CNS lymphoma**, toxoplasmosis, tuberculoma, glioma, or abscess.
  - CNS lymphoma often involves deep periventricular structures or corpus callosum and may show EBV DNA in CSF.
- **Non-enhancing white-matter lesions**:
  - Think of **PML**, HIV encephalopathy, demyelination, or small-vessel disease.
- **Meningitis picture**:
  - Cryptococcus, tuberculosis, syphilis, bacterial meningitis, viral meningitis, and primary HIV meningitis.
- **Myelopathy / radiculopathy**:
  - Vacuolar myelopathy, CMV polyradiculopathy, VZV radiculitis, lymphoma, epidural abscess, TB spine, B12 deficiency, and compressive cord disease.

Diagnostic approach

- Assess **stage of HIV**: duration, ART adherence, opportunistic infection prophylaxis, CD4 count, plasma HIV RNA, prior OI, and current ART drugs.
- Define the neurologic syndrome:
  - **Meningitis / encephalitis**, **focal brain lesion**, **dementia**, **myelopathy**, **neuropathy**, **myopathy**, or **stroke**.
- Urgent investigations:
  - **MRI brain with contrast** is preferred for focal deficits, seizures, altered sensorium, suspected PML, lymphoma, or toxoplasmosis.
  - **CT brain before LP** when raised intracranial pressure, focal deficit, papilledema, or mass lesion is suspected.
  - **CSF**: opening pressure, cells, protein, glucose; Gram stain/culture; cryptococcal antigen; AFB smear/culture/NAAT; VDRL; viral PCRs including HSV/VZV/CMV/JC virus as indicated; cytology/flow cytometry for lymphoma.
  - Blood tests: CD4 count, HIV RNA, complete blood count, electrolytes, renal/liver function, B12, thyroid tests, syphilis serology, hepatitis coinfection, and toxoplasma IgG.
- Neurophysiology:
  - Nerve conduction studies for neuropathy, demyelinating neuropathy, mononeuritis multiplex, or radiculopathy.
  - EMG and creatine kinase for suspected HIV or zidovudine-associated myopathy.
- Brain biopsy is reserved for:
  - Atypical lesions, negative serology, solitary mass, diagnostic uncertainty, or no clinical/radiologic response to appropriate empirical therapy.

Management principles

- **Stabilize first**: airway, breathing, circulation; treat seizures, raised intracranial pressure, sepsis, severe hyponatremia, and hypoglycemia promptly.
- **Start pathogen-specific therapy early** when a treatable OI is likely; do not wait for every test if toxoplasmosis, bacterial meningitis, HSV encephalitis, or TB meningitis is strongly suspected.
- **ART is central**, but timing must be individualized:
  - In most OIs, initiate ART after acute stabilization and early anti-infective therapy.
  - In **cryptococcal meningitis** and **TB meningitis**, very early ART can worsen intracranial inflammation; delayed initiation after induction therapy is often preferred.
- Prevent and treat **IRIS**:
  - Suspect IRIS when a patient worsens after ART despite microbiologic control or when occult infection becomes clinically apparent.
  - Continue ART in most cases, continue OI therapy, and use corticosteroids for severe inflammatory complications after excluding uncontrolled infection.
- Provide **secondary prophylaxis** until immune reconstitution:
  - Toxoplasmosis and cryptococcosis need maintenance therapy until sustained CD4 recovery on ART.
- Supportive care:
  - Rehabilitation for cognitive, gait, and focal deficits; neuropathic pain control; bladder and bowel care; nutrition; fall prevention; psychiatric assessment; adherence counselling.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flowchart: neurologic syndrome in HIV** — labels: acute meningitis, focal brain lesion, diffuse encephalopathy/dementia, myelopathy, peripheral neuropathy; next labels: MRI brain, CSF with opening pressure, CD4 count, targeted PCR/antigen tests, empirical therapy.
- **CD4-linked CNS complications chart** — labels: CD4 <200: PML, TB, lymphoma; CD4 <100: toxoplasmosis, cryptococcus; CD4 <50: CMV encephalitis/polyradiculopathy; any CD4: acute HIV meningitis, neurosyphilis, stroke.

Clinical / Diagnostic significance

- Neurologic symptoms in HIV are often the first clue to **advanced immunosuppression** or ART failure.
- **Ring-enhancing lesion plus seizures or hemiparesis** in advanced HIV is toxoplasmosis until proved otherwise, but lymphoma must be considered if solitary, EBV-positive CSF, or nonresponsive.
- **Headache with high CSF opening pressure** in AIDS is a cryptococcal emergency; pressure control is as important as antifungal therapy.
- **Subacute focal deficits without fever or mass effect** point toward PML; treatment is immune restoration, not conventional antiviral therapy.

- **Rapid flaccid paraparesis with urinary retention** suggests CMV polyradiculopathy, whereas slowly progressive spastic paraparesis suggests vacuolar myelopathy.
- **Cognitive decline** may be HAND, but reversible mimics such as depression, drugs, metabolic disease, OI, and CNS lymphoma must be actively excluded.
- ART has reduced classic HIV dementia and many OIs, but has increased the importance of recognizing **IRIS** and chronic neurocognitive impairment.

High-yield exam pointers

- Classify HIV neurology as **direct HIV**, **opportunistic infection**, **neoplasm**, **immune-mediated/IRIS**, and **drug-related**.
- HAND is a **subcortical** cognitive-motor-behavioral syndrome; severe form is HIV-associated dementia.
- Vacuolar myelopathy causes **spastic paraparesis with posterior-column signs** in advanced AIDS.
- Toxoplasmosis: **multiple ring-enhancing basal ganglia lesions**; treat with pyrimethamine-sulfadiazine-leucovorin or TMP-SMX.
- Cryptococcal meningitis: **measure opening pressure** and repeat LPs for raised pressure.
- PML: JC virus, **non-enhancing white-matter demyelination**, no proven specific antiviral; optimize ART.
- CMV neurologic disease occurs at very low CD4 counts and may cause **ventriculoencephalitis or polyradiculopathy**.
- Primary CNS lymphoma is an AIDS-defining malignancy; think of it in a **solitary enhancing mass** or toxoplasma nonresponse.
- Always mention **CD4 count, HIV RNA, MRI with contrast, CSF studies, ART timing, and IRIS**.

SOURCE & COVERAGE

Harrison 22e — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders"; CMDT 2026 — HIV infection/AIDS and opportunistic infection management.

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Serological tests in infectious diseases

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Serology is the laboratory detection and quantitation of pathogen-specific **antibodies** (or, by extension, microbial **antigens**) in serum and other body fluids, used to infer infection from the **host's immune response** rather than by isolating the organism. Harrison emphasises that serologic diagnosis is the *measurement of the host's response to pathogen exposure* and can typically be made **only in retrospect**, requiring paired **acute- and convalescent-phase serum samples**. It is the mainstay for organisms that are difficult or impossible to culture, but its sensitivity and specificity are variable and it is increasingly complemented (and replaced) by **antigen detection** and **nucleic-acid amplification tests (NAATs)**.

Basic principles & interpretive concepts

- **Antigen–antibody reaction** is the basis: a known antigen detects unknown antibody (or a known antibody detects unknown antigen) in the patient's specimen.
- **Indirect (antibody) detection** vs **direct (antigen) detection** — antibody tests reflect the *host response*; antigen tests detect *structural components of the pathogen* itself.
- **Antibody class**: **IgM** appears early and indicates **recent/acute** infection; **IgG** appears later, persists, and indicates **past exposure, convalescence or immunity**.
- **Seroconversion** — change from antibody-negative to antibody-positive; the **window period** is the interval after infection before antibody becomes detectable (a key cause of false-negatives, classically in HIV).
- **Diagnostic criterion**: a **fourfold (two-dilution) rise in titre** between acute and convalescent sera, or **seroconversion**, confirms recent infection; a single titre is harder to interpret.
- **Limitation flagged by Harrison**: for chronic infections, serology alone often **cannot distinguish active from latent infection** or identify repeat exposure, and sensitivity depends on the **organism and the patient's immune status**.

Classification of serological / immunodiagnostic techniques

Principle	Representative test(s)	Typical infectious-disease use
Agglutination	Widal, Weil–Felix, **latex agglutination**, cold agglutinins, heterophile (Paul–Bunnell/Monospot)	Enteric fever, rickettsioses, **cryptococcal/CSF antigen**, *Mycoplasma*, EBV mononucleosis
Precipitation / flocculation	**VDRL, RPR** (nontreponemal)	Syphilis screening
Complement fixation	CFT (historical Wassermann)	Older viral/fungal serology
Neutralization	**ASO (anti-streptolysin O)** titre	Recent streptococcal infection / rheumatic fever
Immunofluorescence	**FTA-ABS**, direct/indirect IFA	Treponemal confirmation, many viruses

Principle	Representative test(s)	Typical infectious-disease use
Enzyme immunoassay (ELISA/EIA)	Ag/Ab combo assays, capture (MAC) ELISA	**HIV screen**, hepatitis, dengue, many others
Immunoblot / Western blot	Confirmatory immunoblot	Historical HIV & Lyme confirmation
Chemiluminescence / lateral-flow rapid tests	Immunochromatographic strips	Point-of-care HIV, dengue NS1, malaria, **cryptococcal LFA**

(The taxonomy above is standard textbook microbiology — see Coverage note; the specific applications below are anchored in the provided chapters.)

Antibody-based serology in specific infections

- **HIV** — combined **antigen/antibody (4th-generation) immunoassays** detect both **p24 antigen** and **anti-HIV antibody**. Harrison's natural-history model (Fiebig staging) shows **p24 antigenaemia** appearing first in acute infection, transiently disappearing, then **antibody** rising at **seroconversion**, with **viral load** persisting — illustrating why early antibody-only testing missed acute disease and why molecular (PCR) viral-load testing transformed diagnosis and staging.
- **Syphilis** (*Treponema pallidum*) — *notoriously difficult to stage by serology alone*; requires **two tiers**: a **nontreponemal test** (Harrison cites **RPR — rapid plasma reagin**; also VDRL) for screening and activity, plus a **treponemal test** (**fluorescent treponemal antibody, FTA-ABS**; also TPHA/TP-PA) for confirmation. **CSF serology for *T. pallidum*** (CSF-VDRL) is highly useful in selected neurosyphilis patients.
- **Lyme disease** (*Borrelia burgdorferi*) — **IgM and IgG antibody** testing; Harrison gives **IgM early-disease sensitivity ≈50% and specificity ≈80%**, and notes **IgG may reflect prior exposure rather than active disease** in endemic regions — a classic example of serology's interpretive pitfalls (two-tier EIA → immunoblot).
- **Tuberculosis** (immunodiagnosis of host T-cell response) — **tuberculin skin test (PPD)** and **interferon-γ release assays (IGRAs)**, which measure **cytokine release from T lymphocytes in response to *M. tuberculosis*-specific antigens**. Both have **limited sensitivity in immunodeficient hosts**, and **neither distinguishes latent from active infection** — emphasising that *serology is notoriously insensitive for TB*.
- **Fungal CSF serology** — antibody/antigen testing for ***Coccidioides*** is sensitive and useful in selected patients.

Antigen-detection assays (direct serodiagnosis)

- **Viral structural antigens — hepatitis B surface antigen (HBsAg), HIV p24 antigen, SARS-CoV-2 spike protein**.
- **Bacterial surface antigens / urinary antigen tests** — ***Streptococcus pneumoniae*** and ***Legionella pneumophila* serogroup 1**.
- **Fungal antigens** — ***Cryptococcus*** antigen (CrAg; **highly sensitive**) and ***Histoplasma***; less-specific **cell-wall components**: **galactomannan** (*Aspergillus*) and **β-D-glucan** (*Aspergillus* and other fungi).

- **CSF latex agglutination** — for ***Haemophilus influenzae* type b**, **group B *Streptococcus***, ***S. pneumoniae***, and ***Neisseria meningitidis***. Harrison notes these are **not recommended for screening** (no more sensitive than Gram's stain) but help **presumptively identify organisms already seen on Gram's stain**; in contrast, **cryptococcal antigen** testing is highly sensitive and clinically useful.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HIV serological markers in natural history (Fiebig-type curve)** — x-axis: **Time (weeks → years)**; y-axis: **Relative level**; plot three curves labelled **p24 antigen**, **HIV antibody (Ab)**, **Viral load (VL)**; add a dashed **limit of detection** line; mark phases **Acute HIV → Chronic HIV → AIDS** and the **window period / seroconversion**.
- **Acute vs convalescent antibody response** — x-axis **time from onset**, y-axis **antibody titre**; two curves **IgM** (early, transient) and **IgG** (later, persistent); annotate the **fourfold rise in titre** between **acute** and **convalescent** samples as the diagnostic criterion.

Clinical / Diagnostic significance

- Serology is the **diagnostic approach of choice when the organism is unculturable or fastidious**, and for **epidemiological/seroprevalence surveys** and **immunity/vaccination status** (e.g., anti-HBs, rubella IgG).
- **Two-tier strategies** (sensitive screen → specific confirmatory) maximise accuracy — exemplified by **syphilis** (nontreponemal → treponemal) and **Lyme** (EIA → immunoblot).
- **IgM positivity** supports **acute infection**; **paired sera with a fourfold rise** give definitive evidence; **CSF antibody/antigen** localises CNS infection (neurosyphilis, cryptococcal, coccidioidal).
- **Pitfalls**: window-period false-negatives, **cross-reactivity** and false-positives (biological false-positive VDRL), inability to separate **active from latent/past** infection, and **reduced sensitivity in immunocompromised** patients — all argue for correlation with **clinical suspicion** and, increasingly, **NAAT/PCR**, which provide real-time diagnosis and can predict drug resistance.

High-yield exam pointers

- Serology = **host antibody response**; usually a **retrospective** diagnosis needing **acute + convalescent sera**; **fourfold titre rise** or **seroconversion** is confirmatory.
- **IgM = recent/acute; IgG = past/immunity**; beware the **window period**.
- **Syphilis** — nontreponemal **RPR/VDRL** + treponemal **FTA-ABS/TPHA**; **biological false-positive VDRL** is a classic trap.
- **HIV** — 4th-gen **Ag/Ab combo (p24 + antibody)**; p24 antigen precedes antibody (narrows window).
- **Lyme** IgM early sensitivity ~50%, specificity ~80%; **IgG may mean only past exposure**.
- **TB — PPD/IGRA** test cell-mediated immunity, are **insensitive in immunodeficiency**, and **cannot separate latent from active** disease.
- **Antigen tests**: HBsAg, HIV p24, SARS-CoV-2 spike, pneumococcal/Legionella **urinary antigen**, **cryptococcal antigen**, **galactomannan/β-D-glucan**.

- **CSF latex agglutination** (Hib, GBS, pneumococcus, meningococcus) is *not for screening* but aids Gram-stain-guided identification; **CrAg is highly sensitive**.
- Classic eponymous agglutination tests: **Widal** (enteric fever), **Weil–Felix** (rickettsia), **Paul–Bunnell/Monospot** (EBV), **cold agglutinins** (*Mycoplasma*), **ASO** (streptococcal).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 126 "Microbial Genomics and Infectious Disease"** (serologic vs antigen vs nucleic-acid diagnosis; HBsAg/HIV p24/SARS-CoV-2 spike; pneumococcal/Legionella urinary antigen; cryptococcal/histoplasma antigen; galactomannan/β-glucan; HIV antibody–p24–viral-load seroconversion/Fiebig figure; syphilis RPR/FTA; Lyme IgM/IgG sensitivity-specificity; PPD/IGRA) and **Ch 124 "Approach to the Patient with an Infectious Disease"** (pathogen-specific serology/antigen/PCR testing; CSF latex agglutination for Hib, GBS, *S. pneumoniae*, *N. meningitidis*; cryptococcal antigen; CSF serology for *T. pallidum* and *Coccidioides*; high-titre antibody/IVIG).

Coverage note (spec gap = true): The provided chapters carry no dedicated "serology" section, so the **technique-classification table** (agglutination, precipitation/flocculation, complement fixation, neutralization, immunofluorescence, ELISA/EIA, Western blot, immunochromatography) and the **eponymous tests Widal, Weil–Felix, Paul–Bunnell/Monospot, ASO, cold agglutinins, and dengue NS1/MAC-ELISA** are supplied from universally accepted standard internal-medicine/microbiology knowledge, not directly from these two Harrison chapters. The disease-specific applications (HIV, syphilis, Lyme, TB, fungal/CSF antigen) and antigen-detection examples are faithfully grounded in the text above.

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Ebola virus

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Ebola virus (EBOV)* is an enveloped, non-segmented, negative-sense RNA virus of the family **Filoviridae**, genus *Orthoebolavirus*, and is the cause of **Ebola virus disease (EVD)** — the prototype of the filovirid viral haemorrhagic fevers (along with Marburg disease). EVD is a *World Health Organization Risk Group 4* zoonosis that begins as a non-specific influenza-like illness and rapidly evolves to gastrointestinal loss, coagulopathy, multi-organ dysfunction and shock, with a historically very high case-fatality rate. It is highly **infectious but not highly contagious**, spreading by direct contact with body fluids rather than by aerosol.

Etiology & Virology

- Family **Filoviridae** has nine official genera; only two contain human pathogens — *Orthoebolavirus* and *Orthomarburgvirus*. Collectively these cause **filovirid (filovirus) disease (FVD)**.
- **Ebola disease (EBOD)** is caused by four of the orthoebolaviruses; **Marburg disease (MARD)** by the two orthomarburgviruses (Marburg virus, Ravn virus).

- The virion is **pleomorphic and filamentous** (also torus-/"6"-shaped); width ≈91–98 nm, length <1 µm; enveloped, with a helical ribonucleoprotein capsid studded with **GP1,2 glycoprotein spikes**.
- Genome ≈**19 kb**, linear negative-sense RNA with **seven genes encoding seven structural proteins**: nucleoprotein (**NP**), polymerase cofactor (**VP35**), matrix protein (**VP40**), glycoprotein (**GP1,2**), transcriptional activator (**VP30**), ribonucleoprotein-associated protein (**VP24**) and the **L** protein (RNA-dependent RNA polymerase). Orthoebolaviruses *additionally* encode three non-structural proteins — *sGP, ssGP and Δ-peptide*.

Orthoebolavirus	Virus (abbrev.)	Pathogenicity in humans
O. zairense	**Ebola virus (EBOV)** — "Zaire"	Highly pathogenic; cause of the 2013–16 West Africa epidemic
O. sudanense	**Sudan virus (SUDV)**	Pathogenic; re-emerged Uganda/South Sudan 2022–23
O. bundibugyoense	**Bundibugyo virus (BDBV)**	Pathogenic
O. taiense	**Taï Forest virus (TAFV)**	Pathogenic (rare; only one human case)
O. restonense	**Reston virus (RESTV)**	Apparently **non-pathogenic** to humans
O. bombaliense	**Bombali virus (BOMV)**	Non-pathogenic (detected in bats)

Epidemiology & Transmission

- First recognised in **1976** in simultaneous outbreaks in *Zaire (now DR Congo)* and *South Sudan*; >20 outbreaks since, confined to equatorial **Western, Middle and Eastern Africa**.
- The **2013–2016 West Africa outbreak** (Guinea, Sierra Leone, Liberia, with exported cases) was the largest ever — **28,652 cases and 11,325 deaths** — and was the first to constitute a regional and global threat; CMDT cites an average case-fatality rate of ~**60%**.
- **Reservoir:** the cave-dwelling **Egyptian rousette fruit bat (*Rousettus aegyptiacus*)** is the proven reservoir for Marburg/Ravn viruses; fruit/insectivorous **bats are the suspected (but unproven) reservoir for orthoebolaviruses**. Only ≈50 natural host-to-human spillover events have been recorded since 1967.
- **Spillover to humans:** contact with reservoir hosts or with infected/dead mammals — hunting or eating "**bushmeat**" (apes, monkeys, duikers, bush pigs).
- **Human-to-human spread:** direct person-to-person contact or exposure to **infected body fluids/tissues** (blood, vomitus, stool, sweat, semen, breast milk), parenteral inoculation (needlestick, needle reuse), and contact with corpses during **traditional burial/ritual washing**. *There is no natural aerosol or respiratory-droplet transmission.*
- Virus is **not transmissible before symptom onset**; infectivity rises with illness severity and viral load. Health-care workers and family caregivers bear the highest risk; nosocomial amplification drives outbreaks.

Pathogenesis

- Entry is via skin breaks or mucosa; **GP1,2 spikes** determine tropism by engaging the intracellular receptor **NPC1 (Niemann-Pick C1 cholesterol transporter)**.

- **First targets are macrophages, monocytes and dendritic cells.** Structural proteins **VP35, VP40 and VP24 suppress innate immunity** (notably the type-I interferon pathway), permitting uncontrolled replication — serum titres exceed **10^6 PFU/mL** with dissemination to almost all tissues (hepatocytes, adrenal cortex, fibroblasts, endothelium).
- **Immune dysregulation:** infected macrophages release a "cytokine storm"; dendritic cells fail to present antigen; massive **lymphoid (T-cell) apoptosis** in nodes, spleen and thymus causes the profound lymphopenia and predisposes to secondary bacterial/fungal infection.
- **Coagulopathy & endothelial dysfunction:** thrombocytopenia, raised tissue factor, consumption of clotting factors, raised D-dimer, falling protein C → features of **DIC**, fibrin deposition and microvascular thrombosis. Hepatocyte necrosis impairs clotting-factor synthesis.
- **Vascular leak:** cytokines, nitric oxide and direct endothelial infection raise vascular permeability → fluid redistribution, interstitial oedema, and **hypovolaemic/septic (distributive) shock**. *Massive external blood loss is actually uncommon* (though severe around childbirth).

Clinical Features & Disease Course

- **Incubation 2–25 days** (Harrison; CMDT 2–21 days), most often 7–10 days.
- Orthoebolavirus and orthomarburgvirus disease are clinically indistinguishable at the bedside.

Phase	Timing	Features
Prodrome (early)	Days 0–5	Abrupt **fever**, chills, severe headache, intense myalgia/arthralgia, asthenia, pharyngitis, cough; maculopapular rash
Peak / GI phase	≈Day 5–7 onward	Profuse **nausea, vomiting, watery diarrhoea**, abdominal pain → large volume/electrolyte loss; hypotension
Multi-organ / shock	Day 7–14	Hypovolaemic & septic **shock**, AKI, respiratory failure, **encephalitis** (confusion, agitation, seizures, coma), myocarditis/pericarditis, uveitis
Haemorrhagic	Late	Subconjunctival/conjunctival injection, petechiae, gingival bleeding, oozing from puncture sites; epistaxis, haematemesis, melena (overt bleeding in only ~1–5%)
Recovery / convalescence	Week 2–3+	Slow clearance of viraemia in survivors; prolonged sequelae

- **Typical laboratory findings:** early **leukopenia** (with left shift) then leukocytosis; **thrombocytopenia** (as low as 50,000/μL); **transaminitis with AST > ALT**, raised γ-GT; rising urea/creatinine with proteinuria; **electrolyte derangement** (hypo-/hyperkalaemia, hyponatraemia, hypocalcaemia); **hypoglycaemia**, hypoalbuminaemia; prolonged **PT/PTT**, raised D-dimer; raised CPK (rhabdomyolysis); markedly raised CRP.
- **Complications & sequelae:** secondary infection, persistent AKI, neuro-cognitive deficit, myocarditis, venous thrombosis; survivors report arthralgia/myalgia, fatigue, alopecia, **uveitis and hearing loss**, memory loss, and **post-EVD depression/anxiety/PTSD**.
- **Viral persistence in immune-privileged sites — semen (up to ~9–12 months)**, CNS (recrudescent meningoencephalitis), eye (uveitis) and placenta — can cause **sexual transmission and the rare re-ignition of outbreaks** from survivors.

Diagnosis & Investigations

- EVD **cannot be diagnosed clinically**; an *exposure history* (bushmeat, bats, caves/mines, sick contacts, rural hospital clusters) plus compatible illness raises suspicion. Notify infectious-disease specialists and public-health authorities **immediately**.
- **Acute-phase blood/serum** is the preferred specimen (high virion titres).
- **Test of choice: reverse-transcription PCR (RT-PCR)** targeting filovirid genes; field-deployable platforms such as the **Cepheid GeneXpert** give rapid, standardised in-field results. RNA peaks ≈day 7. A negative early sample (<3 days) should be repeated if symptoms persist.
- **Antigen-capture ELISA** and rapid antigen tests aid diagnosis (RDT sensitivity currently restricts use largely to post-mortem samples); **IgM/IgG capture ELISA** detect antibody in later disease and survivors.
- Virus isolation/electron microscopy require **maximum-containment (BSL-4)** facilities. Samples are inactivated (guanidinium for PCR, irradiation/heat for ELISA) and handled as extreme biohazards.
- **Key differentials:** *falciparum malaria* and *typhoid fever* (most important), plus enterohaemorrhagic *E. coli*, gram-negative/meningococcal sepsis, leptospirosis, rickettsioses, fulminant viral hepatitis, measles, **Lassa fever and yellow fever**; also snakebite, warfarin poisoning and other causes of coagulopathy.

Treatment & Prevention

- **Supportive care is the backbone:** aggressive IV fluid and **electrolyte repletion**, vasopressors, oxygen/ventilation, renal replacement, correction of hypoglycaemia, antipyretics/antiemetics/antidiarrhoeals, plus **empirical antimalarials and broad-spectrum antibiotics** in endemic settings. Intensive supportive care alone has cut mortality from 25–90% toward <**20%** in well-resourced units.
- **Specific therapeutics — anti-EBOV monoclonal antibodies** (validated by the **PALM randomised controlled trial**, DR Congo 2018–20):
  - **mAb114 — *ansuvimab* (Ebanga)** — single mAb.
  - **REGN-EB3 — *atoltivimab/maftivimab/odesivimab* (Inmazeb)** — triple-mAb cocktail.
  - Both are single IV infusions given as early as possible; the **2022 WHO guideline strongly recommends** either for PCR-confirmed Zaire EVD (including pregnant women, children and neonates ≤7 days of mothers with confirmed EVD), and conditionally **recommends against remdesivir and ZMapp**.
- **Vaccines:**
  - **rVSV-ZEBOV (Ervebo, Merck)** — live, single-dose recombinant vesicular stomatitis virus expressing EBOV GP; protective from ~**10 days**; deployed as **reactive "ring" vaccination** of contacts-of-contacts and for pre-exposure protection of health workers (FDA/EMA approved 2019). *Preferred in outbreaks.*
  - **Ad26.ZEBOV (Zabdeno) + MVA-BN-Filo (Mvabea)** — heterologous **two-dose** prime-boost (~8 weeks apart); suited to peri-outbreak/pre-exposure use, not for rapid outbreak control.

- **Infection prevention & control:** isolation of cases, contact tracing, barrier nursing, **PPE** (gloves, gown, face shield/goggles; N95/N100 and powered respirators for aerosol-generating procedures), single-use equipment, and **safe burials**. Filovirions are enveloped and readily inactivated — **bleach 1:100 for surfaces, 1:10 for excreta/corpses**.
- **Survivor measures:** sexual abstinence or condom use for **≥12 months** (or until semen tests RNA-negative); vaccine/PEP for high-risk exposed health workers (e.g. needlestick).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **EVD disease-course timeline** (Harrison Fig 216-6): x-axis *Days since onset (−10 → +28)*; phases labelled **Incubation, Early phase, Peak phase, Recovery**. Stack the curves/bars — *non-specific prodrome (fever, fatigue, myalgia, headache)*, *GI symptoms*, *rash*, *haemorrhage*, *shock*, *renal/respiratory/neurologic/cardiac dysfunction*, *uveitis*; overlay **viraemia (survivor vs non-survivor)**, **IgM**, **IgG**, and lab trends (↓WBC/↓PLT early, ↑AST/ALT, ↓glucose, ↑BUN/creatinine, coagulopathy ↑PT/PTT/D-dimer).
- **Filovirion structure:** label the **filamentous enveloped particle** with **GP1,2 surface spikes**, lipid envelope, **VP40 matrix**, helical **nucleocapsid (NP, VP35, VP30, VP24, L) wrapping the −ssRNA genome (~19 kb)**.

Clinical / Diagnostic significance

- A **febrile traveller/contact returning from an Ebola-affected country** must be isolated, risk-assessed and tested by RT-PCR while excluding **malaria and typhoid** first — these are commoner and treatable.
- **AST > ALT**, marked thrombocytopenia, rising creatinine/BUN and high viral load are **adverse prognostic markers**; children <5 years, adults >40 years, pregnancy and immunosuppression carry the worst outcomes (maternal mortality ~86% in 2014–16).
- Early **fluid/electrolyte resuscitation plus a monoclonal antibody** is now standard of care and has transformed prognosis; the "70–90% mortality" figure is outdated.
- **Survivor surveillance** (semen testing, ophthalmology for uveitis, audiology, mental-health support) is essential to prevent relapse, sexual transmission and outbreak re-ignition.

High-yield exam pointers

- Family **Filoviridae**; genus *Orthoebolavirus*; **negative-sense ssRNA**, ~19 kb, **7 genes/7 structural proteins**; receptor **NPC1**.
- Four human-pathogenic ebolaviruses — **EBOV (Zaire, most lethal), SUDV, BDBV, TAFV**; **Reston = non-pathogenic** to humans.
- **WHO Risk Group 4 / BSL-4**; highly **infectious, not aerosol-contagious**.
- Reservoir = **fruit bats (proven for Marburg = *Rousettus aegyptiacus*)**; spillover via **bushmeat/primates**.
- **Incubation 2–21 days**; prodrome → GI loss → shock/MODS; **overt haemorrhage in only ~1–5%**.
- **Diagnosis = RT-PCR** (GeneXpert) on acute serum; AST > ALT, thrombocytopenia, leukopenia.
- **Treatment = supportive care + mAb (Inmazeb / Ebanga)** validated by the **PALM trial**; remdesivir/ZMapp not recommended.

- **Vaccine = rVSV-ZEBOV (Ervebo)**, single-dose, ring vaccination; Zabdeno+Mvabea = 2-dose pre-exposure.
- **Persistence in semen (~12 months), CNS, eye, placenta** → late sexual transmission and outbreak re-ignition.
- IPC: isolation, contact tracing, PPE, safe burials, **bleach 1:10 for corpses/excreta**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Filovirids: Orthoebolavirus and Orthomarburgvirus Infections" (etiology, virology, epidemiology, pathogenesis, clinical course, diagnosis, PALM-trial therapeutics, vaccines, control).
- **CMDT 2026** — "Viral & Rickettsial Infections: Viral Haemorrhagic Fevers — Ebola Viral Disease" (current case definition, clinical findings, WHO 2022 treatment guideline, Inmazeb/Ebanga, Ervebo and Zabdeno-Mvabea vaccines, prognosis, when-to-admit).

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Extensively drug-resistant tuberculosis

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Extensively drug-resistant TB (XDR-TB) is disease caused by *Mycobacterium tuberculosis* in which **MDR-TB is compounded by additional resistance to any fluoroquinolone AND to at least one additional Group A drug** (i.e., **bedaquiline and/or linezolid**). It sits at the apex of a graded spectrum of drug-resistant TB built on **multidrug-resistant TB (MDR-TB)** — bacilli resistant *at least to isoniazid and rifampin*, the two most potent first-line bactericidal agents. XDR-TB represents the most difficult-to-treat, costly and lethal form of TB, demanding all-oral, individualized, drug-susceptibility-testing (DST)–guided regimens delivered in specialized centres.

Spectrum & Definitions of Drug-Resistant TB

- Resistance is graded by the *number and class* of drugs lost; the updated (post-2021) hierarchy reflected in Harrison is summarised below.

Category	Resistance pattern (per Harrison 22e)
Mono-resistant TB	Resistance to a single first-line drug (e.g., isoniazid-resistant, rifampin-susceptible)
RR-TB (rifampin-resistant)	Resistance to rifampin (with/without other drugs); monoresistance to R is rare and treated as MDR
MDR-TB	Resistance **at least to isoniazid + rifampin**
Pre-XDR-TB	MDR/RR-TB strain **also resistant to any fluoroquinolone**
XDR-TB	MDR/RR-TB + **fluoroquinolone resistance + resistance to ≥1 additional Group A drug** (bedaquiline and/or linezolid)

- **Primary resistance** = patient infected from the outset by a resistant strain; **acquired resistance** = develops in the infecting strain during inadequate treatment.

- Drug-resistant TB "almost invariably follows **monotherapy**" — failure to prescribe ≥2 effective drugs, poor adherence, malabsorption, or poor-quality drugs.

Molecular Basis & Mechanism of Resistance

- Resistance arises by **spontaneous chromosomal point mutations** occurring at low, predictable rates (10^{-7}–10^{-10} per drug). There is *no plasmid-mediated* resistance and *no cross-resistance* between unrelated classes, so multi-class resistance is the *product* of individual probabilities — and is therefore generated almost solely by drug pressure on poorly-treated patients.

Drug	Key resistance gene(s) (frequency)
Rifampin	***rpoB*** (95%)
Isoniazid	***katG*** (50–95%); ***inhA*** promoter (up to 45%)
Pyrazinamide	***pncA*** (up to 98%)
Ethambutol	***embB*** (50–65%)
Fluoroquinolones	***gyrA–gyrB*** (75–95%) — target DNA gyrase/topoisomerase IV
Aminoglycosides	***rrs*** (up to 80%); *eis* promoter **C-12T** mutation
Bedaquiline	***atpE*** (ATP synthase subunit c); ***Rv0678/mmpR***, ***pepQ*** (efflux — cross-resistance to clofazimine)
Linezolid	**23S rRNA**; ribosomal proteins **L3** (***rplC***), **L4** (***rplD***)

Epidemiology & Global Burden

- Of ~10.8 million incident TB cases in 2023, an estimated **400,000 MDR/RR-TB** cases occurred; only **189,000** were enrolled on treatment owing to limited DST capacity.
- **>50% of all MDR/RR-TB occurs in: India (27%), Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%)**; the former Soviet states have the highest *proportion* of MDR among new cases (up to one-third).
- *The vast majority of XDR-TB cases remain undiagnosed* because reliable DST methods and laboratory capacity are lacking in low-income settings.

Diagnosis & Drug-Susceptibility Testing

- **Culture remains the gold standard** (liquid **MGIT** faster than solid Löwenstein-Jensen).
- **Rapid molecular DST is mandatory before regimen design**: nucleic-acid amplification **Xpert MTB/RIF / Ultra** detects *M. tuberculosis* + **rifampin resistance** (proxy for MDR); **line-probe assays (LPAs)** extend to isoniazid, fluoroquinolone and second-line resistance.
- For any RR/MDR diagnosis, **DST for fluoroquinolones and (where possible) bedaquiline/linezolid is essential** — these define the pre-XDR/XDR transition and dictate whether moxifloxacin can be retained.
- Continued **monthly bacteriologic (culture) monitoring** detects failure (persistent positivity or reversion after conversion) and emerging amplification of resistance.

WHO Classification of Anti-TB Drugs (for longer regimens)

- For complex MDR/XDR regimens, second-line drugs are ranked into three groups; regimens use **all three Group A drugs + ≥1 Group B**, adding Group C only to complete an effective combination.

Group	Drugs	Rule
A (use all three)	**Levofloxacin/moxifloxacin · Bedaquiline · Linezolid**	Ensures ≥4 likely-effective agents; ≥3 continue if bedaquiline stopped
B (add ≥1)	**Clofazimine · Cycloserine / terizidone**	At least one always included
C (complete regimen)	**Delamanid · Pyrazinamide · Ethambutol · Imipenem-cilastatin/meropenem · Amikacin (or streptomycin) · Ethionamide/prothionamide · p-Aminosalicylic acid**	Used when A/B cannot be

- **Kanamycin and capreomycin are NO LONGER used** (higher failure/relapse, toxicity); the injectables amikacin/streptomycin are reserved (≥18 yr, proven susceptibility, with audiometry).

Treatment of XDR-TB & Highly-Resistant Disease

- **Principle:** select agents *likely to be effective and tolerated*, build from the Group A/B/C hierarchy, give **all-oral**, fully-supervised therapy. **Levofloxacin/moxifloxacin, bedaquiline and linezolid should always be included** in longer regimens where active.
- **Pre-XDR-TB / MDR-RR (FQ retained or excluded):** the preferred regimen is the **6-month all-oral BPaLM — Bedaquiline + Pretomanid + Linezolid 600 mg + Moxifloxacin** (success rates ~90%). In **documented fluoroquinolone resistance, drop moxifloxacin → BPaL**. *(Excluded: pregnancy/breastfeeding, disseminated, CNS and osteoarticular TB, and prior >1-month exposure to these drugs.)*
- **XDR-TB:** because there is FQ + Group A drug resistance, the patient often does **not qualify for the standardized short regimens**; XDR-TB "follows the same principles" as a **longer (≥18–20-month) individualized regimen** (continued **15–17 months after culture conversion**, ~6–7-month intensive phase), assembled from remaining effective Group A/B/C agents per DST.
- **Adjuncts:** aggressive management with early DST, strict DOT, monthly bacteriology and intensive patient support; **surgical resection (lobectomy/wedge)** for localized disease with adequate pulmonary reserve.
- **Key drug profile (the agents that define XDR):**

Drug	Class / mechanism	Dose	Major toxicity
Bedaquiline	Diarylquinoline — inhibits mycobacterial **ATP synthase** proton pump	400 mg/d × 2 wk, then 200 mg thrice-weekly	**QT prolongation** (black-box), hepatotoxicity, ↑ mortality signal; CYP3A4-metabolised
Linezolid	Oxazolidinone — binds **50S ribosome** (protein synthesis)	600 mg once daily	**Myelosuppression/pancytopenia**, optic & peripheral neuropathy, lactic acidosis, serotonin syndrome (weak MAOI)

Drug	Class / mechanism	Dose	Major toxicity
Pretomanid	Nitroimidazole prodrug (PA-824) — inhibits **mycolic acid** synthesis	200 mg daily	Hepatotoxicity
Moxifloxacin/ levofloxacin	Fluoroquinolone — inhibits **DNA gyrase**	Standard	QT prolongation, GI/CNS
Clofazimine (Gp B)	Riminophenazine — reactive oxidants/membrane	—	Orange-brown skin discoloration, QT
Delamanid (Gp C)	Nitroimidazole — mycolic acid synthesis	100 mg twice daily	QT prolongation

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pyramid/ladder of drug-resistant TB** (base → apex): *Drug-susceptible TB → Isoniazid mono-resistant → RR-TB → MDR-TB (H+R) → Pre-XDR-TB (+ fluoroquinolone) → XDR-TB (+ Group A drug: bedaquiline/linezolid)*. Label each tier with the defining resistance.
- **Box diagram of WHO Group A/B/C drugs** with three labelled boxes: **Group A** — Levofloxacin/Moxifloxacin, Bedaquiline, Linezolid; **Group B** — Clofazimine, Cycloserine/Terizidone; **Group C** — Delamanid, Pyrazinamide, Ethambutol, Carbapenem+clavulanate, Amikacin, Ethionamide/Prothionamide, PAS.

Clinical / Diagnostic significance

- **Suspect resistance** in: previously treated TB, contacts of resistant cases, patients from high-MDR regions (≥5% incident MDR), and **failure of sputum-culture conversion at 2 months** — retest immediately and switch regimen.
- **DST drives everything:** FQ and bedaquiline/linezolid susceptibility distinguish pre-XDR from XDR and decide whether BPaLM, a shorter, or a longer regimen is used.
- **Cardiac safety:** multiple regimen drugs (**bedaquiline, delamanid, clofazimine, fluoroquinolones**) prolong QT — perform **baseline + serial ECG**; *withhold if QTc >500 ms or history of ventricular arrhythmia*. Audiometry if amikacin used; haematology/visual monitoring on linezolid.
- **Active TB drug-safety monitoring (aDSM)**, informed consent, and HIV co-management (avoid efavirenz with bedaquiline; prefer dolutegravir-based ART) are integral.
- **Public-health imperative:** prompt diagnosis + effective regimen interrupts transmission of these strains and prevents *further* amplification of resistance.

High-yield exam pointers

- **XDR-TB = MDR + fluoroquinolone resistance + resistance to ≥1 Group A drug (bedaquiline/linezolid). Pre-XDR = MDR + FQ resistance.**
- **MDR = resistant at least to isoniazid + rifampin.** Monoresistant rifampin (RR) is managed as MDR.

- Resistance is by **spontaneous point mutation**; remember **rpoB (R), katG/inhA (H), pncA (Z), embB (E), gyrA/gyrB (FQ), rrs (aminoglycoside), atpE/Rv0678 (bedaquiline), 23S rRNA/rplC/rplD (linezolid)**.
- **Group A (always all three): fluoroquinolone, bedaquiline, linezolid.** Group B: clofazimine, cycloserine/terizidone.
- **BPaLM** = Bedaquiline + Pretomanid + Linezolid 600 mg + Moxifloxacin, 6 months, ~90% success — drop moxifloxacin (→ **BPaL**) if FQ-resistant.
- **Kanamycin and capreomycin are abandoned**; regimens are now **all-oral**.
- **Bedaquiline** inhibits **ATP synthase**, carries a **black-box QT/mortality warning**; **linezolid** causes **myelosuppression + neuropathy**.
- XDR/complex disease → **individualized longer regimen ≥18–20 months**, 15–17 months after culture conversion, with DOT, monthly cultures, aDSM ± surgery.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 183 "Tuberculosis"** (XDR/pre-XDR definitions, epidemiology, resistance genetics, WHO Group A/B/C Table 183-3, MDR/RR & BPaLM regimens) and **Ch 186 "Antimycobacterial Agents"** (BPaLM/BPaL trials, drug mechanisms, doses and toxicities). *Coverage note:* Harrison reflects the post-2021 WHO **revised XDR-TB definition** and does not give a single named "XDR-TB regimen" — XDR-TB is managed under the **longer individualized ≥18–20-month** regimen built from Group A/B/C drugs (Table 183-3), with the short BPaLM/BPaL regimens primarily validated for MDR/RR and pre-XDR disease. Fluoroquinolone mechanism (DNA gyrase) is standard textbook pharmacology consistent with the *gyrA/gyrB* resistance data in the chapter.

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Extrapulmonary tuberculosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Extrapulmonary tuberculosis (EPTB) is *Mycobacterium tuberculosis* infection of any organ system other than the lung parenchyma, resulting from lymphohaematogenous dissemination from a primary or post-primary focus, contiguous spread, or (for gut TB) ingestion. It accounts for **10–40%** of all TB cases depending on host immune status and bacterial strain; among people living with HIV (PLWH) up to **two-thirds** have extrapulmonary or combined disease. In descending order of frequency the sites involved are **lymph nodes > pleura > genitourinary tract > bones and joints > meninges > peritoneum > pericardium**, though virtually any organ may be affected. Most forms are **paucibacillary and essentially non-infectious**, making them diagnostically challenging and demanding tissue/fluid sampling for confirmation.

Pathogenesis and general features

- Tubercle bacilli disseminate via **lymphatics and the bloodstream** during the early bacillaemic phase of primary infection; dormant foci later reactivate when cell-mediated immunity (CMI)

wanes (HIV, diabetes, anti-TNF-α therapy, chronic kidney disease, malnutrition, immunosuppression).

- EPTB is **more common in settings of high HIV prevalence** because failure of CMI permits widespread haematogenous seeding.
- Because lesions are paucibacillary, **smear and culture yields are lower** than in cavitary pulmonary disease, and **histology (caseating granuloma)** plus **nucleic-acid amplification** are pivotal.
- Constitutional ("B") symptoms — low-grade fever, night sweats, anorexia, weight loss — are common but may be absent except in HIV co-infection.

Organ-specific clinical syndromes

Site (approx. share of EPTB)	Key clinical features	Best diagnostic approach
Lymph node (≈35%; >40% in US series)	Painless posterior-cervical/supraclavicular swelling = *scrofula*; discrete nodes → matted mass → cold abscess/sinus draining caseum; systemic symptoms uncommon unless HIV	**FNAC** (yield up to 80%) or excision biopsy; granuloma ± AFB; culture positive in 70–80%; Xpert MTB/RIF on node biopsy near-100% (Ultra)
Pleura (≈20%)	Effusion from hypersensitivity to mycobacterial antigens (recent primary) or contiguous spread; fever, pleuritic pain, dyspnoea	Exudate, protein >50% of serum (≈4–6 g/dL), glucose normal–low, pH ≈7.3, WBC 500–6000/μL **lymphocytic**, rare mesothelial cells; **ADA elevated** (CMDT: >70 U/L ≈90% sens/spec); **pleural biopsy** granuloma/culture ≈80%; *pleural fluid Xpert NOT recommended (low sensitivity)*
Genitourinary (≈10–15%)	Cryptic/protean; dysuria, frequency, nocturia, haematuria, flank pain; female — tubes/endometrium → infertility; male — epididymis → tender mass/fistula	**Sterile (culture-negative) pyuria in acidic urine**; 3 early-morning urine cultures positive in ≈90%; IVP/CT/MRI: calcification, ureteric stricture, hydronephrosis
Skeletal (≈10%)	Spine 40%, hip 13%, knee 10%; **Pott's disease** = spondylitis of ≥2 adjacent vertebral bodies → disc involvement, **kyphosis (gibbus)**, paravertebral **"cold" abscess** (psoas)	CT/MRI; aspiration/bone biopsy (culture usually positive); synovial fluid/biopsy for peripheral joints
CNS — meningitis & tuberculoma (≈5%)	Subacute basal meningitis; weeks of fever/malaise → headache, cranial-nerve (esp. ocular) palsies, vasculitic infarcts, hydrocephalus, coma; tuberculoma → seizures/focal signs	CSF: **lymphocytic** pleocytosis (≤1000/μL), **high protein 1–8 g/L, low glucose**; **Xpert/Ultra preferred initial test (~80%)**; culture gold standard (≈80%); MRI: basal enhancement, hydrocephalus; tuberculoma = ring-enhancing lesion
Gastrointestinal (≈3.5%)	**Ileocaecum** most affected; pain, obstruction, mass, hematochezia; **mimics Crohn disease**; anal fistula → suspect rectal TB	Histology + culture of intraoperative/endoscopic specimens

Site (approx. share of EPTB)	Key clinical features	Best diagnostic approach
Peritoneal	Nonspecific pain, fever, **ascites**; coexisting cirrhosis confounds	Exudative, high-protein, lymphocytic fluid; smear/culture low-yield; **laparoscopic peritoneal biopsy** often required
Pericardial	Subacute or acute with friction rub; effusion → **tamponade**; case-fatality up to 40%	Exudative, lymphocytic, often **haemorrhagic** fluid; smear rarely positive; culture ≈⅔; high **ADA/lysozyme/IFN-γ**; risk of **constrictive pericarditis**

Miliary (disseminated) TB

- Due to **massive haematogenous spread**; primary infection in children, recent infection or reactivation in adults.
- Lesions are **yellowish 1–2 mm granulomas resembling millet seeds** (hence "miliary").
- Protean presentation: fever, night sweats, weight loss, weakness; **hepatosplenomegaly and lymphadenopathy**.
- **Choroidal tubercles are pathognomonic** (fundoscopy positive in up to 30%); meningismus in <10%.
- CXR: **miliary reticulonodular pattern** (early film may be normal, especially in PLWH).
- Haematology: anaemia, leukopenia/lymphopenia, leukaemoid reactions, occasionally pancytopenia or DIC; deranged LFTs with hepatic involvement.
- **TST negative in up to half** of cases (anergy); bronchoalveolar lavage, transbronchial / liver / bone-marrow biopsy give bacteriologic/granulomatous confirmation.
- Variants: **cryptic miliary TB** (elderly, chronic intermittent fever) and **non-reactive (septicaemic) miliary TB** (overwhelming, pancytopenic, rapidly fatal, nongranulomatous lesions).
- **Glucocorticoids have not proved beneficial** in miliary TB; untreated it is lethal but curable with timely therapy.

Diagnostic principles in EPTB

- **High index of suspicion** is the single most important factor — invasive sampling of the involved site is the rule.
- **Tissue/fluid > cytology:** caseating granuloma on histology, AFB smear, mycobacterial culture (MGIT liquid culture positive in 10 days–3 weeks; Löwenstein-Jensen 4–8 weeks), and **drug-susceptibility testing**.
- **Nucleic-acid amplification (Xpert MTB/RIF / Ultra)** is the preferred initial test on **CSF** and a recommended replacement test for selected non-respiratory specimens (FNA, pleural/other biopsy, gastric lavage); it also detects **rifampicin resistance**. Sensitivity varies by specimen — **lowest in pleural fluid (50%; 71% with Ultra), highest in synovial fluid (97%) and lymph-node biopsy (100% with Ultra)**.
- **Biomarkers:** elevated **adenosine deaminase (ADA)**, lysozyme and IFN-γ support TB in pleural, pericardial and peritoneal fluid.

- **Urine LF-LAM (lipoarabinomannan)** assay aids diagnosis in advanced HIV (CD4 ≤200/μL inpatients, <100/μL outpatients).
- **Imaging:** CT for intra-abdominal disease and Pott's spine; **MRI** for bone and intracranial TB.

Treatment

- **Most forms of EPTB are treated with the standard 6-month regimen** used for pulmonary TB: **2 months HRZE (intensive) + 4 months HR (continuation) = 2HRZE/4HR**, daily throughout.
- Standard adult doses: **Isoniazid 5 mg/kg (max 300 mg), Rifampin 10 mg/kg (max 600 mg), Pyrazinamide 25 mg/kg (max 2 g), Ethambutol 15 mg/kg**.
- **TB meningitis:** ATS/CDC/IDSA recommend **extending the continuation phase to 7–10 months** (i.e. ≈9–12 months total). **Children with bone/joint TB, TB meningitis or miliary TB should receive up to 12 months** (2-month induction + 10-month consolidation).
- **Adjunctive glucocorticoids** improve survival/reduce disability in **TB meningitis** (dexamethasone or prednisolone tapered over 6–8 weeks, per WHO) and **may be used** in tuberculous pericarditis (note: the IMPI trial showed no overall benefit; ATS/CDC/IDSA do not advise routine use). Steroids are **not beneficial** in miliary or pleural TB.
- **Surgery** is adjunctive — drainage of large cold/psoas abscesses (paraparesis from spinal cord compression is an emergency), decortication for tuberculous empyema, relief of ureteric stricture/hydronephrosis, pericardiectomy for constriction, and resection in bowel obstruction/perforation.
- **HIV co-infection:** start ART early (within 2 weeks) — **but delay ART for 8 weeks in CNS TB** because of IRIS risk; use rifampicin-compatible ART (e.g. double-dose dolutegravir, or efavirenz; rifabutin as alternative).

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Descending-frequency chart of EPTB sites** — horizontal bars labelled: *Lymph node ≈35%*, *Pleura ≈20%*, *Genitourinary ≈10–15%*, *Bone/joint ≈10%*, *Meninges ≈5%*, *Gastrointestinal ≈3.5%*, *Peritoneum*, *Pericardium*.
> - **Pott's disease (spinal TB) schematic** — label: *two adjacent vertebral bodies*, *destroyed intervertebral disc*, *anterior vertebral wedging/collapse*, *kyphotic angulation = gibbus*, *paravertebral "cold" abscess tracking to psoas/groin*, *spinal cord compression → paraplegia*.

Clinical / Diagnostic significance

- **Culture-negative sterile pyuria in acidic urine** is a classic clue to renal TB; *3 morning urine cultures* clinch it.
- **Pleural fluid ADA / lymphocytic exudate** with **pleural biopsy** (not fluid Xpert) is the practical pathway to pleural TB; *choroidal tubercles* confirm miliary disease at the bedside.
- **Pott's disease** spares the disc early (unlike pyogenic osteomyelitis, which destroys the disc rapidly with sclerosis) — a key differentiating radiological point; paraparesis from a compressing abscess is a **medical emergency**.

- **Tuberculous meningitis** is uniformly fatal if untreated and leaves neurological sequelae in ≈25% even when treated — early empirical therapy on a positive Xpert plus dexamethasone is mandatory.
- **Ileocaecal TB vs Crohn disease** is a recurring diagnostic dilemma; tissue for AFB/culture/granuloma and therapeutic response are decisive.
- EPTB diagnosis frequently mandates **invasive sampling** — FNAC/excision biopsy (node), needle pleural biopsy, D&C (endometrium), laparoscopy (peritoneum), pericardiocentesis/biopsy.

High-yield exam pointers

- EPTB = 10–40% of TB; **lymph node** is the commonest form (scrofula = cervical/supraclavicular nodes).
- **Pleural fluid:** lymphocytic exudate, **ADA >70 U/L** (≈90% sens/spec); **do NOT Xpert the fluid** — biopsy the pleura.
- **Renal TB:** sterile pyuria in acid urine; 3 morning urine cultures ≈90% positive.
- **Pott's spine:** ≥2 adjacent vertebrae, disc spared early, **gibbus**, **psoas cold abscess**, paraplegia.
- **TB meningitis:** basal, cranial-nerve palsies, lymphocytic CSF (high protein, low glucose); **Xpert preferred**, culture gold standard; **add steroids**; extend therapy to 9–12 months.
- **Miliary TB:** millet-seed granulomas, **choroidal tubercles pathognomonic**, TST often negative; steroids not helpful.
- **Pericardial TB:** haemorrhagic lymphocytic effusion, high ADA, risk of constriction; tamponade is the acute danger.
- Standard treatment = **2HRZE/4HR** for most EPTB; **CNS/skeletal/miliary in children → up to 12 months**.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Tuberculosis" (extrapulmonary forms, diagnosis, regimens, drug doses, special clinical situations).
- CMDT 2026 — "Pulmonary Disorders: Tuberculosis" (pleural fluid ADA, NAAT/Xpert diagnostics, imaging).

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Gastrointestinal tuberculosis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Gastrointestinal (GI) tuberculosis (TB) is infection of the gut lumen, peritoneum, mesenteric lymph nodes and solid abdominal viscera by *Mycobacterium tuberculosis* (and, where bovine disease persists, *M. bovis*). It is the sixth commonest form of extrapulmonary TB and accounts for only ~3.5% of extrapulmonary cases in low-burden settings, but is common in India and other high-burden regions. The **terminal ileum and caecum** are the sites most often involved. Because it mimics Crohn disease, ileocaecal carcinoma, lymphoma and amoebiasis, it is a notorious "great imitator" requiring a high index of suspicion.

Epidemiology & Pathogenesis

- **Burden** — uncommon in the United States/Europe (mainly immigrants and patients with untreated AIDS); common in underdeveloped/high-prevalence countries including India.
- **Routes of seeding** (any may operate concurrently):
  - **Swallowing of infected sputum** with direct mucosal seeding (in active pulmonary TB).
  - **Haematogenous spread** from a pulmonary or miliary focus (explains peritoneal and solid-organ disease).
  - **Ingestion of milk** from cows with bovine TB (*M. bovis*) — relevant where pasteurisation is incomplete.
  - **Direct/contiguous spread** and **retrograde lymphatic spread** from ruptured mesenteric nodes and adjacent intra-abdominal organs (e.g., genital TB in women causing peritonitis).
- **Association with pulmonary TB** — coexistent **active pulmonary disease is present in <50%** of patients, so a normal chest radiograph does *not* exclude abdominal TB.
- **Ileocaecal predilection** is attributed to abundant lymphoid (Peyer patch) tissue, physiological stasis and increased contact time of bacilli with the mucosa at this site.

Pathology & morphological types

- The basic lesion is the **caseating epithelioid-cell granuloma**; in the gut these are characteristically **large, confluent, submucosal and few in number**, with surrounding lymphoid cuffs.
- Three classical macroscopic forms (standard surgical/pathological classification):
  - **Ulcerative** — multiple superficial, **transversely orientated ("girdle") ulcers** of the antimesenteric border; the predominant pattern in florid disease and a cause of bleeding/perforation.
  - **Hypertrophic** — marked fibroblastic reaction with a thickened, mass-like bowel wall (especially ileocaecal), mimicking carcinoma and producing a palpable mass.
  - **Ulcero-hypertrophic (stricturing)** — mixed pattern with ulceration plus fibrosis causing **strictures and obstruction**.
- Healing by fibrosis produces **short, concentric strictures**, a contracted caecum and a **patulous/incompetent ileocaecal valve**.

Clinical patterns & features

GI TB presents in four overlapping clinico-anatomical forms — luminal (intestinal), peritoneal, nodal and visceral.

- **Intestinal (luminal) TB** (commonest; ileocaecal):
  - Chronic **abdominal pain** (right iliac fossa pain at times mimicking appendicitis), **subacute/recurrent intestinal obstruction**, abdominal distension.
  - **Weight loss, low-grade fever, anorexia, night sweats**, diarrhoea or altered bowel habit.
  - A **palpable doughy mass** in the right iliac fossa (hypertrophic disease).
  - **Hematochezia/GI bleeding**, fistulae and, less often, free perforation.
  - With wall involvement, ulcers and fistulae **simulate Crohn disease** — the differential is "always difficult"; **anal fistulae should prompt evaluation for rectal TB**.
- **Tuberculous peritonitis** — follows rupture of caseous mesenteric nodes / spread from intra-abdominal organs (e.g., female genital TB) or haematogenous seeding. Three subtypes are recognised: **wet (ascitic)**, **dry/plastic (fibroadhesive)**, and **encysted (loculated)**. The classic triad is **nonspecific abdominal pain, fever and ascites**; "doughy abdomen" is described in the plastic form.
- **Nodal TB** — mesenteric/peripancreatic lymphadenopathy, often with central (caseous) necrosis on CT.
- **Visceral TB** — hepatic, splenic, pancreatic and peritoneal-fold involvement (uncommon).
- *Caveat:* coexisting **cirrhosis** greatly complicates recognition of tuberculous peritonitis, as both cause ascites.

Investigations / Diagnosis

- **Ascitic fluid (paracentesis) in peritonitis** — **exudative** fluid with **high protein**, **lymphocyte-predominant** leucocytosis (neutrophils occasionally early), and a **low serum–ascites albumin gradient (SAAG <1.1 g/dL)**. Direct smear and culture have **low yield**; culturing a large volume improves it. Elevated **adenosine deaminase (ADA)** supports the diagnosis (a value >~39 U/L is the commonly cited threshold).
- **Imaging** — **abdominal CT** shows thickening of the **caecum and ileocaecal valve**, mural thickening, **necrotic ("caseous") mesenteric lymphadenopathy**, omental/peritoneal thickening and ascites; CT is also useful for other intra-abdominal/Pott disease.
- **Colonoscopy/ileoscopy with biopsy** — ulcerated mass, **ulcers with steep/undermined edges, transversely oriented ulcers, sessile inflammatory polyps, deformed patulous ileocaecal valve**, strictures, or pseudodiverticula, most often in the ileocaecal region; multiple deep biopsies from ulcer edges raise yield.
- **Histology/microbiology of biopsy or operative specimen** — diagnosis is confirmed by **caseating granuloma**, **acid-fast bacilli (AFB)** and/or **positive culture**. **PCR / nucleic-acid amplification on tissue is now the most sensitive means of diagnosis.**
- **Molecular tests** — **Xpert MTB/RIF** and **Xpert MTB/RIF Ultra** are the preferred initial tests on nonrespiratory specimens (FNA, biopsy, fluid); they confirm TB and detect **rifampin resistance** in <2 h.

- **Peritoneal biopsy (best obtained at laparoscopy)** is often required when fluid studies are nondiagnostic; laparoscopy permits direct visualisation and biopsy of peritoneum, liver and nodes.
- **Tuberculin skin test (PPD)** may be **negative**, especially with weight loss or AIDS, so a negative test does not exclude disease. Because surgery is needed in many obstructive/complicated cases, diagnosis is frequently established on **intra-operative histology and culture**.

Intestinal TB vs Crohn disease

Feature	Intestinal tuberculosis	Crohn disease
Ulcers	**Transverse / circumferential ("girdle")**	**Longitudinal, aphthous; cobblestoning**
Distribution	Short segment, ileocaecal; **patulous IC valve**	Skip lesions; long segment; perianal disease
Granuloma	**Caseating, large, confluent, submucosal, few**	Non-caseating, small, discrete, numerous
AFB / culture / TB-PCR	May be positive	Negative
Strictures/fistulae	Short concentric strictures	Long strictures, multiple fistulae
Response to ATT	Mucosal healing on anti-TB therapy	No response to ATT

Note: misdiagnosing TB as Crohn (and giving steroids/anti-TNF) can cause fulminant dissemination — hence a **diagnostic anti-TB trial** is used when distinction is impossible.

Treatment / Management

- **First-line chemotherapy** is the same as for pulmonary TB: **2 months HRZE → 4 months HR (2HRZE/4HR)**; this cures >90% of drug-susceptible cases. Many authorities extend the continuation phase to give a **total of 6–9 months** for extensive abdominal disease, but the corpus-supported standard is the **6-month regimen**.
- **Standard adult daily doses** (Harrison Table 183-2):
  - **Isoniazid (H)** 5 mg/kg, max 300 mg
  - **Rifampin (R)** 10 mg/kg, max 600 mg
  - **Pyrazinamide (Z)** 25 mg/kg, max 2 g
  - **Ethambutol (E)** 15 mg/kg
  - (paediatric doses are higher per kg, e.g., H 10 mg/kg).
- **Drug-resistant disease** — if rifampin resistance is detected (e.g., on Xpert), manage as MDR-TB with WHO Group A–C agents (bedaquiline, levofloxacin/moxifloxacin, linezolid, clofazimine, cycloserine, etc.).
- **Surgery** is reserved for complications — **obstruction unrelieved by medical therapy, perforation, massive haemorrhage, fistula or abscess**; stricturoplasty/limited resection is preferred over extensive resection. Anti-TB therapy must continue post-operatively.
- **Supportive care** — nutritional rehabilitation, correction of anaemia, and monitoring for **hepatotoxicity** (H/R/Z) and **ethambutol ocular toxicity**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled ileocaecal TB diagram:** terminal ileum, **thickened/contracted caecum**, **incompetent (patulous) ileocaecal valve**, **transverse "girdle" ulcers**, short fibrotic **stricture**, enlarged **caseous mesenteric lymph nodes**, and a hypertrophic ileocaecal mass.
- **Diagnostic algorithm box:** Suspected abdominal TB → CT abdomen + colonoscopy/ascitic tap → biopsy/fluid for **histology (caseating granuloma), AFB, culture, Xpert MTB/RIF, TB-PCR** → if nondiagnostic → **laparoscopy + peritoneal biopsy** → start **2HRZE/4HR**.

Clinical / Diagnostic significance

- **Right-iliac-fossa mass + constitutional symptoms** in an endemic-area patient should trigger work-up for ileocaecal TB before labelling it appendicular mass or carcinoma.
- **Low-SAAG, high-protein, lymphocytic ascites with raised ADA** strongly suggests tuberculous peritonitis; laparoscopy is the most reliable confirmatory step.
- The **TB-vs-Crohn dilemma** has major therapeutic consequences — immunosuppression of misdiagnosed TB is dangerous; TB-PCR on biopsy and a therapeutic ATT trial resolve most cases.
- A **negative PPD and normal chest film do not exclude** the diagnosis (active pulmonary disease in <50%).

High-yield exam pointers

- Commonest GI site = **terminal ileum + caecum**; commonest extra-luminal form = **tuberculous peritonitis**.
- Three pathological types = **ulcerative, hypertrophic, ulcero-hypertrophic**; ulcers are **transverse**, valve becomes **patulous**.
- TB granuloma = **caseating, large, confluent, submucosal, few**; Crohn = **non-caseating, small, many**.
- **Xpert MTB/RIF/Ultra** = preferred rapid test (also gives rifampin resistance); **tissue TB-PCR = most sensitive**.
- Ascites: **exudate, high protein, lymphocytic, SAAG <1.1, raised ADA**; low smear/culture yield → **laparoscopic peritoneal biopsy**.
- Treatment = **2HRZE/4HR**, cures >90%; doses H 5 / R 10 / Z 25 mg/kg, E 15 mg/kg.
- Surgery only for **obstruction, perforation, bleeding, fistula** — continue ATT after.
- **Anal fistula → think rectal TB**; **bovine TB (M. bovis) via unpasteurised milk** is a recognised route.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Tuberculosis" (extrapulmonary section: *Gastrointestinal TB* and *Tuberculous peritonitis*; diagnosis — nucleic-acid amplification/Xpert MTB/RIF; Table 183-2 drug dosages; Table 183-4 regimens 2HRZE/4HR).
- **CMDT 2026** — "Gastrointestinal Disorders" (*Intestinal Tuberculosis*: ileocaecal predilection, CT/colonoscopy findings, PPD, biopsy/PCR diagnosis) and the ascites/SAAG and laparoscopy discussion for tuberculous peritonitis.
- *Coverage note:* The cited corpus (Harrison 22e + CMDT 2026) covers epidemiology, pathogenesis, ileocaecal disease, peritonitis, diagnostics and therapy directly. The three **morphological types** (ulcerative/hypertrophic/ulcero-hypertrophic), the wet/dry/encysted peritonitis subtypes, the detailed **TB-vs-Crohn histology/ulcer comparison**, and the **ADA cut-off (~39 U/L)** are presented as universally accepted standard textbook internal medicine/surgical pathology, used to organise (not contradict) the corpus, which states only that intestinal TB "may simulate Crohn disease" and that ADA elevation supports a tuberculous aetiology.

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Genital ulcerations due to infections

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Genital ulcer disease (GUD) is a syndrome of one or more breaks in the skin or mucosa of the genitalia, perineum or anus, most often sexually transmitted. It is clinically important because the same ulcers sharply **increase the risk of sexual acquisition and shedding of HIV**, and because the cause cannot be reliably named on inspection alone—syndromic, test-supported management is therefore standard. Five classic infectious causes dominate: **genital herpes (HSV), primary syphilis, chancroid, lymphogranuloma venereum (LGV) and donovanosis (granuloma inguinale)**; today *genital herpes is by far the commonest cause worldwide*.

Aetiology and epidemiology

- **The five major infectious causes**: HSV-1/HSV-2 (genital herpes); *Treponema pallidum* (primary syphilis – the chancre); *Haemophilus ducreyi* (chancroid/soft sore); *Chlamydia trachomatis* serovars L1–L3 (LGV); *Klebsiella granulomatis* (donovanosis / granuloma inguinale).
- **Relative frequency**: In a 1996 study of genital ulcers in 10 U.S. cities with the highest rates of primary syphilis, PCR detected **HSV in 62%, *T. pallidum* in 13%, and *H. ducreyi* in 12–20%**. With PCR testing, genital herpes is now the **single commonest cause** of genital ulceration in both industrialised and most developing countries.
- In Asia and Africa, **chancroid** was once the commonest ulcer, followed by primary syphilis then herpes; control programmes, broad-spectrum antibiotic use and HIV-driven persistence of herpes have shifted the balance toward HSV.

- **LGV** had nearly disappeared from industrialised nations but is re-emerging as outbreaks of **proctitis in MSM**, frequently with concurrent **HIV and/or hepatitis C** infection.
- **Donovanosis** and LGV remain endemic causes of ulceration in some developing countries.

Clinical features — the five classic ulcers

- **Genital herpes (HSV)** — short incubation (2–7 days); a *vesicle* progresses to multiple small (1–2 mm), shallow, *painful/tender* ulcers on an erythematous base; tender, often bilateral inguinal nodes with the first episode; recurrences are common (more so with HSV-2). "Atypical" or trivial ulcers may be commoner than classic vesiculopustular lesions.
- **Primary syphilis (chancre)** — incubation 9–90 days (average ~2–6 weeks, rarely >6 weeks). A **single painless papule that erodes and becomes indurated** with a characteristic firm, *cartilaginous* edge and base; usually solitary (multiple in a minority); base smooth, relatively non-vascular. Regional inguinal nodes are **firm, non-suppurative, painless and bilateral**, appearing within ~1 week. Heals spontaneously in 4–6 weeks (range 2–12 weeks). Sites: penis (heterosexual men); anal canal, rectum or mouth (MSM); cervix, vaginal wall, labia (women)—hence often unrecognised in women and MSM.
- **Chancroid (*H. ducreyi*)** — incubation 1–14 days; begins as a *pustule* that breaks down into multiple, deep, *excavated, very tender* ulcers with **undermined, ragged, irregular edges** and a purulent base that **bleeds easily**; tender, suppurative, loculated, usually unilateral inguinal nodes (bubo).
- **Lymphogranuloma venereum (*C. trachomatis* L1–L3)** — a small, often painless, transient papulo-vesicular ulcer that is frequently *not noticed*; dominated instead by **tender inguinal/femoral lymphadenopathy**. The "**sign-of-the-groove**" (nodes above and below *Poupart's* (inguinal) ligament) is suggestive but *not specific*. Anogenital LGV presents as severe **proctitis/proctocolitis** that can mimic Crohn's disease.
- **Donovanosis / granuloma inguinale (*K. granulomatis*)** — incubation 1–4 weeks (up to 6 months); elevated, **beefy-red, velvety** ulcer that bleeds readily; usually painless; true lymphadenopathy is absent but subcutaneous granulomas form *pseudobuboes*.

Comparison table (Harrison Table 141-7)

Feature	Syphilis (chancre)	Genital herpes	Chancroid	LGV	Donovanosis
Organism	*T. pallidum*	HSV-1 / HSV-2	*H. ducreyi*	*C. trachomatis* L1–L3	*K. granulomatis*
Incubation	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 mo)
Primary lesion	Papule	Vesicle	Pustule	Papule/ pustule/vesicle	Papule
Number	Usually one	Multiple	Multiple, may coalesce	Usually one (often missed)	Variable

Feature	Syphilis (chancre)	Genital herpes	Chancroid	LGV	Donovanosis
Edge / base	Sharply demarcated, indurated; smooth base	Erythematous, serous	Undermined, ragged; purulent, bleeds	Variable	Elevated, beefy-red, velvety; bleeds
Pain	Uncommon (painless)	Frequently tender	Very tender	Variable / mild	Uncommon
Lymphadenopathy	Firm, non-tender, bilateral	Firm, tender, often bilateral (first episode)	Tender, suppurative, loculated, unilateral	Tender, may suppurate, unilateral	None; pseudobuboes

- **Memory aid**: *painful* ulcers = **herpes + chancroid**; *painless* ulcers = **syphilis + LGV + donovanosis**.

Non-classic and non-venereal causes (to exclude)

- Candidiasis and **traumatised genital warts**; genital involvement by widespread **dermatoses**.
- Cutaneous manifestations of **systemic disease** — e.g. genital mucosal ulceration in **Stevens-Johnson syndrome** or **Behçet's disease**.
- **Superinfection** of an originally STI lesion (e.g. MRSA complicating an HSV-2 ulcer).
- **Localised drug reactions** (e.g. topical paromomycin or boric acid preparations).
- A persistent ulcer must also raise suspicion of **carcinoma** and other non-venereal dermatoses.

Diagnostic approach

- **Order a rapid serologic test for syphilis in *every* genital ulcer**, and **counsel and test all patients for HIV** (and consider other STIs).
- **Syphilis**: dark-field microscopy, direct fluorescent antibody (DFA), or NAAT/PCR for *T. pallidum* from the lesion; serology = a **lipoidal (non-treponemal) test (VDRL/RPR)** plus a **treponemal test (TPPA, EIA/CIA, FTA-ABS)**. Caveat: **~30% of chancres have an initially non-reactive serology** (both lipoidal and treponemal tests may be negative in very early primary syphilis)—so treat presumptively and repeat serology.
- **Herpes**: PCR/NAAT (most sensitive), culture, direct FA, or ELISA from the lesion; type-specific HSV-2 serology has limited value (may be falsely negative early/with HSV-1, and a positive result does not prove the current lesion is herpetic).
- **Chancroid**: culture (or PCR where available) for *H. ducreyi*—most useful when ulcers are painful and purulent with fluctuant nodes; **aspirate fluctuant nodes** for culture/PCR and Gram stain.
- **Persistent ulcer** (beyond the natural history—herpes 2–3 weeks, chancroid/syphilis up to ~6 weeks) that fails syndromic therapy → **biopsy** to exclude **donovanosis, carcinoma** and non-venereal causes.

Syndromic management (Harrison Table 141-8)

- **Principle**: after collecting all diagnostic specimens at the first visit, give **immediate syndrome-based treatment** without waiting for all results, because early therapy of HSV, syphilis and chancroid reduces morbidity and onward HIV transmission.
- **Herpes (confirmed/suspected)**: oral **acyclovir, valacyclovir or famciclovir**.
- **Syphilis**: **benzathine penicillin G 2.4 million units IM single dose** (treat patient and recent—within ~3 months—seronegative partners). Penicillin G is the drug of choice for all stages; alternatives for non-pregnant penicillin-allergic patients are **doxycycline 100 mg PO BD** or **tetracycline 500 mg PO QID for 2 weeks**.
- **Chancroid (confirmed/suspected)**: **ciprofloxacin 500 mg PO single dose**, *or* **ceftriaxone 250 mg IM single dose**, *or* **azithromycin 1 g PO single dose**.
- **LGV (e.g. proctitis)**: **doxycycline 100 mg PO BD for 21 days** (alternative: azithromycin 1 g once weekly × 3 weeks).
- **Partner management, HIV testing/counselling and STI screening** are integral.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Five classic genital ulcers" comparison chart**: five labelled boxes/columns — *Syphilis (chancre)*, *Herpes*, *Chancroid*, *LGV*, *Donovanosis* — each labelled with **Organism**, **Incubation**, **Painful/Painless**, **Edge (indurated / undermined / beefy-red)**, **Lymphadenopathy (non-tender bilateral / tender bilateral / suppurative unilateral bubo / sign-of-the-groove / pseudobuboes)**.
- **Diagram 2 — Syndromic algorithm for a genital ulcer**: boxes labelled *Genital ulcer → take history + examine → collect specimens (dark-field/PCR for T. pallidum, PCR/culture for HSV ± H. ducreyi) + RPR/VDRL + offer HIV test → vesicles/painful = treat herpes; painless indurated = treat syphilis (benzathine penicillin 2.4 MU IM); painful purulent + bubo = treat chancroid → review; persistent ulcer → biopsy (exclude donovanosis/carcinoma)*.

Clinical / Diagnostic significance

- GUD is a powerful **co-factor for HIV transmission and acquisition**—ulcer control is an HIV-prevention strategy.
- **Jarisch-Herxheimer reaction** can follow the first dose of penicillin in syphilis: self-limited fever, chills, myalgia, headache, tachycardia and increased respiratory rate from lipoproteins released by dying treponemes; occurs in ~50% of primary and ~90% of secondary cases—warn the patient (and pregnant women, in whom it may cause mild contractions).
- **Post-treatment serologic follow-up** of syphilis: monitor quantitative VDRL/RPR for a **fourfold (two-dilution) decline**; review primary/secondary syphilis at 6 and 12 months (more often if HIV-co-infected).
- LGV rectal biopsy shows crypt abscesses, granulomas and giant cells—**mimicking Crohn's disease**; recognition matters because LGV is curable with doxycycline.
- Recognise non-infectious ulcers (**Behçet's, Stevens-Johnson, fixed drug eruption, malignancy**) to avoid missing serious systemic disease.

High-yield exam pointers

- **Painful** ulcers → herpes + chancroid; **painless** ulcers → syphilis + LGV + donovanosis.
- **Genital herpes is now the commonest cause of GUD** worldwide (HSV 62%, *T. pallidum* 13%, *H. ducreyi* 12–20% in the classic 10-city study).
- **Chancre** = single, painless, indurated, *cartilaginous* ulcer with firm, non-tender, **bilateral** inguinal nodes; **~30% have non-reactive serology** initially.
- **Chancroid** = multiple, deep, painful ulcers with **undermined ragged edges** + tender **suppurative unilateral bubo**.
- **LGV** = inconspicuous ulcer + tender adenopathy with the "**sign-of-the-groove**"; re-emerging as **proctitis in MSM**; Rx **doxycycline 21 days**.
- **Donovanosis** = **beefy-red, velvety, bleeding** ulcer, **pseudobuboes**, diagnosed on **biopsy** (Donovan bodies).
- **Always do syphilis serology and offer HIV testing in every genital ulcer.**
- Syphilis Rx = **benzathine penicillin 2.4 MU IM single dose**; chancroid Rx = single-dose **azithromycin / ceftriaxone / ciprofloxacin**.
- **Biopsy any ulcer persisting** beyond its natural history (to exclude donovanosis and carcinoma).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 141 "Sexually Transmitted Infections: Overview and Clinical Approach" (Tables 141-7 clinical features and 141-8 initial management of genital/perianal ulcer) and Ch 187 "Syphilis" (primary chancre, serology, treatment, Jarisch-Herxheimer reaction). *Coverage note*: detailed clinical descriptions of chancroid, LGV and donovanosis are summarised within Ch 141; their dedicated chapters (Ch 162 chancroid, Ch 178 donovanosis, Ch 197 HSV) were not provided, so organism-level detail (e.g. LGV serovars L1–L3, Donovan bodies) is given from universally accepted standard internal-medicine teaching consistent with the provided text.

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Immune reconstitution inflammatory syndrome (IRIS)

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Immune reconstitution inflammatory syndrome (IRIS) is a *paradoxical clinical deterioration* that follows the recovery of pathogen-specific immunity, most classically after initiation of effective antiretroviral therapy (ART) in a person with advanced HIV disease. It represents a dysregulated, exaggerated inflammatory response — directed against the antigens of a treated, partially treated, or previously undiagnosed opportunistic infection (or, less often, a tumour or autoimmune antigen) — that emerges precisely *because* immune function is restored. It is therefore not a treatment failure but a sign of immune recovery, and is a diagnosis of exclusion.

Pathogenesis / Immunology

- Triggered by the rapid restoration of antigen-specific (predominantly CD4+ T-cell) immunity as plasma HIV-RNA falls and CD4 counts rise after ART.
- The underlying mechanism resembles a **type IV (delayed/cell-mediated) hypersensitivity reaction** — a vigorous immune response mounted against the antigens of organisms present in the tissues.
- Antigenic stimulus is provided both by *viable* organisms and by **antigens released as bacilli/fungi are killed** during effective antimicrobial chemotherapy; the recovering immune system suddenly "sees" this antigen load and reacts intensely.
- Characterised by a surge of pro-inflammatory cytokines — **IL-6, TNF-α, IFN-γ, IL-12p40, IL-10 and IFN-γ-inducible protein-10 (IP-10)** — whose suppression underlies the benefit of glucocorticoids.
- The term **immune reconstitution disease (IRD)** is sometimes used to separate IRIS due to *opportunistic infections/tumours* from IRIS related to *autoimmune* disease; IRD is especially common with underlying untreated mycobacterial or fungal infection.

Classification (two clinical forms)

Feature	Paradoxical IRIS	Unmasking IRIS
Underlying condition	Known, already-diagnosed (often partially treated) opportunistic infection / neoplasm	Previously **undiagnosed**, subclinical infection
What ART does	Causes worsening/flare of the existing, treated condition	"Unmasks" a latent infection that becomes clinically apparent
Typical example	Worsening lymphadenitis or new pulmonary infiltrates in a treated TB patient	New active TB or cryptococcal disease appearing after ART start
Inflammatory component	Prominent	Prominent, may mimic acute primary infection

- Beyond infections, ART may also **exacerbate pre-existing autoimmune conditions or trigger new ones** (e.g. *Graves' disease*, sarcoidosis).

Epidemiology & risk factors

- Some form of IRIS occurs in **10–30%** of patients after starting ART (varies with setting); TB-associated IRIS occurs in ~**10%** of HIV-infected TB patients.
- **Strongest risk factor:** starting ART at a very low **CD4+ count (<50 cells/µL)** together with a *precipitous drop in HIV-RNA*.
- The **earlier** ART is begun after starting treatment of the opportunistic infection, and the **lower the baseline CD4 count**, the **greater the risk** of IRIS.
- Disseminated / **extrapulmonary** disease and **advanced immunosuppression** increase risk.
- IRIS is largely confined to ART-treated HIV patients but analogous syndromes occur in **transplant recipients** (after reduction of immunosuppression), in **neutropenia recovery**, post-partum, and occasionally even in non-immunocompromised hosts (e.g. cryptococcosis).
- **Timing of onset:** anywhere from **2 weeks to 2 years** after ART; for TB-IRIS typically **1–3 months** after ART initiation.

Clinical spectrum (organism-specific manifestations)

Pathogen / condition	Characteristic IRIS presentation
Mycobacterium tuberculosis	Fever, enlarging lymphadenopathy, worsening pulmonary infiltrates, new pleural effusion; *CNS-TB → serious neurological deterioration, can be fatal*
Mycobacterium avium complex	Focal, often suppurative lymphadenitis or granulomatous masses
Cryptococcus neoformans	Recurrent meningitis-like picture, fever, headache, lymphadenopathy, raised ICP; hard to distinguish from relapse
CMV retinitis	Immune-recovery **vitreitis/uveitis**
JC virus (PML)	Atypical/worsening course of progressive multifocal leukoencephalopathy
Kaposi sarcoma	Flare/worsening of lesions shortly after ART start
Hepatitis B/C	Flare of hepatitis (immune-mediated hepatic injury)
Autoimmune	*Graves' disease*, sarcoidosis, new autoimmune phenomena

- General manifestations from Harrison: localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, raised intracranial pressure, uveitis, sarcoidosis and Graves' disease. The course can be protracted and severe cases may be **fatal**.

Diagnosis

- **There is no confirmatory diagnostic test** — IRIS is a **clinical diagnosis of exclusion** resting on case definitions that combine clinical and laboratory data.
- Essential first step: **exclude the alternatives** —
  - *failure of the antimicrobial therapy* (e.g. drug-resistant or inadequately treated TB),
  - *a new/second opportunistic infection*,
  - *drug toxicity or hypersensitivity*, and
  - *non-adherence / poor drug levels*.

- Supportive features: temporal link to ART, documented **fall in HIV-RNA and rise in CD4**, and an inflammatory (rather than purely infective) clinical picture.
- For cryptococcosis, a tissue biopsy may be required to distinguish inadequately treated infection from IRIS.

Management & timing of ART (prevention)

- **General principle:** *continue ART* wherever possible — IRIS reflects desirable immune recovery; stopping ART is reserved for life-threatening situations.
- **Mild–moderate paradoxical reactions:** symptomatic/supportive management; these do not worsen TB-treatment outcomes.
- **Severe reactions: glucocorticoids** to blunt inflammation while specific antimicrobial therapy continues. For severe TB-IRIS, **prednisolone for 4 weeks** (*1.5 mg/kg/day for 2 weeks, then half that dose for the remaining 2 weeks* — the Meintjes regimen) reduces hospitalisation and therapeutic procedures and hastens symptom relief, mediated by suppression of IL-6, IL-10, IL-12p40, TNF-α, IFN-γ and IP-10.
- **Optimising the timing of ART** is the key preventive strategy:

Co-infection	Recommended ART timing	Rationale
TB meningitis	**Do NOT start ART within the first 8 weeks** of anti-TB therapy	CNS-TB IRIS can cause fatal neurological deterioration
Cryptococcal meningitis	Start ART **4–6 weeks** after starting antifungal therapy	Early ART increases IRIS and mortality
Cryptococcal antigenaemia (no active disease)	Pre-emptive fluconazole; start ART **2 weeks** after antifungal therapy	Treat occult infection before immune recovery

- **Prophylactic dexamethasone is NOT recommended** in HIV-associated cryptococcosis — it is associated with **reduced fungal clearance and increased mortality**.
- Screen high-risk patients (CD4 <100–200/μL) with **serum cryptococcal antigen (CRAg)** before ART to detect occult infection and avert unmasking IRIS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Timeline / mechanism schematic:** horizontal time-axis labelled "ART started". Two crossing curves — one **falling "HIV-RNA / viral load"**, one **rising "CD4+ T-cell count"**. Mark the inflammatory peak ("IRIS: 2 weeks–2 years; TB-IRIS 1–3 months") at the crossover. Side boxes labelled: *Antigen load (live organisms + dead-organism antigens)* → *Restored CD4 / Type IV hypersensitivity response* → *Cytokine surge (IL-6, TNF-α, IFN-γ, IP-10)* → *Tissue inflammation*.
- **Two-arm classification box:** central node "IRIS" branching to **"Paradoxical (known, treated infection worsens)"** and **"Unmasking (previously undiagnosed infection appears)"**, each with one example (TB lymphadenitis flare; new cryptococcal meningitis).

Clinical / Diagnostic significance

- Anticipate IRIS in any patient who deteriorates *after* starting ART, particularly with baseline CD4 <50/μL — recognising it avoids the dangerous reflex of stopping life-saving ART or escalating (unnecessary) second-line antimicrobials.
- Mandates a careful **work-up to exclude treatment failure and new OIs** before attributing deterioration to IRIS.
- Drives the **sequencing of therapy**: treat the opportunistic infection first, then introduce ART after an appropriate interval (immediately–2 weeks for most OIs if CD4 very low, but **defer 8 weeks in TB meningitis** and **4–6 weeks in cryptococcal meningitis**).
- Justifies **CRAg screening** and pre-emptive antifungal therapy in advanced HIV to prevent unmasking cryptococcal IRIS.
- Glucocorticoids are a double-edged tool — beneficial in severe paradoxical reactions but harmful as *prophylaxis* in cryptococcosis.

High-yield exam pointers

- IRIS = paradoxical worsening after ART due to *restored immunity*; **not** drug or treatment failure.
- Two forms: **paradoxical** (known infection flares) vs **unmasking** (latent infection revealed).
- Highest risk: **CD4 <50/μL** + steep fall in viral load; commonest with **TB and cryptococcosis**.
- Onset **2 weeks–2 years** post-ART (TB-IRIS **1–3 months**); incidence **10–30%** overall, **~10%** in HIV-TB.
- Mechanism = **type IV hypersensitivity-like** reaction; cytokines IL-6, TNF-α, IFN-γ, IP-10.
- **Diagnosis of exclusion** — rule out treatment failure, new OI, drug toxicity.
- Management = **continue ART** + supportive care; **glucocorticoids only for severe disease** (TB-IRIS: prednisolone 1.5 mg/kg/day × 2 wk, then half × 2 wk).
- Timing rules: **TB meningitis → no ART in first 8 weeks**; **cryptococcal meningitis → ART at 4–6 weeks**; prophylactic dexamethasone contraindicated in cryptococcosis.
- Other faces: CMV immune-recovery uveitis/vitreitis, MAC suppurative lymphadenitis, KS flare, hepatitis B/C flare, Graves' disease.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (IRIS section + Table 208-12, Characteristics of IRIS); "Tuberculosis" (TB-IRIS, ART timing in TB meningitis, prednisolone regimen, cytokine profile); "Cryptococcosis" (cryptococcal IRIS, ART timing 4–6 weeks, dexamethasone caution, CRAg screening).
- **CMDT 2026** — "HIV Infection & AIDS" (Inflammatory Reactions / IRIS — diagnosis of exclusion, conservative management, corticosteroids for severe reactions, CMV/MAC/KS examples).

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Immunisation for travel in adults

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Travel immunization is the pre-travel administration of vaccines to protect the international traveller against infections encountered en route or at the destination, and to satisfy entry/exit regulations of host countries. About 30% of travellers report a travel-related illness, and vaccine-preventable infections (influenza/COVID-19 most common, then typhoid and hepatitis A) are an important, preventable subset. Because several vaccines are given as a **series** and all take roughly a week to induce protective immunity, travellers should ideally be referred to a travel clinic **at least 4–6 weeks before departure**, though even last-minute consultation provides benefit.

Framework: the pretravel consultation and the three vaccine categories

- The pretravel consultation has four pillars: **(1) trip risk assessment** (itinerary + traveller), **(2) immunizations**, **(3) prevention of arthropod-borne infection (malaria/vector)**, and **(4) prevention of gastrointestinal illness** — with shared decision-making on whether to travel.
- Travel vaccines are traditionally grouped into three (overlapping) categories:
  - **Routine** — those on the national child/adult schedule (e.g., MMR, Tdap, influenza, hepatitis B); travellers must simply be *up to date*, since these infections occur worldwide.
  - **Recommended** — not on the routine schedule but advised because of *anticipated risk* from the specific itinerary (e.g., typhoid, hepatitis A, Japanese encephalitis, rabies).
  - **Required** — *mandated* by international regulation or by a specific country for entry/exit; proof is documented on the **International Certificate of Vaccination or Prophylaxis (ICVP, the "yellow card")**. The prototype is **yellow fever**; cholera and meningococcal (Hajj/Umrah) requirements also exist.
- A traveller without proof or a documented **medical waiver** for a required vaccine may face entry barriers, vaccination on arrival, quarantine or other penalties.

Vaccines to consider for most destinations

Vaccine	Primary series in unvaccinated adults	Booster	Key travel point
Hepatitis A (Havrix, Vaqta)	2 doses 6–12 mo (Havrix) / 6–18 mo (Vaqta) apart	Not required after series	One of the commonest VPIs in travellers; a single dose protects healthy young adults before travel; consider Ig 0.1 mL/kg if >40 y or immunocompromised
Hepatitis B (recombinant; Heplisav-B)	3 doses 0,1,6 mo; Heplisav-B 2 doses 0,1 mo	Not after routine series	Important for long-term travellers, HCWs, sexual exposure; **Twinrix accelerated** schedule (days 0,7,21–30) if departing soon
Influenza + COVID-19	Per current seasonal recommendation	Seasonal	*Most common* VPIs in travel; give influenza even if local season has peaked (year-round risk in tropics)
Measles–mumps–rubella (MMR)	2 doses ≥28 days apart	None	Resurgent worldwide; ensure 2-dose evidence of immunity; **immune if born before 1957**; only MMR available for adults
Tetanus–diphtheria–pertussis (Td/Tdap)	Age-appropriate per schedule	Td q10y	Early tetanus booster (<10 y) for high-injury trips; diphtheria booster within 5 y if outbreak destination
Varicella	2 doses	—	Evidence of immunity needed; **immune if born in US before 1980** or prior disease/zoster
Poliomyelitis (IPV)	3 doses if never vaccinated	**Single lifetime adult booster**	One IPV booster before travel to countries with wild-type or circulating vaccine-derived poliovirus in prior 12 months

Destination- or activity-specific travel vaccines

Vaccine	Schedule / type	Indication / pearl
Yellow fever (live attenuated)	1 dose; valid for **life**, from day 10	Sub-Saharan Africa & tropical S. America; *required* — see below
Typhoid	**Vi capsular polysaccharide** (injectable, 1 dose, booster 2 y) or **oral live attenuated** (4 doses 48 h apart, booster 5 y)	Highest risk **South Asia**; oral vaccine **contraindicated if immunocompromised**; *no protection against paratyphoid*
Japanese encephalitis (IXIARO, inactivated Vero-cell)	2 doses, days 0 and 7–28	Risk <1 per million travellers but ↑ in long-term/rural/evening exposure in Asia & W. Pacific
Rabies (HDCV/PCECV, pre-exposure)	**2 doses days 0 and 7** (revised 2022)	Endemic on all continents except Antarctica; 3rd dose (21 d–3 y) or titre check if >3-y risk; PrEP still needs urgent post-exposure boosters

Vaccine	Schedule / type	Indication / pearl
Meningococcal ACWY (conjugate)	1 dose	African "**meningitis belt**" in dry season (Dec–June); **required for Hajj/Umrah** within preceding 3 y; conjugate preferred over polysaccharide
Cholera (Vaxchora, live oral)	1 oral dose	Efficacy ~90% at 10 days, 80% at 3 months; for outbreak areas/HCWs who cannot maintain hygiene
Tick-borne encephalitis (inactivated)	3 doses; 2 doses adequate for short-term travel	Forested Europe/Asia; *Ixodes* tick; also via unpasteurised dairy
Chikungunya (live, 2023)	1 dose, age ≥18 y	For increased-exposure travellers; **contraindicated if immunocompromised**
Dengue	No FDA-approved vaccine for travellers	Dengvaxia only for seropositive endemic residents; Qdenga (EU, age ≥4) may be considered

Yellow fever — the prototype "required" vaccine

- **Live attenuated** vaccine, available **only at state-authorised yellow-fever clinics**, recorded on the **ICVP**; valid for entry from **day 10** after administration and for the **lifetime** of the vaccinee — the 10-yearly booster requirement was **removed from the WHO International Health Regulations in 2016**.
- **Booster after 10 years is still advised** for: women pregnant during primary immunization, persons with HIV at the time of vaccination, post-HSCT recipients, and those at especially high risk (epidemics, prolonged stay, peak season).
- Requirement triggers: arrival from an endemic country within 10 days, or a transit stop ≥12 h in an endemic country.
- **Contraindications:** severe immunosuppression (immunosuppressive therapy, primary immunodeficiency, symptomatic HIV or CD4 <200/μL), malignancy, thymus disorders, severe egg allergy. **Precautions:** age ≥60 y, pregnancy, breastfeeding, asymptomatic HIV with CD4 200–499/μL.
- **Adverse events:** mild fever/myalgia/lymphadenopathy/rash; rare serious events include anaphylaxis, neurologic disease (GBS, meningitis, encephalitis) and **yellow fever vaccine–associated viscerotropic disease (YEL-AVD)** (~0.3 per 100,000 doses, higher in the elderly/immunosuppressed).

Co-administration, special populations and general principles

- **All routine travel vaccines may be given on the same day.** Exceptions: **oral typhoid must be given ≥8 h after oral cholera**; and **live-virus vaccines** (yellow fever, MMR, live-attenuated influenza, varicella) should be given on the **same day or spaced ≥28 days apart** (otherwise repeat the second dose after ≥28 days).

- **Pregnancy:** live-virus vaccines (MMR, varicella, and yellow fever as a precaution) are generally **contraindicated**; inactivated vaccines (Tdap each pregnancy at 27–36 weeks, inactivated influenza, hepatitis B) are safe and recommended.
- **Immunocompromised:** avoid live vaccines (yellow fever, oral typhoid, live chikungunya, MMR, varicella) when severely immunosuppressed; risk of vaccine-virus dissemination. A true **contraindication** is anaphylaxis to the vaccine or a component; a precaution is moderate/severe acute illness.
- **Malaria is NOT vaccine-preventable in travellers** — prevention rests on **mosquito-bite avoidance** (DEET 20–50%, permethrin-treated clothing, insecticide-treated nets) plus **chemoprophylaxis** (atovaquone-proguanil, chloroquine/hydroxychloroquine, doxycycline, mefloquine, primaquine, tafenoquine — tailored to species and resistance) and early recognition of fever.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pretravel consultation flow box** with four labelled arms: *Risk assessment (Itinerary + Traveller) → Immunizations (Routine / Recommended / Required–ICVP) → Vector/Malaria prevention → GI-illness prevention.*
- **Yellow fever endemicity map (schematic):** outline of *Africa* and *South America* shaded for **sub-Saharan Africa** and **tropical South America**, labelled "Yellow fever endemic / vaccine recommended"; annotate *ICVP valid from day 10, lifelong.*

Clinical / Diagnostic significance

- A focused **itinerary + traveller history** (destinations, season, rural vs urban, duration, accommodation, activities, pregnancy, immune status, drug interactions) drives vaccine selection and chemoprophylaxis choice.
- **Documentation matters medico-legally:** the ICVP/"yellow card" is the legal proof for required vaccines; medical waivers must be issued by authorised clinics.
- **Returning febrile traveller:** always consider **malaria** (leading cause of life-threatening infection in travellers) and typhoid/dengue; urge early evaluation — a key counselling point at the pretravel visit.
- Counsel on **rabies wound care** (immediate soap-and-water/povidone-iodine washing, urgent assessment for PEP = rabies immune globulin + vaccine series) and on **travellers' diarrhoea** food/water precautions.

High-yield exam pointers

- Three categories: **Routine, Recommended, Required** — required = ICVP-documented (yellow fever prototype).
- Refer **4–6 weeks before travel**; vaccines need ~1 week for immunity.
- **Yellow fever:** single dose = lifelong protection; 10-yearly booster dropped by WHO (2016); YEL-AVD ~0.3/100,000.
- **Meningococcal ACWY required for Hajj/Umrah** within preceding 3 years; meningitis belt epidemics Dec–June.

- **Oral typhoid and oral cholera are live** → contraindicated in immunocompromised; give oral typhoid ≥8 h after oral cholera.
- **Live-virus vaccines:** same day or ≥28 days apart; contraindicated in pregnancy and severe immunosuppression.
- **Rabies pre-exposure:** 2 doses (days 0, 7) since 2022; still requires post-exposure boosters.
- Immunity benchmarks: **measles — born before 1957; varicella — US-born before 1980.**
- **Malaria has no traveller vaccine** — bite avoidance (DEET 20–50%, permethrin, nets) + chemoprophylaxis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 130 "Health Recommendations for International Travel" (primary; Tables 130-1 and 130-3, Fig. 130-1) and Ch 129 "Immunization Principles and Vaccine Use" (general contraindications/precautions, pregnancy and immunocompromised principles). Coverage note: Harrison gives vaccine *types and schedules* but not granular antigen content/dosage in mL; chemoprophylaxis regimen specifics are deferred to Ch 231 (Malaria) and are summarised here only at the level stated in Ch 130. US-centric immunity criteria (birth-year cut-offs) are quoted verbatim from the text and should be adapted to local epidemiology.

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HACEK group infections

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — **HACEK** is an acronym for a group of *fastidious, slow-growing, capnophilic (CO_2-requiring) gram-negative bacilli/coccobacilli* that are normal commensals of the **oral cavity and upper respiratory tract**. The members are **H**aemophilus species (classically *H. aphrophilus*, now reclassified), **A**ggregatibacter species (formerly *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*), **C**ardiobacterium hominis, **E**ikenella corrodens, and **K**ingella kingae. Their clinical importance lies chiefly in being the principal **gram-negative cause of subacute infective endocarditis (IE)** on native and prosthetic valves; they also produce a spectrum of localised oral, skeletal, and abscess-forming infections. They account for ~0.8–6% of all IE (CMDT: <5%).

Microbiology and taxonomy of the HACEK group

- Common biology: fastidious, **slow-growing**, gram-negative; require an atmosphere **enriched with CO_2 (capnophilic)**; do **not grow on MacConkey/enteric media**; normal flora of the mouth.
- Taxonomy has been revised — the modern names differ from the original acronym:

Letter	Modern genus/species	Former name	Key disease niche
H	*Haemophilus parainfluenzae* (commonest *Haemophilus* in HACEK IE)	—	Subacute IE, polymicrobial abscess

Letter	Modern genus/species	Former name	Key disease niche
A	*Aggregatibacter actinomycetemcomitans*, *A. aphrophilus*, *A. paraphrophilus*	*Actinobacillus*; *Haemophilus aphrophilus*	**Commonest cause of HACEK IE**; brain abscess; periodontitis
C	*Cardiobacterium hominis* (and *C. valvarum*)	—	**Aortic-valve** subacute IE
E	*Eikenella corrodens*	—	Human-bite/clenched-fist wounds; **least common** HACEK IE
K	*Kingella kingae*	—	Paediatric **septic arthritis/osteomyelitis**; IE in older children/adults

- **HACEK bacteraemia is strongly predictive of underlying IE** (overall positive predictive value ~60%), but the association is organism-dependent: IE found in **62–100%** of *A. actinomycetemcomitans*, **17–55%** of *H. parainfluenzae*, **~50%** of *C. hominis*, but only **0–6%** of *Eikenella* bacteraemias.

Pathogenesis and routes of entry

- Reside as commensals in the **gingival crevice/oropharynx**; gain bloodstream access after **dental procedures, periodontal disease, or nasopharyngeal infection** — hence the typical history of recent dental work in a patient with valvular disease.
- *Eikenella corrodens* is inoculated through **human bites / clenched-fist ("fight-bite") injuries**.
- *Kingella kingae* invasion is preceded by **upper respiratory tract infection or stomatitis in ~80%**; oropharyngeal colonisation peaks (≈5–10%) in the **first 3 years of life** and is higher in **daycare attenders**, explaining its age-restricted invasive disease (6 months–4 years) and reported child-to-child **outbreaks**.

HACEK infective endocarditis — clinical profile

- Predisposition: nearly always **pre-existing valvular disease or a prosthetic valve**; *Aggregatibacter* is linked to **prosthetic-valve endocarditis (PVE)** more than *Haemophilus*.
- Course is usually **subacute/indolent** (especially *Aggregatibacter* and *Cardiobacterium* — patients ill for weeks–months before diagnosis); *K. kingae* IE may be **more aggressive**.
- Compared with non-HACEK IE, HACEK IE occurs in **younger patients** and shows **more embolic, vascular and immunologic phenomena**.
- **Large vegetations** and **systemic embolism** are characteristic: major emboli in **28–71%** of series; echocardiographic vegetations seen in **up to 85%**.
- Valve localisation: *Aggregatibacter* and *Haemophilus* → **mitral**; *Cardiobacterium* → **aortic**.
- Complications: **congestive heart failure** (19–50% with *Haemophilus*), septic emboli (including **CNS emboli**), **mycotic aneurysms**, immune-complex glomerulonephritis, vasculitis, and renal failure.

Diagnosis

- **Alert the microbiology laboratory** when HACEK IE is suspected.
- Most clinically significant cultures turn **positive within the first week** using modern automated systems (**BACTEC**); studies have **not** shown that *prolonged incubation* improves recovery (CMDT: HACEK now usually grows within the standard 5-day incubation).
- Inoculating fluids (e.g., synovial fluid for *K. kingae*) into **aerobic blood-culture bottles** enhances recovery.
- **Molecular/rapid tools**: broad-range **16S rRNA gene PCR** (blood/valve tissue) and **MALDI-TOF mass spectrometry** on colonies improve speed and accuracy; **real-time PCR** is increasingly recovering *K. kingae* from culture-negative cases.
- HACEK organisms are listed among the **"typical" IE pathogens** that fulfil the **microbiologic major criterion** of the modified Duke / 2023 Duke-ISCVID criteria.
- Because of **slow growth, β-lactamase production may be missed** on susceptibility testing; **Etest** improves accuracy. Resistance is most common in *Haemophilus* and *Aggregatibacter*; in recent studies **ceftriaxone and levofloxacin were active against all isolates**.

Treatment of HACEK infections

Organism / setting	Preferred therapy	Alternatives / notes
HACEK IE (all five genera)	**Ceftriaxone 2 g IV once daily**	Favourable outcome in **80–90%**; NVE **4 weeks**, PVE **6 weeks**
β-lactam–intolerant	**Levofloxacin 750 mg/day** (data limited)	Fluoroquinolones **not** for patients **<18 years**
Alternative β-lactam	**Ampicillin/sulbactam** (3 g ampicillin q6h)	Amp/sulbactam resistance described in *Haemophilus* & *Aggregatibacter*
If β-lactamase excluded & susceptible	Penicillin 16–18 MU q4h **or** ampicillin 2 g q4h	Susceptibility hard to confirm due to slow growth

- **Surgery is usually NOT required** — unlike PVE from other gram-negative bacilli, HACEK IE is **often cured by antibiotics alone**.
- *Eikenella corrodens* is **resistant to clindamycin, metronidazole, and aminoglycosides** — relevant in bite-wound polymicrobial cover.
- **Prognosis is excellent**, significantly better than non-HACEK IE; 1-year mortality is lower than that of viridans-streptococcal IE.
- **Prophylaxis** (high-risk cardiac lesions before dental manipulation): **amoxicillin 2 g PO 1 h before**; if penicillin-allergic — cephalexin 2 g, azithromycin/clarithromycin 500 mg, or doxycycline 100 mg PO. This is directly relevant because HACEK organisms originate from the oral flora.

Organism-specific pearls (beyond endocarditis)

- ***Haemophilus parainfluenzae*** — commonest *Haemophilus* in HACEK IE; also pneumonia, meningitis, and brain/dental/pelvic/liver abscess; septicaemia often **polymicrobial**.

- ***Aggregatibacter*** — **commonest HACEK IE**; *A. actinomycetemcomitans* co-isolated with ***Actinomyces israelii*** in soft-tissue abscesses; *A. aphrophilus* is an important cause of **brain abscess** (10% of brain abscesses in one series) and bone/joint infection.
- ***Cardiobacterium hominis*** (± *C. valvarum*) — **aortic** vegetations; presents with long-standing infection, embolisation, **mycotic aneurysms**, immune-complex glomerulonephritis, vasculitis, arthritis.
- ***Eikenella corrodens*** — eponymous **"corroding"/pitting of agar**; human-bite wounds, head-and-neck and visceral abscesses, osteomyelitis, IUD-associated gynaecologic infection; usually part of **mixed** infection.
- ***Kingella kingae*** — has **surpassed *S. aureus* as the leading cause of septic arthritis and osteomyelitis in young children**; bacteraemia can present with a **petechial rash mimicking meningococcaemia**; adult/older-child IE is aggressive (arterial emboli, CVA, tricuspid insufficiency, cardiovascular collapse).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled heart with HACEK endocarditis:** draw a left heart in long-axis; label **mitral valve vegetation (Aggregatibacter/Haemophilus)**, **aortic valve vegetation (Cardiobacterium)**, **large friable vegetation → systemic/CNS embolus**, **mycotic aneurysm**, and **immune-complex glomerulonephritis** as peripheral consequences.
- **Flow box of HACEK pathway:** *Oral/upper-respiratory commensal → dental procedure / periodontitis / bite → transient bacteraemia → adherence to damaged or prosthetic valve → subacute vegetation → embolic + immunologic complications.* Label each arrow.

Clinical / Diagnostic significance

- Consider HACEK in any **culture-negative or "fastidious-organism" subacute IE**, particularly with **poor dentition, recent dental work, prosthetic valve, large vegetations, or prominent embolic phenomena**.
- Maintain the blood-culture incubation and **flag the lab**; add **16S rRNA PCR / MALDI-TOF** when conventional cultures are negative.
- Differentiate from other culture-negative IE causes — *Coxiella burnetii*, *Bartonella*, *Tropheryma whipplei*, *Brucella*, nutritionally-variant streptococci (*Granulicatella/Abiotrophia/Gemella*) — which need **serology/special media**, not just longer incubation.
- A positive HACEK blood culture (especially *Aggregatibacter*, *Cardiobacterium*) should **prompt echocardiography** given the high predictive value for IE.

High-yield exam pointers

- HACEK = **H**aemophilus, **A**ggregatibacter (was *Actinobacillus*), **C**ardiobacterium hominis, **E**ikenella corrodens, **K**ingella kingae — fastidious, **CO_2-requiring**, oral commensals.
- **Commonest gram-negative cause of subacute IE**; ~0.8–6% of all IE.
- **Aggregatibacter** = commonest HACEK IE and commonest in **PVE**; **Cardiobacterium → aortic**, **Aggregatibacter/Haemophilus → mitral**.

- HACEK bacteraemia PPV for IE ≈ **60%**; highest with *A. actinomycetemcomitans*, lowest with *Eikenella*.
- **Large vegetations + frequent emboli** (28–71%); younger patients; vegetations on echo up to 85%.
- First-line therapy = **ceftriaxone 2 g/day**; **NVE 4 weeks, PVE 6 weeks**; often **cured medically without surgery**; **excellent prognosis**.
- *Eikenella* resists **clindamycin, metronidazole, aminoglycosides**; think of it in **clenched-fist bite** wounds.
- *Kingella kingae* = top cause of **paediatric septic arthritis/osteomyelitis**; inoculate joint fluid into **blood-culture bottles**; **petechial rash** mimics meningococcaemia.
- HACEK qualifies as a **"typical" organism (major criterion)** in the modified Duke / Duke-ISCVID criteria.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria" (Tamar F. Barlam) and "Infective Endocarditis" (etiology, modified Duke/Duke-ISCVID criteria, HACEK treatment regimens, antibiotic prophylaxis).
- **CMDT 2026** — "Bacterial & Chlamydial Infections" (Infective Endocarditis: HACEK organisms; culture-negative endocarditis) for current management and the classic acronym expansion.

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Infective endocarditis

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Infective endocarditis (IE) is microbial infection of the endocardial surface of the heart, most often the valves, whose prototypic lesion is the **vegetation** — a mass of platelets, fibrin, microorganisms and scant inflammatory cells. Infection may also involve the low-pressure side of a ventricular septal defect, mural endocardium damaged by aberrant jets or foreign bodies, or intracardiac devices; the analogous process on arteriovenous/arterio-arterial shunts (patent ductus, coarctation) is termed **infective endarteritis**. In developed countries the incidence is ~**15 cases per 100,000 population/year** and is rising, with predisposition shifting from chronic rheumatic heart disease (still dominant in developing countries) towards injection drug use, degenerative valve disease and intracardiac devices.

Classification

IE is classified by temporal course, site, cause, or predisposing risk factor:

- **By tempo:** *Acute IE* — hectically febrile, rapidly destroys cardiac structures, seeds distant sites, fatal in weeks if untreated (β-haemolytic streptococci, *S. aureus*, pneumococci). *Subacute IE* — indolent, slowly progressive, rarely metastasises (viridans streptococci, enterococci, CoNS, HACEK).

- **By valve type:** Native-valve endocarditis (NVE), prosthetic-valve endocarditis (PVE — 16–30% of cases), transcatheter aortic valve replacement (TAVR)-PVE, and cardiovascular implantable electronic device IE (CIED-IE).
- **By setting:** Community-acquired, **health care–associated** (25–35% of NVE), IE in people who inject drugs (PWID).
- **PVE timing:** *Early* (<2 months post-surgery — nosocomial: *S. aureus*, CoNS, gram-negative bacilli, diphtheroids, fungi); *late* (>12 months — microbiology like community NVE). Risk is highest in the first year, higher for bioprosthetic than mechanical valves.

Etiology (microbiology)

- **Staphylococcus aureus** — now the **most common** overall cause; predominates in health care–associated IE (~52%) and PWID (often methicillin-resistant).
- **Viridans streptococci** (oral portal) — classic subacute NVE; *Streptococcus gallolyticus* (formerly *S. bovis*) arises from the gut and signals **colonic polyps/tumours**.
- **Enterococci** (genitourinary portal), **coagulase-negative staphylococci** (chief cause of PVE; usually methicillin-resistant), and the **HACEK** group — *Haemophilus*, *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* (upper-respiratory portal).
- **Culture-negative IE (5–15%):** one-third to one-half due to prior antibiotics; remainder due to fastidious organisms — *Coxiella burnetii* (Q fever, predilection for prosthetic valves), *Bartonella* spp., *Tropheryma whipplei*, and nutritionally variant *Granulicatella, Abiotrophia, Gemella*. *Mycobacterium chimaera* has caused a global PVE outbreak from contaminated heater–cooler units.
- Mimics of culture-negative IE: atrial myxoma, marantic (non-bacterial thrombotic) endocarditis, antiphospholipid antibody syndrome.

Pathogenesis

- Intact endothelium resists most bacteria. **Endothelial injury** (high-velocity jets, low-pressure side of a lesion) → deposition of a platelet–fibrin thrombus = **nonbacterial thrombotic endocarditis (NBTE)**, the nidus for bacterial attachment during transient bacteraemia.
- Cardiac lesions prone to NBTE: mitral regurgitation, aortic stenosis, aortic regurgitation, VSD, complex congenital disease. NBTE also arises from hypercoagulable states (marantic endocarditis in malignancy; bland vegetations in SLE/antiphospholipid syndrome).
- Organisms adhere via **MSCRAMMs** (microbial surface components recognising adhesive matrix molecules) — fibronectin-binding proteins, clumping factor (*S. aureus*), FimA/glucans (streptococci). *S. aureus* can invade even **intact** endothelium via von Willebrand factor and fibronectin-binding proteins.
- Organisms deep in the vegetation are **metabolically inactive (nongrowing)** and relatively resistant to antibiotics — the rationale for prolonged, bactericidal, parenteral therapy.

Clinical features

Feature	Frequency
Fever	80–90%
Heart murmur	80–85%
New/worsened regurgitant murmur	20–50%
Arterial emboli	20–50%
Splenomegaly	15–50%
Neurologic manifestations	20–40%
Peripheral stigmata (Osler, Janeway, splinter, Roth)	2–15%
Anaemia	70–90%
Elevated CRP	>90%

- **Cardiac:** new regurgitant murmur (valve/chordal destruction); congestive heart failure in 30–40% (chief surgical indication); paravalvular abscess (commonest with aortic valve) burrowing into the septum → **heart block**; coronary embolism (2%).
- **Peripheral stigmata:** ***Osler nodes*** (painful, immunologic, finger/toe pulps), ***Janeway lesions*** (painless, septic-embolic, palms/soles), ***Roth spots*** (retinal exudates), **splinter/subungual haemorrhages**, **petechiae** (palate, conjunctiva), **clubbing**.
- **Embolic/metastatic:** stroke or encephalopathy (15–35%); renal/splenic infarcts; mycotic aneurysm; spondylodiscitis. *S. aureus*, vegetations **>10 mm**, and mitral anterior-leaflet involvement independently raise embolic risk; embolic rate falls sharply after effective therapy.
- **Immune-mediated:** diffuse hypocomplementaemic glomerulonephritis (immune-complex), positive rheumatoid factor, microscopic haematuria.
- **PWID:** 35–60% have isolated **tricuspid** IE — fever with faint/absent murmur, septic pulmonary emboli causing cough, pleuritic pain, nodular infiltrates.

Diagnosis — 2023 Duke-ISCVID criteria

Definite IE = 2 major **or** 1 major + 3 minor **or** 5 minor (clinical), or pathologic confirmation in a vegetation/abscess. **Possible IE** = 1 major + 1 minor or 3 minor.

Major criteria	Minor criteria
Positive blood cultures: typical IE organism in ≥2 sets (e.g. *S. aureus*, *S. lugdunensis*, *E. faecalis*, all streptococci except *S. pneumoniae*/*S. pyogenes*, *Granulicatella*/*Abiotrophia*/*Gemella*, HACEK); atypical organism in ≥3 sets	**Predisposition** (prior IE, IV drug use, prosthetic/repaired valve, congenital disease, CIED, >mild regurgitation/stenosis, HCM)
Positive lab test: PCR for *Coxiella*/*Bartonella*/*T. whipplei*; *C. burnetii* phase I IgG ≥1:800; *Bartonella* IgG ≥1:800	**Fever** >38.0°C

Major criteria	Minor criteria
Imaging: echocardiography **or cardiac CT** showing vegetation, perforation, abscess, pseudoaneurysm, fistula, new dehiscence, or new regurgitation	**Vascular phenomena** (arterial/septic pulmonary emboli, mycotic aneurysm, intracranial/conjunctival haemorrhage, Janeway lesions)
FDG-PET/CT abnormal uptake on a prosthetic valve/graft/lead	**Immunologic phenomena** (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor)
Direct evidence at heart surgery	Microbiologic evidence not meeting major criteria

- **Blood cultures (gold standard):** three two-bottle sets (10 mL/bottle) from separate venipunctures before antibiotics; in stable suspected subacute IE, withhold empirical therapy to allow uncontaminated cultures.
- **Echocardiography: TTE** misses vegetations <2 mm and is inadequate in ~20%; **TEE** detects vegetations in >90% — a negative TEE with high suspicion warrants repeat in **7–10 days**. **CTA** is superior for pseudoaneurysm/abscess; **FDG-PET/CT** boosts sensitivity for **PVE/TAVR-PVE**, CIED and graft infection — CTA and PET findings now count as **major** criteria.
- Routine TEE is recommended in *S. aureus* bacteraemia because of the high prevalence of underlying IE (8–14%).

Management

Principles: all bacteria in the avascular, metabolically dormant vegetation must be killed → **prolonged, parenteral, bactericidal** therapy; duration is timed from the first negative blood culture. Manage with infectious-disease consultation, especially for *S. aureus*.

Organism	Representative regimen
Penicillin-susceptible streptococci (MIC ≤0.12)	Penicillin G or ceftriaxone 2 g/day × 4 wk (vancomycin if allergic)
Enterococci	Ampicillin + ceftriaxone, or ampicillin/penicillin + gentamicin × 4–6 wk
MSSA, native valve	Nafcillin/oxacillin/flucloxacillin (or cefazolin) × 4–6 wk; gentamicin **not** recommended
MRSA, native valve	Vancomycin or daptomycin (8–10 mg/kg/day) × 4–6 wk
Staphylococcal **PVE**	Vancomycin/antistaphylococcal penicillin + **rifampin** + gentamicin × 6–8 wk
HACEK	Ceftriaxone 2 g/day × 4 wk
Coxiella burnetii	Doxycycline + hydroxychloroquine ≥18 mo (24 mo if prosthetic)

- **Empirical:** acute IE → vancomycin + gentamicin/cefepime (covers MRSA, gram-negatives); subacute NVE → vancomycin + ceftriaxone.
- **Right-sided uncomplicated MSSA** IE may respond to a 2-week course; left-sided staphylococcal IE needs ≥6 weeks.

- **Rifampin** is essential in staphylococcal PVE (kills biofilm-embedded organisms) but is added only after bacteraemia clears, to avoid resistance.
- **CIED-IE:** antibiotics are **adjunctive to complete device removal** (percutaneous lead extraction preferred).
- **Anticoagulation:** neither anticoagulant nor antiplatelet therapy prevents emboli and both risk haemorrhagic transformation; reserve for independent indications (mechanical valve, AF) and reverse after acute stroke/haemorrhage.

Surgical indications (Table 133-6): moderate–severe CHF from valve dysfunction (commonest); paravalvular extension (abscess, fistula, heart block); persistent bacteraemia despite 7–10 days of therapy; lack of effective therapy (fungal, *Brucella*, multidrug-resistant gram-negatives); unstable dehisced prosthesis; large (**>10 mm**) hypermobile vegetation with prior embolus and valve dysfunction; very large (**>30 mm**) vegetation. Surgery for NVE confers a survival benefit of ~27–55%, greatest with the most pressing indications.

Prevention

- Antibiotic prophylaxis is limited to **highest-risk lesions** (Table 133-9): prosthetic valves/material, prior IE, unrepaired cyanotic congenital disease (or repair with residual defect/within 6 months), LVAD/transplant valvulopathy — and **only** before procedures that manipulate gingiva/periapical tissue or perforate oral mucosa.
- **Regimen: amoxicillin 2 g PO** 1 h before procedure (ampicillin/cefazolin/ceftriaxone IV if NPO; doxycycline/azithromycin if penicillin-allergic). The AHA now **advises against clindamycin** (*C. difficile* risk). Good dental hygiene matters more than prophylaxis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Valve vegetation:** cross-section of a valve leaflet — label *vegetation (platelets + fibrin + microorganisms)*, *endothelial injury site*, *underlying NBTE*, *regurgitant jet*, *paravalvular abscess*, *embolus shedding into bloodstream*.
- **Peripheral stigmata figure:** label *Osler nodes (painful, finger pulps)*, *Janeway lesions (painless, palms/soles)*, *splinter/subungual haemorrhages*, *Roth spots (retina)*, *petechiae (conjunctiva/palate)*, *clubbing*, *splenomegaly*.

Clinical / Diagnostic significance

- A new or changing regurgitant murmur with fever, or fever plus an IE-associated organism on blood culture, mandates echocardiography and the Duke-ISCVID work-up.
- *S. aureus* bacteraemia without an obvious focus is presumptive IE/CIED-IE until echocardiography proves otherwise.
- *S. gallolyticus* IE warrants **colonoscopy** to exclude colonic neoplasia.
- Persistent fever beyond 7 days on appropriate therapy demands a search for paravalvular/extracardiac abscess or embolic complication.
- Overall survival in developed countries is 80–85%; worse with prosthetic valves, *S. aureus*/resistant pathogens, neurologic complications and early PVE (40–50% mortality).

High-yield exam pointers

- **Vegetation** = platelets + fibrin + microorganisms + scant inflammatory cells; deep organisms are dormant → need prolonged bactericidal therapy.
- ***S. aureus* is now the commonest cause** of IE overall; viridans streptococci classically cause subacute NVE.
- **HACEK** = *Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*.
- **Osler nodes** = painful (immune); **Janeway lesions** = painless (septic emboli); **Roth spots** = retinal.
- Diagnosis by **2023 Duke-ISCVID criteria**: definite = 2 major / 1 major + 3 minor / 5 minor; CTA and FDG-PET/CT now count as major.
- **TEE** sensitivity >90% (vs TTE ~55–65%); repeat in 7–10 days if negative but suspicion high.
- PWID → **tricuspid** valve, *S. aureus* (often MRSA), septic pulmonary emboli.
- Staphylococcal **PVE** triple therapy includes **rifampin** (biofilm) + gentamicin.
- Prophylaxis only for high-risk lesions before dental/oral-mucosal procedures: **amoxicillin 2 g**; clindamycin no longer advised.
- Commonest surgical indication = **refractory heart failure** from valve dysfunction.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Infective Endocarditis" (microbiology, pathogenesis/NBTE-MSCRAMMs, 2023 Duke-ISCVID criteria, organism-specific regimens, surgical indications and timing, prophylaxis tables).
- CMDT 2026 — "Infective Endocarditis" (Bacterial & Chlamydial Infections): clinical findings, 2023 Duke-ISCVID summary, empirical and organism-specific treatment, role of surgery and anticoagulation.

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Lepra reactions

Asked in: Paper II May 2022 · Paper IV Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Lepra (leprosy) reactions* are acute, immunologically mediated inflammatory episodes that interrupt the otherwise chronic, stable course of leprosy and may occur **before, during, or after** multidrug therapy (MDT). They are *medical emergencies* because they cause acute neuritis and nerve-function impairment; if not diagnosed and treated early they lead to permanent deformity, disability, and blindness. Two principal types are recognised — **Type 1 reaction (T1R / reversal reaction)**, a delayed (cell-mediated) hypersensitivity event, and **Type 2 reaction (T2R / erythema nodosum leprosum, ENL)**, an immune-complex–mediated event — with *Lucio's phenomenon* as a third, distinct reactional state.

Overview & immunological basis

- Reactions reflect a sudden shift in the host immune response to *Mycobacterium leprae* antigens along the Ridley–Jopling spectrum (TT–BT–BB–BL–LL).
- Immunologic resistance is strongest at the tuberculoid (TT) pole and weakest at the lepromatous (LL) pole; the **unstable borderline groups (BT, BB, BL)** are most prone to reactions.
- Reactions can occur in untreated patients but are commonest after starting MDT; new reactions and nerve damage may appear **up to 3 years after completion** of therapy.
- The two types differ fundamentally in immunopathology — **T1R = Type IV (delayed) hypersensitivity** with upgrading cell-mediated immunity (CMI); **T2R = Type III (immune-complex) hypersensitivity / Arthus phenomenon**.

Type 1 Lepra Reaction (T1R / Reversal Reaction)

- A **delayed hypersensitivity reaction** associated with a *sudden alteration of CMI status* and a shift in the patient's position on the leprosy spectrum.
- Histologically marked by infiltration of lesions by **activated CD4+ T lymphocytes (especially T helper cells)**.
- Termed a "**reversal reaction**" because of the *upgrading* of CMI status; usually seen in the **borderline** portion of the spectrum (BT especially susceptible).
- **Skin:** existing lesions undergo *acute swelling and redness* (erythema and oedema of pre-existing patches/plaques), which may ulcerate.
- **Nerves:** painful, tender nerve trunks (*neuritis*) with consequent nerve damage and disfigurement; in severe T1R, **nerve abscesses** may form.
- "**Silent neuritis**" ("quiet nerve paralysis"): progressive sensory and/or motor impairment of hands, feet, and face *without* the usual inflammatory signs — easily missed, hence routine nerve assessment is essential.
- Less common features: arthralgia/arthritis; rarely fever, malaise, tenosynovitis, and oedema of the feet and hands.

Type 2 Lepra Reaction (T2R / Erythema Nodosum Leprosum)

- An **immune-complex–mediated syndrome** (antigen–antibody reaction involving complement) causing inflammation of skin, nerves, and other organs with systemic malaise — a **Type III hypersensitivity reaction (Coombs & Gell) / Arthus phenomenon**.
- Occurs in the **multibacillary (BL and LL)** end of the spectrum, mostly during MDT but also in untreated patients.
- **Skin:** crops of evanescent, *pink-to-red, tender, warm* maculopapular/papular/nodular or plaque lesions on the **outer aspects of thighs, legs, and face**; lesions blanch with light finger pressure and last a few days, changing colour pink/red → bluish/brownish (24–48 h) → dark over a week.
- Severe forms become vesicular, pustular, bullous, or necrotic and ulcerate — **erythema nodosum necroticans**.
- **Systemic / multi-organ involvement:** fever and constitutional symptoms, lymph-node enlargement, myositis, arthritis, synovitis, rhinitis, epistaxis, laryngitis, iridocyclitis and glaucoma, painful dactylitis, acute epididymo-orchitis, nephritis and renal failure, hepatosplenomegaly, anaemia, and — at a late stage — **amyloidosis**.
- **Severe T2R** includes swollen, painful, tender nerve trunks with sensory and motor deficits (i.e. it too causes neuritis).

Lucio's Phenomenon

- A distinct reactional state seen in **diffuse leprosy of Lucio and Latapí** (*"lepra bonita"*), occurring chiefly in Mexico and Central America; may be a variant of erythema nodosum necroticans.
- Pathology: **marked vasculitis with thrombosis** of superficial and deep dermal vessels → cutaneous haemorrhage and infarction.
- Lesions: slightly indurated, bluish-red, ill-defined, painful, rarely palpable plaques with an erythematous halo, usually on one limb; irregular/triangular shape, becoming purplish centrally with a *central haemorrhagic infarct* ± blister and an easily detached **necrotic eschar**, leaving an irregular ulcer that heals with a superficial scar.
- Patients remain **afebrile** throughout.

Comparison: Type 1 vs Type 2 reactions

Feature	Type 1 (Reversal)	Type 2 (ENL)
Immunology	Type IV / delayed (cell-mediated) hypersensitivity	Type III / immune-complex (Arthus)
Mechanism	Upgrading of CMI; CD4+ T-cell infiltration	Antigen–antibody complexes + complement
Spectrum affected	Borderline (BT, BB, BL)	Multibacillary (BL, LL)
Skin lesions	Acute erythema & swelling of *existing* lesions	*New* crops of tender erythematous nodules
Systemic upset	Usually mild	Prominent — fever, malaise, multi-organ
Neuritis	Common and often severe	Occurs, mainly in severe T2R

Feature	Type 1 (Reversal)	Type 2 (ENL)
Drug of choice	Oral prednisolone (glucocorticoid)	Thalidomide / high-dose prednisolone

Treatment of lepra reactions

- **General:** identify and treat early; assess nerve function; reassure regarding non-contagiousness; continue MDT through the reaction.
- **Type 1 reaction:** oral short-acting **glucocorticoids** are the treatment of choice — **prednisolone 1 mg/kg/day once daily (max 60–80 mg)**; WHO programmes commonly use an initial dose of **40 mg**, tapered slowly by **5 mg every 2 weeks over ~20 weeks** (better outcomes and lower relapse than the older 12-week regimen). Review every 2 weeks with nerve assessment; reactions often flare again as the dose falls to <10–20 mg.
- **Type 2 reaction (ENL):**
  - *Mild, first episode (localised nodules):* aspirin and **pentoxifylline**.
  - *Rapid control:* **thalidomide** is the most effective drug (rapidly suppresses skin signs, neuritis, and iritis); **100–200 mg once or twice daily**, tapered and stopped after 1–2 weeks in acute first episodes; maintenance **50 mg/day** for severe recurrent ENL. *Strictly contraindicated in pregnancy* (teratogenic) — use only in women of child-bearing age after counselling, a negative pregnancy test, and strict contraception.
  - *Where thalidomide is restricted:* **high-dose oral prednisolone**, quickly tapered over 2–3 weeks to zero or a low maintenance dose; ENL is usually transient (resolving in ~2 weeks).
  - *Recurrent ENL:* **high-dose clofazimine** — 300 mg/day for 1 month → 200 mg/day for 1 month → 100 mg/day maintenance (maximal effect takes several weeks; GI side-effects and skin discolouration with prolonged use).
- **Silent neuropathy / neuritis without skin signs:** managed as for T1R — **high-dose prednisolone** is the drug of choice; nerve-decompression surgery is of unproven benefit (no RCT evidence).
- **Nerve-recovery prognosis:** good if steroids are started soon after onset of nerve-function impairment; some recovery possible up to 6 months, but impairment persisting >6 months rarely benefits from steroids.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Ridley–Jopling spectrum bar** (left = TT, right = LL): label *TT – BT – BB – BL – LL*; mark a bracket over **BT–BB–BL** as "Type 1 (reversal) reaction zone" and a bracket over **BL–LL** as "Type 2 (ENL) reaction zone"; annotate "high CMI / paucibacillary" at the TT end and "low CMI / multibacillary" at the LL end.
- **Comparison schematic of skin lesions:** (a) T1R — *existing* plaque becoming red and swollen; (b) T2R — *new* crop of tender erythematous nodules on the leg. Labels: "Type IV hypersensitivity (T1R)", "Type III / immune complex (T2R)", "neuritis – tender thickened nerve".

Clinical / Diagnostic significance

- Reactions are the *leading cause of nerve damage and disability* in leprosy; recognition prevents permanent deformity and blindness.
- **Neuritis** (tender, thickened nerve trunks with sensory/motor loss) is the key emergency component of both reactions — palpate the **greater auricular, ulnar, radial, radial cutaneous, median, lateral popliteal, posterior tibial, sural, and superficial peroneal nerves** at every visit.
- Eye involvement in T2R (iridocyclitis, glaucoma) is sight-threatening and demands urgent treatment.
- Differentiate ENL nodules from the lesions of T1R, cellulitis, and vasculitis; necrotic ulcerating lesions raise the possibility of erythema nodosum necroticans or Lucio's phenomenon.
- Monitor for steroid- and thalidomide-related toxicity; counsel rigorously on thalidomide teratogenicity.

High-yield exam pointers

- **T1R = reversal reaction = Type IV (delayed/CMI) hypersensitivity**, borderline spectrum, *upgrading* CMI, CD4+ T-cell infiltration.
- **T2R = ENL = Type III (immune-complex/Arthus) hypersensitivity**, BL/LL spectrum, *new* tender nodules + systemic features.
- T1R inflames *pre-existing* lesions; ENL produces *new* crops of nodules.
- **Prednisolone 1 mg/kg/day** is first-line for T1R; **thalidomide 100–200 mg/day** is the most effective drug for ENL (teratogenic — pregnancy contraindicated).
- **Silent neuritis** = progressive nerve impairment without inflammatory signs — treat as T1R with steroids.
- **Lucio's phenomenon** = vasculitis/thrombosis with cutaneous infarction in diffuse (Lucio–Latapí) leprosy; patient afebrile.
- Reactions can occur **before, during, or after MDT**, up to **3 years** after completing treatment — MDT is continued during a reaction.
- Erythema nodosum necroticans = necrotic/ulcerating severe ENL; late ENL complication = **amyloidosis**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 184 "Leprosy" (sections: *Leprosy Reactions*; *Treatment of Leprosy Reactions*; *Treatment and Prognosis of Nerve Function Impairment*; *Ridley–Jopling Classification*). Coverage note: the chapter fully supports both reaction types, Lucio's phenomenon, and management; the explicit "Type IV" and "multibacillary BL/LL" labels for T1R/T2R respectively are standard textbook immunology consistent with the chapter's description (delayed CMI for T1R; immune-complex/Type III for T2R).

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Leptospirosis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Leptospirosis is a globally important **zoonotic** spirochaetal infection caused by pathogenic *Leptospira* species, transmitted to humans chiefly through contact with water, soil or animal tissue contaminated by the urine of infected reservoir hosts (especially rats). It produces a wide clinical spectrum from asymptomatic/anicteric febrile illness to fulminant multi-organ disease; the classic severe form — the triad of **jaundice, acute kidney injury and haemorrhage** — is termed **Weil's syndrome**. Severe pulmonary haemorrhage is an increasingly recognised, highly lethal presentation. An estimated ~1 million severe cases occur annually with a mean case-fatality of nearly 10%.

Aetiologic agent & microbiology

- *Leptospira* are spirochaetes of order **Spirochaetales**, family **Leptospiraceae**. Traditional dichotomy: pathogenic *L. interrogans* (sensu lato) and free-living *L. biflexa* (sensu lato).
- Modern phylogenetic (core-genome) analysis defines **64 species — 17 pathogenic, 21 intermediate, 26 non-pathogenic (saprophytic)**.
- For clinical/epidemiologic purposes, **serologic** classification is used: pathogenic leptospires are divided into **>260 serovars** arranged in **26 serogroups** by antigenic (LPS) composition.
- Morphology: coiled, thin, highly motile organisms with **hooked ends** and **two periplasmic (axial) flagella**; **6–20 µm long, ~0.1 µm diameter**. Stain poorly — visualised by **dark-field microscopy** and **silver impregnation** of tissue.
- Fastidious: require special media and **weeks to months** to grow in culture. Double-membrane cell wall rich in lipoproteins; **LPS has relatively low endotoxic potency**, yet protective humoral immunity is **serovar-specific anti-LPS antibody**.

Epidemiology & transmission

- Worldwide distribution; greatest in **tropics/subtropics** (warm, humid climate, poor sanitation favour survival). Most cases in **men**, peaking in **summer–autumn** (temperate) and the **rainy/monsoon season** (tropics).
- **Reservoir:** almost all mammals; **rodents — especially rats — are the most important**. Leptospires colonise the host renal tubule symbiotically and are shed in urine for years.

- Characteristic **serovar–host associations:** *Icterohaemorrhagiae* and *Copenhageni* — rats; *Grippotyphosa* — voles; *Hardjo* — cattle; *Canicola* — dogs; *Pomona* — pigs.
- **Transmission:** direct contact with infected animal urine/blood/tissue, or (more commonly) environmental exposure — **water is the key vehicle** (leptospires survive months in moist conditions). Outbreaks follow **floods**, recreational freshwater activity (triathlons, rafting, mud-runs), and sporting events.
- **High-risk occupations:** veterinarians, agricultural/rice-field workers, sewage and abattoir workers, fishing-industry workers; also urban slum/unhoused populations exposed to rat urine. Also a recognised **traveller's disease**.

Pathogenesis

- **Portal of entry:** cuts, abraded skin, or mucous membranes (conjunctival, oral).
- **Leptospiraemic phase:** highly motile organisms proliferate, cross tissue barriers and **disseminate haematogenously to all organs**, evading complement-mediated killing and phagocytosis. An exaggerated **pro-inflammatory** response correlates with mortality.
- **Immune phase:** appearance of antibody coincides with clearance from blood, but organisms persist in **kidney, liver, lung, heart and brain**; leptospires are then shed in **urine**.
- **Kidney:** acute tubular damage + **interstitial nephritis** → interstitial oedema and acute tubular necrosis; dysregulated tubular transporters cause impaired Na^+ absorption, **K^+ wasting and polyuria** (non-oliguric hypokalaemic renal failure).
- **Liver:** focal hepatocellular necrosis (widespread necrosis unusual), inflammation, disruption of intercellular junctions and **bile-canalicular plugging/leakage** → jaundice with relatively preserved synthetic function.
- **Haemorrhage:** widespread petechiae/haemorrhages; **thrombocytopenia** (platelet consumption), consumptive coagulopathy/**DIC**, and **endothelial-cell activation** (raised soluble E-selectin, von Willebrand factor) increasing vascular permeability — histology shows endothelial swelling **without overt vasculitis or necrosis**.

Clinical features — biphasic course

- **Incubation:** usually 1–2 weeks (range **2–30 days**). Disease is classically **biphasic**: an acute **leptospiraemic phase** (fever 3–10 days, organism culturable/PCR-positive in blood) followed by an **immune phase** (antibodies appear, leptospires shed in urine). Severe disease may be **monophasic and fulminant**.

Feature	Mild (anicteric) leptospirosis	Severe (icteric) leptospirosis — Weil's syndrome
Frequency	~99% of infections; often unrecognised	~1% of infections
Onset	Abrupt flu-like illness	May be indistinguishable initially, then rapidly progressive
Hallmarks	Fever, chills, intense **frontal/retro-orbital headache** (dengue-like), **conjunctival suffusion**, **myalgia of calves/back/abdomen**, nausea/vomiting	**Triad — jaundice + acute kidney injury + haemorrhage**; pulmonary haemorrhage; hypotension/shock

Feature	Mild (anicteric) leptospirosis	Severe (icteric) leptospirosis — Weil's syndrome
CNS	**Aseptic meningitis** (commoner in children); usually benign	Altered sensorium, leptospiral meningitis
Course/ mortality	Self-limited over 7–10 (4–30) days; low mortality	Case-fatality **5–40%** (CMDT); multi-organ failure

- **Conjunctival suffusion** (redness without exudate) and severe **calf myalgia** are characteristic clues.
- **Pulmonary haemorrhage** (cough, chest pain, respiratory distress, haemoptysis ± jaundice) is a major, often lethal presentation and may not be apparent until intubation.
- **Jaundice** occurs in **5–10%**; can be deep/orange-tinged but rarely reflects fulminant hepatic necrosis; tender hepatomegaly.
- **AKI** common — oliguric or non-oliguric; **hypokalaemia, hyponatraemia, and urinary magnesium loss** (uniquely associated with leptospiral nephropathy). Dialysis can be life-saving; renal recovery is the rule in survivors.
- **Other:** myocarditis with non-specific ST–T changes/arrhythmias (poor prognostic sign), pancreatitis (raised amylase), rhabdomyolysis (raised CK), and late **autoimmune uveitis** (chronic sequela).
- **Poor prognostic factors:** age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.

Investigations & diagnosis

- **Supportive non-specific findings:** leukocytosis with left shift, raised CRP/procalcitonin/ESR; **thrombocytopenia (platelets ≤100 × 10^9/L)** correlating with bleeding and renal failure; raised bilirubin with only **moderate** aminotransferase/ALP rise; **elevated serum CK** (helps distinguish from viral hepatitis, where CK is normal); coagulation markers of DIC in pulmonary haemorrhage (↑PT/PTT/D-dimer, ↓fibrinogen).
- **Non-oliguric hypokalaemic renal insufficiency** is characteristic of early disease; urine shows leukocytes, erythrocytes, casts, mild proteinuria.
- **CSF (if meningitic):** pleocytosis (few to >1000 cells/μL), early polymorphonuclear then lymphocytic predominance; protein normal/mildly raised, glucose normal.
- **Definitive diagnosis** — isolation of the organism, positive PCR, seroconversion, or a rising titre:
  - **Microscopic agglutination test (MAT)** — reference standard (live antigen panel); a single titre of **1:200–1:800** with strong clinical evidence, or preferably a **≥4-fold rise** between acute and convalescent sera. Identifies presumptive serogroup.
  - **ELISA** — broadly reacting antigen; plus commercial **rapid lateral-flow/agglutination** tests for resource-limited settings.
  - Antibodies usually undetectable until the **second week**; serology is insensitive in the first ~5 days.
  - **PCR (real-time)** — confirms diagnosis during the **first 5 days** of illness, detecting leptospiral DNA in blood, urine, CSF and aqueous humour — its key advantage over serology.

- **Imaging:** chest radiograph shows **patchy bilateral alveolar infiltrates** (alveolar haemorrhage, lower-lobe predominant), pleural-based densities, or ARDS-pattern ground-glass.

Differential diagnosis

- **Febrile/myalgic phase:** influenza, SARS-CoV-2, **dengue, chikungunya**, malaria, **typhoid**, scrub typhus/rickettsioses, viral hepatitis, acute HIV.
- **Haemorrhagic/renal presentation:** dengue haemorrhagic fever, **hantavirus** (HFRS/HCPS), yellow fever, and other viral haemorrhagic fevers. Co-infection (e.g. with dengue/rickettsiae) occurs — test for these when leptospirosis is suspected.

Treatment

- **General principle:** start antibiotics **early** (especially in severe disease, as soon as the diagnosis is *considered*) — benefit diminishes once organ damage is established. Leptospires are susceptible to β-lactams, cephalosporins, aminoglycosides and macrolides, but **not** to vancomycin, rifampicin, metronidazole or chloramphenicol. Resistance has not been reported.

Indication	Regimen (7 days)
Mild	Doxycycline 100 mg PO bid **or** Amoxicillin 500 mg PO tid **or** Ampicillin 500 mg PO tid (azithromycin 500 mg OD ×3 days an alternative; doxycycline/azithromycin preferred where rickettsioses co-endemic)
Moderate/severe	**Penicillin G 1.5 million units IV/IM q6h or** Ceftriaxone 2 g/day IV **or** Cefotaxime 1 g IV q6h **or** Doxycycline 200 mg IV load then 100 mg IV q12h
Chemoprophylaxis	Doxycycline 200 mg PO once weekly **or** Azithromycin 250 mg PO once/twice weekly

- Randomised trials show **no significant difference** between penicillin, ceftriaxone, cefotaxime and doxycycline for severe disease (a 2024 meta-analysis found no clear survival benefit for any single antibiotic).
- **Supportive care is essential and can be life-saving:** aggressive fluid/electrolyte resuscitation in non-oliguric renal dysfunction; **early haemodialysis/peritoneal dialysis** for oliguric renal failure (reduces mortality, usually needed only briefly); **lung-protective low-tidal-volume ventilation** for pulmonary haemorrhage/ARDS. Evidence for **glucocorticoids and desmopressin** in pulmonary involvement is contradictory.
- A **Jarisch–Herxheimer reaction** may occur within hours of starting therapy.

Prevention

- Avoid exposure to contaminated water/soil and animal urine/tissue; use protective **footwear, eyewear and clothing**; targeted **rodent control**.
- **Pre-/post-exposure doxycycline** for well-defined short-term exposure (e.g. monsoon flooding) — efficacy disputed; a 2024 meta-analysis did not show reduced infection or mortality.
- **Vaccines:** animal (veterinary) bacterin vaccines must match local serovars; human bacterin vaccines (Japan, China, Cuba, France) give short-term serovar-specific immunity with significant side effects and limited availability.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Biphasic natural history (timeline):** x-axis weeks 1–4 then months–years. Mark **Incubation period (2–30 days)** → **Acute/leptospiraemic phase (fever; *Leptospira* in blood & CSF)** → **Immune/convalescent phase (antibody rise; *Leptospira* in urine; uveitis, interstitial nephritis)**. Overlay curves for **leptospiraemia**, **antibody titre (MAT)**, and specimen windows for **blood culture/PCR** (early) vs **urine PCR/culture** and **serology** (late). Labels: *Leptospiraemia, Leptospiruria & immunity, Fever, Antibody titre*.
- **Weil's syndrome triad (Venn/triangle):** three overlapping circles labelled **Jaundice (liver)**, **Acute kidney injury (kidney)**, **Haemorrhage (pulmonary/GI/skin)** with central label **Weil's syndrome**.

Clinical / Diagnostic significance

- Suspect leptospirosis in any **febrile illness with myalgia, conjunctival suffusion and an exposure history** (flood/freshwater/occupational/animal contact), particularly post-monsoon in endemic India.
- The combination of **jaundice + AKI + thrombocytopenia/haemorrhage** with only modestly raised transaminases but **high CK** strongly favours leptospirosis over viral hepatitis.
- **Non-oliguric hypokalaemic AKI** and **urinary magnesium loss** are near-pathognomonic renal clues.
- Use **PCR in the first 5 days** and **paired MAT serology** thereafter — do not withhold empirical antibiotics awaiting serology.

High-yield exam pointers

- Cause: *Leptospira interrogans* (sensu lato); **>260 serovars in 26 serogroups**; hooked-ended motile spirochaete seen on **dark-field**.
- Main reservoir = **rats**; serovar *Icterohaemorrhagiae/Copenhageni* causes severe disease; **water-borne**, monsoon/flood-associated.
- **Weil's syndrome = jaundice + AKI + haemorrhage**; **pulmonary haemorrhage** is a leading cause of death.
- **Conjunctival suffusion + calf myalgia** = classic bedside clues; headache is **frontal/retro-orbital** (dengue-like).
- Diagnosis: **MAT** (≥4-fold rise / titre 1:200–1:800) is reference; **PCR** best in first 5 days; antibodies appear in **week 2**.
- Renal hallmark: **non-oliguric hypokalaemic** renal insufficiency; **CK elevated** (normal in viral hepatitis).
- Treatment: **IV penicillin / ceftriaxone / cefotaxime** (severe) or **oral doxycycline/amoxicillin/azithromycin** (mild) ×7 days; early **dialysis** and **lung-protective ventilation** are life-saving.
- Prophylaxis: **doxycycline 200 mg weekly** for short-term high-risk exposure (efficacy disputed). Watch for **Jarisch–Herxheimer** reaction.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Leptospirosis" (Goeijenbier & Wagenaar) — aetiology, pathogenesis, clinical syndromes, diagnosis, Table 189-1 treatment/chemoprophylaxis.
- CMDT 2026 — "Spirochetal Infections: Leptospirosis" — anicteric vs icteric (Weil syndrome) classification, laboratory criteria, current drug regimens, 2024 meta-analyses on antibiotic and prophylaxis efficacy.

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Mechanisms of antibiotic drug resistance

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Resistance* is the reduction in or loss of an antibacterial agent's effect on a bacterium, and the bacterial properties or alterations that produce this reduced activity are termed *resistance mechanisms*. It is quantified in the laboratory by the **minimal inhibitory concentration (MIC)** — the lowest drug concentration that inhibits growth under standardised conditions — which, compared against regulatory **breakpoints**, classifies an isolate as susceptible, intermediate, or resistant. Resistance may be **intrinsic** (a natural property of the species) or **acquired** (via mutation or gene transfer), and bacteria frequently carry combinations of mechanisms conferring **multidrug resistance (MDR)**.

Genetic basis — how resistance arises and spreads

- **Chromosomal mutation** — spontaneous point mutations during DNA replication, selected under antibiotic pressure (e.g. *rpoB* for rifampin, *gyrA*/*parC* for quinolones, ribosomal mutations).
- **Acquisition of new genes by horizontal transfer** — usually on self-replicating **plasmids** or other mobile elements (**transposons**, gene cassettes) carrying one or several resistance genes, so a single plasmid can confer multidrug resistance.
- **Transformation** — uptake of fragments of environmental DNA from related species and direct recombination into the chromosome; important in *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* (generates **mosaic PBP** genes).
- **Origin and selection** — many resistance genes originated in antibiotic-**producer** organisms (self-protection) and were later mobilised onto plasmids; antimicrobial exposure in humans, animals and the environment then **selects** resistant strains. Initial fitness costs are often offset over time by **compensatory mutations**, allowing resistant strains to persist even without ongoing drug pressure.

The three broad mechanistic categories

All resistance mechanisms fall into three groups (Harrison, Table 150-1; Fig. 150-1):

Category	Strategy	Representative examples
1. Altered / bypassed target	Modify or substitute the drug's binding site so binding falls	Altered PBPs (MRSA *mecA*/PBP2a, mosaic PBPs); d-Ala-d-Lac in VRE; *gyrA*/*parC* mutations; *rpoB*; ribosomal methylation; bypass DHFR/DHPS
2. Altered access to target	Reduce uptake (porin loss) or increase active **efflux**	Loss of OprD/porins (carbapenems); MexXY, broad-spectrum multidrug efflux pumps
3. Drug inactivation / modification	Enzymatically destroy or chemically modify the drug	β-lactamases (ESBL, AmpC, carbapenemases); aminoglycoside-modifying transferases; chloramphenicol acetyltransferase

Mechanism by drug class

- **β-Lactams (penicillins, cephalosporins, monobactams, carbapenems):** Three routes — (a) **β-lactamase** degradation of the β-lactam ring (commonest in gram-negatives, concentrated in the periplasmic space); (b) **altered PBP targets**; (c) **reduced porin diffusion**. β-Lactamase classes: *plasmid* enzymes inactivating penicillins/early cephalosporins; **extended-spectrum β-lactamases (ESBLs)** that also degrade ceftriaxone, cefotaxime, ceftazidime, aztreonam (some also cefepime); **AmpC** (chromosomal in *Enterobacter*; inducible/derepressed, degrades most cephalosporins except cefoxitin/cefepime); and **carbapenemases** that destroy nearly all β-lactams — *Klebsiella pneumoniae* carbapenemase (**KPC**), **New Delhi metallo-β-lactamase (NDM**, originally Indian subcontinent), and **OXA-48**. PBP-mediated resistance: **mosaic PBPs** (penicillin-resistant pneumococcus, gonococcus, meningococcus) and **PBP2a** encoded by *mec* in **MRSA** (a bypass transpeptidase of low affinity; only **ceftaroline** binds PBP2a). β-Lactamase **inhibitors** — clavulanate, sulbactam, tazobactam, avibactam, vaborbactam, relebactam, durlobactam — restore activity; only *avibactam, vaborbactam, relebactam* inhibit AmpC and KPC-type carbapenemases (but **not** metallo-enzymes such as NDM).
- **Glycopeptides (vancomycin, teicoplanin):** Acquisition of **van** gene cassettes in enterococci (**VRE**) replaces the terminal d-Ala-**d-Ala** of the peptidoglycan stem peptide with d-Ala-**d-Lac**, which vancomycin binds with **1000-fold lower affinity**; *van* genes are transposon/plasmid-borne and have rarely transferred to *S. aureus* (true VRSA). **VISA** (intermediate resistance) arises instead from stepwise chromosomal mutations producing a thickened, poorly cross-linked cell wall that traps vancomycin at decoy d-Ala-d-Ala termini away from the synthesis site.
- **Aminoglycosides (gentamicin, tobramycin, amikacin, plazomicin):** Mainly plasmid-encoded **aminoglycoside-modifying enzymes** adding acetyl, adenyl or phosphate groups (amikacin/plazomicin spared by most); **16S rRNA methylases** confer resistance to *all* aminoglycosides including plazomicin; ribosomal-protein mutation (streptomycin); MexXY **efflux** in *Pseudomonas*.
- **Tetracyclines & glycylcyclines:** Plasmid-mediated **active efflux** and **ribosomal protection proteins** (*TetM/TetO*). Newer agents (tigecycline, eravacycline, omadacycline) evade common mechanisms but can be lost to broad-spectrum efflux overexpression.
- **Macrolides/lincosamides/streptogramins (MLS):** Acquired **Erm methylases** modify the 23S rRNA binding site (the **MLSB** phenotype, inducible or constitutive); plus **efflux** pumps and, for

streptogramins/chloramphenicol, drug-modifying enzymes. 23S rRNA mutational resistance is commoner in organisms with few rRNA gene copies (mycobacteria, *H. pylori*, *Treponema*).

- **Oxazolidinones (linezolid, tedizolid):** 23S rRNA mutations (more in enterococci) and the plasmid **Cfr methylase** (cross-resistance with chloramphenicol/lefamulin).
- **Quinolones:** Chromosomal **target mutations** in DNA gyrase and topoisomerase IV; **efflux** overexpression; and acquired plasmid genes — *qnr* (target protection), *aac(6')-Ib-cr* (modifies ciprofloxacin/norfloxacin), and efflux determinants — that also enrich for higher-level resistance and link to multidrug-resistance plasmids.
- **Rifamycins (rifampin, rifabutin, rifapentine):** A **single mutation in the β subunit of RNA polymerase (*rpoB*)** gives high-level resistance — hence rifamycins are always used in **combination**.
- **Sulfonamides & trimethoprim:** Plasmid-acquired **resistant DHPS** and **resistant DHFR** that *bypass* inhibition of the native enzymes; resistance to co-trimoxazole needs both.
- **Polymyxins (colistin, polymyxin B):** Mutations reducing the **negative charge of LPS**, and the transferable plasmid **mcr-1** (and variants) encoding a phosphoethanolamine transferase that masks the LPS target.
- **Daptomycin / metronidazole / nitrofurantoin:** Daptomycin — multigene mutations altering membrane charge; metronidazole — loss of activating nitroreductase / *nim* genes; nitrofurantoin — stepwise loss of nitroreductase activity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Gram-negative bacterium showing antibiotic targets and resistance mechanisms"** (after Harrison Fig. 150-1). Draw the cell with **outer membrane + porin**, **periplasmic space**, **inner membrane**, **ribosome**, **DNA**, and a **resistance plasmid**. Label: *Loss of porins → carbapenem resistance*; *β-lactamases in periplasmic space*; *Overexpressed transmembrane efflux pump (β-lactams, quinolones, aminoglycosides, tetracyclines, chloramphenicol)*; *Altered iron-uptake pathway (cefiderocol)*; *Bypass targets — trimethoprim (DHFR), sulfonamides (DHPS)*; *Antibiotic-modifying enzymes (aminoglycosides, ciprofloxacin)*; *Ribosomal mutation/methylation (tetracyclines, oxazolidinones, aminoglycosides)*; *Target mutations (DNA gyrase, topoisomerase IV)*; *LPS modification (polymyxins)*.
- **Simple flow box:** *Three categories of resistance* — (1) Altered/bypassed target → (2) Reduced uptake / increased efflux → (3) Drug inactivation — each with one example arrow.

Clinical / Diagnostic significance

- **Laboratory detection:** MIC by broth/agar microdilution, disk diffusion, or **E-test** (gradient strip) interpreted against breakpoints; phenotypic tests for ESBL, AmpC and carbapenemase; molecular detection of *mecA*, *vanA/B*, KPC/NDM/OXA, *mcr*.
- **Empiric vs definitive therapy:** Because prevalence varies by geography and institution, empirical choice should follow the **local antibiogram**; therapy must then be **de-escalated** to the *narrowest-spectrum* agent for the *shortest effective duration* once susceptibilities return.

- **Apparent treatment failure** despite "susceptible" report — consider undrained pus/foreign body, poor drug penetration (CNS, intracellular sites), superinfection, emergence of resistance on therapy, polymicrobial infection, impaired host defences, or non-infective causes (drug fever).
- **Salvage agents for MDR gram-negatives:** ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, **cefiderocol** (siderophore cephalosporin taken up via iron transport, stable to many β-lactamases including carbapenemases), and polymyxins.
- **Combination therapy** is used for synergy and to *prevent emergence of resistance* (classically rifampin, antitubercular regimens), not merely for broad coverage.

High-yield exam pointers

- Three mechanistic categories: **target alteration/bypass, reduced access (porin loss/efflux), drug inactivation**.
- **MRSA = mecA → PBP2a** (bypass transpeptidase); **ceftaroline** is the anti-MRSA β-lactam.
- **VRE = van genes → d-Ala-d-Lac** (1000× lower vancomycin affinity); **VISA = thickened cell wall**, not van.
- **ESBL** spares carbapenems; **carbapenemases = KPC, NDM, OXA-48**; avibactam/vaborbactam/relebactam cover KPC but **not NDM** (metallo-).
- **Rifampin resistance = single *rpoB* mutation** → never use as monotherapy.
- **Quinolone resistance** = gyrA/parC mutations + efflux + plasmid *qnr* / *aac(6')-Ib-cr*.
- **Colistin resistance = plasmid mcr-1** (phosphoethanolamine transferase on LPS).
- **16S rRNA methylase** defeats *all* aminoglycosides, including plazomicin.
- CDC 2019: **>2.8 million** resistant infections, **~35,900 deaths/year**; **urgent threats** — CRE, carbapenem-resistant *Acinetobacter*, drug-resistant *N. gonorrhoeae*, *C. difficile*, *Candida auris*. Countered by the **five core actions** and a **One Health** approach.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bacterial Resistance to Antimicrobial Agents" (definitions, MIC/breakpoints, genetic basis, the three mechanistic categories, per-class mechanisms, β-lactamase/inhibitor detail, CDC 2019 threats and core actions); and "Treatment and Prophylaxis of Bacterial Infections" (principles of combination therapy and stewardship).
- **CMDT 2026** — "Common Problems in Infectious Diseases & Antimicrobial Therapy" (susceptibility testing/MIC, antibiogram-guided empirical therapy, de-escalation, causes of apparent treatment failure).

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Melioidosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Melioidosis (*Whitmore's disease*) is a potentially fatal infection caused by **Burkholderia pseudomallei**, a gram-negative, facultative intracellular saprophyte of soil and surface water in the tropics. It is geographically restricted chiefly to **Southeast Asia and northern Australia**, with sporadic cases from India, China and other tropical zones. Among the pseudomonads, *B. pseudomallei* is one of the most virulent species: host compromise is **not** a prerequisite for disease, the clinical spectrum runs from asymptomatic infection to fulminant septicaemia, and the organism's capacity for intracellular survival permits prolonged **latency and late reactivation** (the so-called *"Vietnamese time-bomb"*).

Etiology & microbiology

- **Organism**: *Burkholderia pseudomallei* — a non-lactose-fermenting, oxidase-positive, motile gram-negative bacillus of the genus *Burkholderia* (formerly *Pseudomonas*).
- A **facultative intracellular** pathogen that replicates within polymorphonuclear leukocytes (PMNs) and macrophages; survival is aided by a **polysaccharide capsule**.
- A close relative, *B. mallei*, causes **glanders** (an equine zoonosis) — covered in the same chapter and a frequent comparison point (see below).
- **Environmental reservoir**: soil and water; the organism is a *primary pathogen* (unlike opportunistic *P. aeruginosa* and *Stenotrophomonas*). Humans are **never colonised without being infected**.
- A recognised **potential agent of biological warfare**, which has stimulated interest in vaccine development; it is handled as a high-consequence select agent and has caused point-source outbreaks (e.g. contaminated *aromatherapy spray*).

Epidemiology & risk factors

- **Endemic zones**: Southeast Asia (notably Thailand) and tropical northern Australia; occasional cases in India and China. Should be suspected in **returning travellers and military personnel** from endemic regions — symptoms may appear only later because of latency.
- **Routes of acquisition** — three principal portals:
  - *Percutaneous inoculation* through skin abrasions (the commonest route; rice-paddy and soil exposure).
  - *Inhalation* of contaminated aerosols/dust (associated with severe pneumonic and septicaemic disease, e.g. during monsoon/heavy rains).
  - *Ingestion* of contaminated water.
- **Person-to-person transmission is rare.**
- **Predisposing host factors** (present in many, though not all, patients): **diabetes mellitus** (the single most important association), **chronic renal failure**, **alcohol abuse**, and other chronic illness.
- A significant cause of **fatal community-acquired pneumonia and septicaemia** in endemic areas, with reported mortality as high as **44% (Thailand)**.

Pathogenesis

- After inoculation/inhalation, *B. pseudomallei* is taken up by phagocytes but **survives intracellularly**, escaping killing within PMNs and macrophages.
- The **polysaccharide capsule** and a functional **type III secretion system** (which mediates intracellular survival and cell-to-cell spread) are key virulence determinants.
- Intracellular persistence underlies the characteristic **latency** and ability to relapse months to years after primary exposure.
- Infection provokes a **florid inflammatory/granulomatous (abscess-forming) response**; haematogenous dissemination, most often in debilitated hosts, seeds multiple deep organs and produces the highly lethal septicaemic forms.

Clinical manifestations

B. pseudomallei causes a **wide spectrum**, from asymptomatic infection to multifocal abscesses, pneumonia and disseminated septic disease. The major recognised forms:

Clinical form	Key features
Acute pulmonary (commonest diagnosed form)	Ranges from mild illness with **upper-lobe infiltrates** on chest film to **severe necrotizing pneumonia**; high fever, cough
Chronic pulmonary	*Mimics pulmonary tuberculosis* — chronic cough, fever, **haemoptysis, night sweats, cavitary lung disease**
Cutaneous / localised	**Skin ulceration** with associated **lymphangitis and regional lymphadenopathy**
Septicaemic / disseminated	Spread from lung or skin (esp. in debilitated patients) → bacteraemia with **multi-organ abscesses** (liver, spleen, prostate, kidney) and septic shock; **high mortality**
Neurological (CNS) melioidosis	Endemic in South Asia and Australia; encephalomyelitis / brain abscess / meningitis
Latent / reactivation	Quiescent infection reactivating later, often when host defences fall

Diagnosis / investigations

- **Definitive diagnosis is by culture**, which is the gold standard — *B. pseudomallei* isolated from blood, sputum, pus/abscess aspirate, urine or wound swab confirms the disease (isolation from any site is diagnostic, as humans are not colonised).
- The organism is a non-fermenting, **oxidase-positive** gram-negative rod; on Gram stain it classically shows **bipolar ("safety-pin") staining**, and it grows well on selective **Ashdown's agar** (wrinkled colonies). *[microbiology details: standard, see Coverage note]*
- **Imaging** to map deep abscesses: chest radiograph (upper-lobe infiltrates / cavitation), and ultrasound or CT of liver, spleen, prostate and kidneys to detect visceral abscesses; MRI for suspected CNS disease.
- Screen for and assess **underlying diabetes and renal impairment**, which modify prognosis and management.

- **Differential diagnosis**: pulmonary tuberculosis (the chronic cavitary form is a classic mimic), other causes of community-acquired pneumonia, and disseminated pyogenic abscesses.

Treatment

Treatment is prolonged and deliberately divided into **two sequential phases** — an IV *intensive (eradication-initiation)* phase to control sepsis, followed by a long oral *eradication* phase to clear intracellular organisms and **prevent relapse**.

Phase	Regimen (Harrison, Table 170-2)	Duration
Intensive (IV)	**Ceftazidime 2 g IV q6h** *or* **meropenem 1 g IV q8h** *or* **imipenem 500 mg IV q6h**	**≥2 weeks**; *4–8 weeks* (Australian guidelines) for severe infection, osteomyelitis and CNS disease
Eradication (oral)	**Trimethoprim-sulfamethoxazole (TMP-SMX) 1600/320 mg PO q12h**	**≥3 months (12 weeks)**

- The intensive IV phase must be **lengthened** for deep-seated disease (severe sepsis, osteomyelitis, neurological melioidosis), and large abscesses require **drainage** alongside antibiotics.
- The prolonged oral eradication course is essential because intracellular persistence causes **relapse** if treatment is curtailed.
- *B. pseudomallei* is **intrinsically resistant** to many agents (e.g. aminoglycosides, many early penicillins/cephalosporins) — empirical "sepsis" regimens that omit ceftazidime/carbapenems may fail; susceptibility is to advanced penicillins, ceftazidime and carbapenems.
- **Glanders (*B. mallei*)** is treated with the same drugs for the same duration as melioidosis (and is additionally susceptible to the macrolides azithromycin and clarithromycin).

Melioidosis vs glanders (companion comparison)

Feature	Melioidosis (B. pseudomallei)	Glanders (B. mallei)
Reservoir	Environmental — soil & water	**Not environmental**; persists only in **equine** hosts
Acquisition	Inoculation / inhalation / ingestion	Contact with infected horses; respiratory secretions highly infectious; at-risk = horse handlers, equine butchers, veterinarians
Distribution	SE Asia, N Australia, India, China	Africa, Asia, South America (eradicated from Europe/N America)
Capsule	Major virulence factor	Critical virulence determinant
Treatment	Ceftazidime/carbapenem → TMP-SMX	Same as melioidosis (+ azithromycin/clarithromycin susceptible)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis / portals-of-entry schematic**: a central soil-and-water reservoir with three arrows to a human — labels: *Percutaneous inoculation*, *Inhalation*, *Ingestion → B. pseudomallei (facultative intracellular) → uptake & survival in macrophage/PMN (capsule, Type III secretion system)* → branching to *Localised skin ulcer + lymphangitis*, *Acute/chronic pneumonia*, *Haematogenous dissemination → multi-organ abscesses (liver, spleen, prostate, kidney) + septicaemia*, and a dashed loop labelled *Latency / relapse*.
- **Two-phase treatment timeline bar**: Label segment 1 *Intensive IV phase — ceftazidime / meropenem (≥2 wks; 4–8 wks if severe/osteomyelitis/CNS)*; Label segment 2 *Oral eradication phase — TMP-SMX ≥3 months (prevents relapse)*.

Clinical / Diagnostic significance

- Consider melioidosis in any **febrile patient from an endemic area — especially a diabetic** — presenting with community-acquired pneumonia, sepsis, or multifocal abscesses; it is a **great mimic of tuberculosis** and of pyogenic abscess disease.
- **Isolation of the organism from any clinical specimen is diagnostic** — alert the microbiology laboratory, both for biosafety (select agent) and because the organism may be misidentified by automated systems.
- Therapeutic success hinges on choosing the **right drug class** (ceftazidime/carbapenem, not aminoglycosides) and **completing the long eradication course** — incomplete therapy leads to relapse.
- Search systematically for **occult visceral abscesses** (prostate, liver, spleen) and treat underlying **diabetes/renal disease**, as these influence outcome.

High-yield exam pointers

- *Melioidosis* = **Whitmore's disease**, caused by **Burkholderia pseudomallei**, a **facultative intracellular** gram-negative saprophyte of **soil and water**.
- **Endemic in SE Asia (esp. Thailand) and northern Australia**; sporadic in India/China — suspect in returning travellers/soldiers.
- **Diabetes mellitus** is the dominant predisposing factor; renal failure and alcohol abuse also predispose; *host compromise is not essential*.
- Three portals: **inoculation, inhalation, ingestion**; person-to-person spread is rare.
- **Acute pulmonary disease** is the commonest form; **chronic cavitary pneumonia mimics TB**; septicaemic disease carries mortality up to **44%**.
- Virulence: **polysaccharide capsule + type III secretion system** → intracellular survival, **latency and relapse**.
- **Diagnosis = culture (gold standard)**; isolation from any site is significant.
- **Treatment = two phases**: intensive IV **ceftazidime/meropenem ≥2 wks** → oral **TMP-SMX ≥3 months**; drain abscesses; *intrinsically resistant to aminoglycosides*.
- Closely related **B. mallei → glanders** (equine zoonosis); both are **potential bioterrorism (select) agents**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species" (*Burkholderia pseudomallei*/melioidosis and *B. mallei*/glanders sections, incl. Table 170-2 antibiotic regimens); "Acute Meningitis" (CNS melioidosis as a regional cause); and the genomic-epidemiology chapter (point-source *B. pseudomallei* aromatherapy-spray outbreak).
- **CMDT 2026** — antimicrobial-spectrum/treatment tables listing *B. pseudomallei* (melioidosis) and *B. mallei* (glanders).
- *Coverage note*: Harrison covers the etiology, epidemiology, pathogenesis, clinical spectrum and staged treatment of melioidosis well, but does not detail laboratory morphology. The **bipolar "safety-pin" Gram appearance**, growth on **Ashdown's selective agar**, the eponym **Whitmore's disease**, and the **"Vietnamese time-bomb"** latency nickname are universally accepted standard microbiology/clinical facts added for completeness and are not verbatim from the cited chapters.

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Neurocysticercosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Neurocysticercosis (NCC) is the term for involvement of the **brain, spinal cord, or cerebrospinal fluid (CSF)** by the **larval (cysticercus) stage of the pork tapeworm *Taenia solium***. It follows ingestion of *T. solium* eggs, in which humans act as the *intermediate* (dead-end) host. NCC is the **single most important cause of acquired epilepsy** in the developing world and in immigrants from endemic regions, and is highly prevalent in **India, Latin America, sub-Saharan Africa, China and Southeast Asia**. Globally an estimated 20 million people carry cysticerci, ~400,000 develop neurological symptoms and ~50,000 die each year.

Aetiology, life cycle and pathogenesis

- ***T. solium* causes two distinct human infections** — *taeniasis* (adult tapeworm in the gut, acquired by eating undercooked pork containing cysticerci) and *cysticercosis* (tissue larval infection, acquired by ingesting **eggs**). Humans are the **only definitive host**; the **pig is the usual intermediate host**.
- **Route to cysticercosis** — faecal–oral ingestion of eggs from a **human tapeworm carrier**. Eggs are sticky and found under the carrier's fingernails; **autoinfection** can occur (carrier ingests own ova). Hence cysticercosis can occur even in people who never eat pork, including vegetarians, if exposed to a carrier's faeces.
- **Pathogenesis** — Ingested eggs release **oncospheres** that penetrate the intestinal wall and disseminate haematogenously to tissues, preferentially the **CNS, skeletal muscle, subcutaneous tissue and eye**. The oncosphere matures into a fluid-filled **cysticercus** (single invaginated scolex) over ~60–90 days.

- **Worm morphology (helps distinguish from *T. saginata*)** — scolex bears an **armed rostellum with two rows of hooklets** plus four suckers; mature tapeworm up to **3 m** with up to **1000 proglottids**; each gravid proglottid has **8–12 uterine branches** (vs 15–30 in *T. saginata*) and releases ~50,000 immediately-infective eggs.
- **Symptom generation** — clinical effects depend on **location, number, size and viability** of cysts and, critically, on the **host inflammatory response** to a degenerating cyst. A live (vesicular) cyst evades immunity and may stay silent; symptoms typically arise when the larva **degenerates** and provokes oedema and gliosis.

Classification and clinical manifestations

NCC is classified by **anatomical location and parasite viability** (Harrison Fig. 242-1), which dictates presentation and treatment.

Location / form	Key features	Typical clinical picture
Parenchymal (viable cyst)	Round cyst 5–20 mm, often with visible scolex	**Seizures** (commonest); usually benign course
Single enhancing lesion	Solitary degenerating cyst with ring/disc enhancement + perilesional oedema	New-onset focal seizures (classic *Indian* presentation — solitary cysticercus granuloma)
Parenchymal calcification	Old, dead, calcified larva	Recurrent seizures, especially if perilesional oedema/enhancement
Intraventricular	Thin-walled cyst, fluid isodense to CSF	**Obstructive hydrocephalus**, raised ICP, *Bruns' syndrome*
Subarachnoid / basal (racemose)	Grape-like proliferating cysts up to 6 cm, no scolex	Chronic meningitis, **arachnoiditis**, vasculitis/strokes, communicating hydrocephalus — most aggressive form
Spinal / ocular	Cord or subretinal/vitreous cysts	Progressive myelopathy; visual loss

- **Seizures** are the most frequent manifestation — focal, focal with secondary generalisation, or generalised — driven by inflammation of parenchyma surrounding the cyst.
- **Headache** accompanies virtually all CNS forms.
- **Hydrocephalus** results from CSF-flow obstruction by ventricular cysts and/or inflammation, or from **communicating hydrocephalus due to arachnoiditis**; raised-ICP features include headache, vomiting, dizziness, ataxia, papilloedema and visual loss.
- ***Bruns' syndrome*** — intermittent acute hydrocephalus precipitated by **head movement/position change**, the mobile ventricular cyst acting as a **ball valve**.
- **Racemose cysticercosis** — proliferating clusters of cysts at the base of the brain → altered consciousness and death if untreated.
- **Extra-neural disease** — muscle (asymptomatic **cigar-shaped calcifications**), painless **subcutaneous nodules**, and ocular disease (subretinal/vitreous cyst, or ptosis from extra-ocular muscle involvement).

Diagnosis — imaging, serology, CSF and Del Brutto criteria

- **Neuroimaging is the primary diagnostic tool.** A cystic lesion containing an eccentric **mural scolex ("dot-in-hole" appearance)** is pathognomonic. Parenchymal cysts are 5–20 mm and round; subarachnoid cysts may reach 6 cm and be lobulated.
- **CT vs MRI — CT is superior for calcified lesions**; **MRI is superior for small cysts, the scolex, enhancement, and ventricular/subarachnoid cysts** (best seen on **FIESTA / 3D-CISS** sequences). Performing both is ideal.
- **Serology** — the **enzyme-linked immunoelectrotransfer blot (EITB)** using *lentil-lectin–purified glycoprotein* antigens is **>99% sensitive and specific** in patients with **multiple** cysts; sensitivity falls with **single lesions or calcifications** (may be seronegative). **Serum is more sensitive than CSF.** Crude-antigen ELISAs have high false-positive/negative rates and **should be avoided**. Antigen-detection (monoclonal antibody) and real-time PCR aid diagnosis/follow-up of extraparenchymal disease.
- **CSF** — lymphocytic, neutrophilic **or eosinophilic pleocytosis**; raised protein; glucose usually normal **but may be markedly reduced** (mimics tuberculous/fungal meningitis in basal disease).
- **Revised Del Brutto diagnostic criteria (2017)** — diagnosis is graded *definitive* or *probable* by combining the following, **after excluding mimics**:

Tier	Criteria
Absolute	Histology of parasite; subretinal cysticercus on funduscopy; conclusive scolex-in-cyst on neuroimaging
Neuroimaging — major	Cystic lesions without scolex; typical enhancing lesions; multilobulated subarachnoid cysts; typical parenchymal calcifications
Neuroimaging — confirmative	Resolution of cysts after cysticidal drugs; migration of ventricular cyst on serial imaging
Neuroimaging — minor	Obstructive hydrocephalus or abnormal basal-leptomeningeal enhancement
Clinical/exposure — major	Positive **EITB** antibody or cysticercal antigen; cysticercosis outside CNS; household *T. solium* contact
Clinical/exposure — minor	Symptoms suggestive of NCC; residence in/origin from an endemic area

- ***Indian* validated criteria** — in a patient from an endemic area with a **single enhancing lesion**, seizures, a normal examination and no systemic disease, a **round lesion 5–20 mm without midline shift** is almost always NCC (the *solitary cysticercus granuloma*).

Management

Principle: treat the **complications first** (seizures, raised ICP, hydrocephalus); **antiparasitic therapy is never an emergency** and must never be started while ICP is elevated or before ocular disease is excluded.

Problem	Approach
Seizures	Antiseizure drugs; taper after **6 months** in single-lesion disease if imaging normalises and seizure-free; after **2 years** in multilesional disease if lesions resolve without calcification. Calcified lesions = higher recurrence risk.

Problem	Approach
Viable parenchymal cysts	**Albendazole 15 mg/kg/day** for 8–28 days (CMDT: 10–15 mg/kg/day; may escalate to 30 mg/kg/day). For **>2 cysts**, add **praziquantel 50 mg/kg/day** (combination superior).
Subarachnoid / giant cysts	Prolonged or combination antiparasitics **plus** prolonged glucocorticoids for arachnoiditis/vasculitis; shunt if hydrocephalus.
Anti-inflammatory cover	**High-dose glucocorticoids during all antiparasitic therapy** — dexamethasone 0.1–0.4 mg/kg/day or prednisone 60 mg/day. **Methotrexate / TNF inhibitors** as steroid-sparing agents for prolonged courses.
Hydrocephalus / intraventricular cyst	Reduce ICP first; **neuroendoscopic/surgical cyst removal** (lateral & 3rd ventricle endoscopically; 4th ventricle by posterior microdissection). **Avoid antiparasitics before surgery** (they make cysts friable). **VP shunt** if removal impossible; antiparasitics + steroids reduce shunt failure.
Diffuse cerebral oedema (cysticercotic encephalitis)	**Glucocorticoids are the mainstay; antiparasitic drugs are contraindicated.**
Ocular / spinal	Drug-induced inflammation may cause irreversible damage; **intraocular disease → surgery**; spinal disease → combined medical + surgical.

- **Drug interaction pearl** — corticosteroids **lower** praziquantel levels but **raise** albendazole levels, favouring albendazole when steroids are co-administered.
- **Taeniasis (gut carrier)** — single-dose **praziquantel 10 mg/kg** (or niclosamide 2 g); praziquantel may rarely trigger CNS inflammation if cryptic cysticercosis coexists.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Label the *T. solium* life cycle** (cause of taeniasis vs cysticercosis): *Human definitive host → gravid proglottids/eggs in faeces → Pig (intermediate host) ingests eggs → oncosphere → cysticercus in pig muscle → undercooked pork eaten by human → adult tapeworm (taeniasis)*; AND the **cysticercosis loop**: *Human ingests eggs (faecal–oral/autoinfection) → oncosphere → cysticercus in CNS/muscle/eye → neurocysticercosis.* Mark the **scolex with hooklets** on the larva.
- **Axial MRI/CT cartoon** labelling: *vesicular cyst with eccentric scolex ("dot-in-hole"), ring-enhancing single lesion with perilesional oedema, intraventricular cyst causing hydrocephalus, and a parenchymal calcified nodule.*

Clinical / Diagnostic significance

- **Leading infective cause of adult-onset focal epilepsy** in endemic India — any young adult from an endemic area with new focal seizures and a normal exam should have neuroimaging for a solitary cysticercus granuloma.
- **Basal/subarachnoid NCC with low-glucose, lymphocytic CSF closely mimics tuberculous meningitis** — a crucial differential in Indian practice; EITB serology and characteristic imaging help separate them.

- **Calcified NCC** is the commonest imaging finding in endemic regions and a marker of remote infection; perilesional oedema around a calcification can cause **recurrent seizures**.
- **Public-health link** — household screening of a tapeworm carrier (the egg source) prevents new cases; control needs mass chemotherapy of humans and pigs, meat inspection, sanitation, and the **pig vaccine licensed in India**.

High-yield exam pointers

- NCC = larval *T. solium* in CNS; acquired by ingesting **eggs** (faecal–oral), *not* by eating pork — even vegetarians can get it.
- **Seizure = commonest manifestation**; NCC = top cause of acquired epilepsy in the developing world.
- **"Dot-in-hole"** scolex sign is diagnostic; **CT best for calcification, MRI best for scolex/cysts (FIESTA/3D-CISS)**.
- **EITB (immunoblot) >99% sensitive/specific for multiple cysts**; single/calcified lesions may be seronegative; serum > CSF.
- **Del Brutto 2017 criteria** = absolute + neuroimaging (major/confirmative/minor) + clinical/exposure (major/minor).
- ***Bruns' syndrome*** = positional intermittent obstructive hydrocephalus from a mobile ventricular ball-valve cyst.
- **Always give glucocorticoids with antiparasitics**; **never give antiparasitics with raised ICP or in cysticercotic encephalitis**.
- **Albendazole** is first-line; **add praziquantel** for >2 viable cysts; manage seizures/hydrocephalus **before** killing the parasite.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Cestode Infections" (Taeniasis solium & Cysticercosis; Revised Diagnostic Criteria Table 242-1; Fig. 242-1)** and "Seizures and Epilepsy" (NCC as a cause of acquired epilepsy).
- **CMDT 2026 — "Protozoal & Helminthic Infections" (Cysticercosis: epidemiology, racemose form, treatment regimens, steroid–antiparasitic interaction).**
- *Coverage note:* The corpus is solid on aetiology, the Del Brutto criteria, imaging and management. It classifies NCC by **location and viability** (parenchymal/intraventricular/subarachnoid/calcified) rather than by the named four-stage radiological evolution (*vesicular → colloidal-vesicular → granular-nodular → nodular-calcified*); that staging is universally accepted standard neurology and is reflected here in descriptive terms faithful to the source.

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Nipah virus

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Nipah virus (NiV)* is a highly virulent, enveloped negative-sense RNA virus of the family **Paramyxoviridae**, genus **Henipavirus** (alongside *Hendra virus*), first recognised in humans in 1998–99. It is a bat-borne zoonosis that causes a severe **acute encephalitis with prominent respiratory involvement** and a very high case-fatality rate (≈67–92%). It is a classic *emerging infectious disease* — the Malaysian emergence in 1998 was driven by deforestation and intensive pig farming — and is a recurrent public-health threat in South and Southeast Asia (Malaysia, Singapore, Bangladesh, India). It must be handled at **biosafety level 4 (BSL-4)** and is a *WHO R&D Blueprint priority pathogen* for which there is no licensed human vaccine or proven specific therapy.

Etiology and Virology

- **Family Paramyxoviridae, genus *Henipavirus***; the two prototype species are *Nipah virus* and *Hendra virus* — the most lethal members of the family. Named after **Sungai Nipah** village, Malaysia, the site of the index outbreak.
- **Enveloped, non-segmented, negative-sense single-stranded RNA** virus; pleomorphic.
- Two key surface glycoproteins: **G (attachment) glycoprotein** and **F (fusion) glycoprotein**. The G protein binds host cell-surface receptors **ephrin-B2 and ephrin-B3**, which are highly expressed on **neurons and vascular endothelium** — explaining the dual neuro-vascular tropism.
- F-protein–mediated cell–cell fusion produces multinucleated **syncytia**, a hallmark cytopathic effect.
- Unusually **broad host range** (bats, pigs, horses, humans) and the ability to infect both CNS and respiratory epithelium underlie its severity.

Epidemiology and Transmission

- **Natural reservoir:** fruit bats of the genus *Pteropus* (flying foxes), which are persistently infected but asymptomatic.
- **Geography:** cases concentrated in **Malaysia, Singapore, Bangladesh and India**; a distinct *Malaysian strain* and a more virulent, more transmissible *Bangladesh/India strain* are recognised.
- **Transmission routes (well documented):** *pig-to-human*, *cow-to-human*, *human-to-human*, and **nosocomial** spread. Consumption of **raw date-palm sap** contaminated by bat saliva/excreta is the principal vehicle in Bangladesh/India; close contact with respiratory secretions of cases (and caregiving) drives person-to-person and hospital clusters.

Outbreak setting	Vehicle / amplifier	Key features
Malaysia 1998–99 / Singapore	Intermediate amplifying host = **pigs**; abattoir workers	First recognition; linked to **deforestation + intensive pig farming** (Harrison); predominantly encephalitis
Bangladesh (e.g., 2010–14 cluster: 14 cases, 8 fatal)	**Raw date-palm sap**; person-to-person	Higher CFR, more human-to-human and nosocomial transmission

Outbreak setting	Vehicle / amplifier	Key features
India (West Bengal, Kerala)	Date-palm sap / bat contact; hospital clusters	Recurrent seasonal outbreaks; high mortality

- **Incubation period** is typically *4–14 days* (occasionally longer).
- High **case-fatality rate (67–92%)** — far exceeding most arboviral encephalitides.

Pathogenesis

- After mucosal/respiratory entry, the virus targets **endothelial cells and neurons** via ephrin-B2/B3 receptors.
- Produces a **systemic vasculitis** with endothelial syncytia, vasculitis-induced thrombosis, ischaemia and microinfarction — most marked in the **CNS** (and also lung, heart, kidney).
- Combined **direct neuronal infection** plus **vasculitic microinfarcts** generates the characteristic disseminated, multifocal encephalitic picture.
- Respiratory tract infection produces an **acute respiratory distress syndrome (ARDS)-like** illness and facilitates aerosol/droplet person-to-person spread.

Clinical Features

- Spectrum ranges from **asymptomatic/mild** infection to **fulminant encephalitis** and ARDS; the dominant syndrome is **acute febrile encephalitis**.

Phase / syndrome	Manifestations
Prodrome	Fever, headache, myalgia, vomiting, sore throat — non-specific
Acute encephalitis	Altered sensorium, **encephalopathy**, **cranial nerve palsies**, **dystonia**, segmental myoclonus, areflexia, hypotonia, seizures; **brain-stem signs** carry a grave prognosis
Respiratory	Cough, atypical pneumonia, ARDS — a key distinguishing feature from arboviral encephalitides; aids transmission
Autonomic/vascular	Tachycardia, hypertension, features of disseminated vasculitis
Late / relapsing	**Relapsing or late-onset encephalitis** weeks–months after recovery (≈3.4–7.5%), due to recrudescence of latent CNS infection

- **Neurologic sequelae** (cranial nerve palsies, persistent encephalopathy, dystonia, cognitive/behavioural deficits) persist in **≈15–32%** of survivors.

Diagnosis

- **Strong epidemiological clues are essential:** travel/residence in an endemic area, **date-palm sap** ingestion, contact with sick pigs/bats, or contact with a known case; consider NiV in any **cluster of severe encephalitis with respiratory features** in South/Southeast Asia.
- **Laboratory confirmation (CMDT):**
  - **ELISA** — IgM/IgG antibody detection in **serum and CSF**.
  - **RT-PCR** — viral RNA in **urine and respiratory secretions** (note: **not reliably detected in blood**); CSF and throat/nasal swabs are also used.

- **Virus isolation / immunohistochemistry** on tissue — performed only under **BSL-4** containment.

- **CSF:** features of viral encephalitis (mild–moderate pleocytosis, raised protein, normal glucose).
- **Neuroimaging:** MRI typically shows **multiple small (2–7 mm) disseminated subcortical and deep white-matter T2/FLAIR hyperintensities** corresponding to microinfarcts (a relatively characteristic pattern).
- **Differential diagnosis** (per Harrison): Japanese encephalitis, herpes simplex and other viral encephalitides, cerebral malaria, leptospirosis, scrub typhus, bacterial meningoencephalitis — empirical **acyclovir** and antibacterials should cover treatable mimics until NiV is confirmed.

Management and Prevention

- **No proven specific antiviral therapy; care is largely supportive** — ICU-level management of encephalitis (seizure control, raised intracranial pressure, SIADH) and of respiratory failure/ARDS (oxygen, mechanical ventilation).
- **Ribavirin** was used in the Malaysian outbreak with a *possible* reduction in mortality, but benefit is unproven; **remdesivir** and the experimental human monoclonal antibody **m102.4** (targets the G-glycoprotein ephrin-binding site) are investigational/compassionate-use agents.
- **Infection prevention and control (critical):** strict **contact + droplet (and airborne for aerosol-generating procedures) precautions**, isolation of cases, PPE for caregivers, safe handling/burial practices, and BSL-4 handling of specimens — nosocomial amplification is a recurring feature of outbreaks.
- **Public-health prevention:** avoid raw date-palm sap (cover collection pots/use bamboo skirts), avoid contact with sick pigs/bats and bat-bitten fruit, surveillance of *Pteropus* populations, and rapid outbreak containment with contact tracing and quarantine.
- **No licensed human vaccine** (a recombinant Hendra-G subunit equine vaccine exists for horses; human candidates are in trials).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Nipah virus transmission cycle (label):** *Pteropus* fruit-bat reservoir → contamination of **date-palm sap** and **fruit** (Bangladesh/India route) and infection of **pigs (amplifying host)** (Malaysia route) → **human** infection → **human-to-human / nosocomial** spread; annotate **ephrin-B2/B3 receptor** tropism for **neurons + endothelium**.
- **Virion structure (label):** envelope, **G (attachment) glycoprotein**, **F (fusion) glycoprotein**, helical nucleocapsid with **negative-sense ssRNA**, matrix protein.

Clinical / Diagnostic significance

- NiV is the **most lethal paramyxovirus** and a model **One-Health emerging zoonosis** — its emergence illustrates how **ecological disruption (deforestation, intensive farming, sap harvesting)** precipitates spillover.
- Suspect NiV in **clustered, rapidly progressive encephalitis with respiratory illness** in endemic regions; early suspicion enables containment and prevents nosocomial catastrophe.

- Diagnostic pearl: **PCR is positive in urine/respiratory secretions but not blood**; paired **serum + CSF ELISA** confirms the diagnosis.
- Survivors require **neurological follow-up** for late/relapsing encephalitis and persistent deficits.

High-yield exam pointers

- **Family Paramyxoviridae, genus Henipavirus**; sister virus = **Hendra**; named after *Sungai Nipah*, Malaysia (1998).
- **Reservoir = *Pteropus* fruit bats**; **pigs = amplifying host** (Malaysia); **raw date-palm sap** (Bangladesh/India).
- Receptors **ephrin-B2/B3 → neuro-vascular tropism**; pathology = **endothelial syncytia + vasculitis → microinfarcts**.
- Syndrome = **acute encephalitis + respiratory illness**; signs include **cranial nerve palsies, segmental myoclonus, dystonia, brain-stem involvement**.
- **CFR 67–92%**; neurologic **sequelae 15–32%**; **relapsing/late encephalitis 3.4–7.5%**.
- **Dx:** ELISA (serum + CSF) and **RT-PCR (urine/respiratory secretions, NOT blood)**; MRI = multiple small disseminated lesions; handle at **BSL-4**.
- **Rx:** supportive ICU care; ribavirin/remdesivir/**m102.4 mAb** investigational; **no licensed human vaccine**.
- **Prevention:** droplet/contact isolation, avoid raw sap & sick animals; a **WHO priority/Blueprint pathogen** with pandemic potential.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Emerging and Re-Emerging Infectious Diseases" (Nipah as an emerging zoonosis; Malaysia 1998 emergence linked to deforestation + intensive pig farming; Hendra/Nipah listed); "Acute Meningitis and Encephalitis" chapter (Nipah, a Paramyxoviridae, as a cause of Southeast-Asian encephalitis outbreaks); "Arthropod-Borne and Rodent-Borne Virus Infections" (Nipah in the encephalitis differential).
- **CMDT 2026** — "Viral & Rickettsial Infections" (Nipah under paramyxoviruses): first described 1999; geography; fruit-bat reservoir; Bangladesh date-palm-sap cluster (14 cases, 8 fatal); pig-/cow-/human-/nosocomial transmission; CFR 67–92%; neurologic sequelae 15–32%; relapses 3.4–7.5%; ELISA (serum/CSF) and PCR (urine/respiratory secretions, not blood) diagnosis.
- **Coverage note:** The corpus covers Nipah only briefly — Harrison treats it as an emerging-disease/encephalitis example and CMDT provides the main clinical paragraph; there is **no dedicated Nipah chapter**. Standard, universally-accepted virology and management details not explicitly in the corpus but added for completeness and accuracy: genus *Henipavirus* and ephrin-B2/B3 receptors; G/F glycoproteins and syncytia; *Pteropus* genus; incubation 4–14 days; MRI microinfarct pattern; ribavirin/remdesivir/m102.4 and the absence of a licensed human vaccine; BSL-4 and WHO-priority-pathogen status; and Indian (West Bengal, Kerala) outbreaks.

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Antibiotic resistance prevention in intensive care units

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Antimicrobial resistance (AMR)* is the reduction or loss of an antibacterial agent's activity, arising from spontaneous chromosomal **mutation** or **horizontal acquisition** of resistance genes (plasmids, transposons, transformation). The multidisciplinary ICU is the hospital's *epicentre of resistance* because it concentrates the three drivers of resistance simultaneously — intense **antibiotic selection pressure**, a dense reservoir of **colonised/infected hosts** (high colonisation pressure), and abundant opportunities for **cross-transmission** via invasive devices and the hands of staff. Prevention is therefore not a single measure but a coordinated, institution-wide programme resting on **two complementary pillars — antimicrobial stewardship** (rational prescribing) and **infection prevention and control** (interrupting transmission) — backed by surveillance and a *One Health* perspective. The CDC estimates >2.8 million resistant infections and 35,900 deaths annually in the United States, underscoring the stakes.

Why the ICU breeds resistance (the rationale to target)

- **Selection pressure:** broad-spectrum empirical regimens, prolonged courses and unnecessary antibiotics select resistant strains and "bystander" organisms; prior antibiotic exposure, prior resistant infection and prior hospitalisation each raise the odds of harbouring a resistant pathogen.

- **Colonisation pressure:** the proportion of patients on a ward who are colonised is itself a risk factor for spread; antibiotic-altered microbiota become readily colonised by **multidrug-resistant organisms (MDROs)**, which then act as silent reservoirs.
- **Cross-transmission:** transmitted on hands, shared equipment (stethoscopes, glucometers, ultrasound, BP cuffs), contaminated environment, plumbing and water.
- **Devices and breached barriers:** central lines, urinary catheters, endotracheal tubes and surgical wounds are portals of entry — catheter-associated bloodstream infection alone *triples* in-hospital mortality risk, and ventilator-associated pneumonia (VAP) occurs in up to 10% of ventilated patients.
- **The MDRO targets:** CDC *urgent* threats — carbapenem-resistant *Acinetobacter*, *Candida auris*, *Clostridioides difficile*, **carbapenem-resistant Enterobacterales (CRE)** and drug-resistant *N. gonorrhoeae*; *serious* threats include ESBL-producing Enterobacterales, VRE, MDR *Pseudomonas aeruginosa*, MRSA and drug-resistant *S. pneumoniae*. Key enzymes: **ESBLs**, **AmpC**, and carbapenemases **KPC**, **NDM** (originally Indian subcontinent) and **OXA-48**; plasmid-borne colistin resistance via *mcr-1*.

Pillar 1 — Antimicrobial stewardship (ASP)

Stewardship promotes the appropriate drug, dose, route and duration, with four goals: (1) improve patient care, (2) preserve antibiotics by curbing resistance, (3) reduce adverse effects (e.g. C. difficile), and (4) control cost. Mandated/supported by **CDC** core elements, **The Joint Commission** Medication Management Standards, **CMS** Conditions of Participation and the 2015 **National Action Plan for Combating Antibiotic-Resistant Bacteria**.

- **Multidisciplinary team:** infectious-disease physician + clinical pharmacist with ID training (core dyad), plus clinical microbiologist, infection-prevention practitioner, hospital epidemiologist and information-systems specialist.

Strategy	What it involves
Prospective audit + feedback	ID physician/pharmacist reviews broad-spectrum orders (carbapenems) or costly agents (daptomycin, ceftazidime-avibactam) and recommends alternatives
Formulary restriction	Limited set of agents on formulary to curb indiscriminate use
Preauthorisation	Approval required before using restricted agents — via CPOE criteria or ID consultation
De-escalation / streamlining	Narrow therapy once culture & susceptibility known; stop the "anti-pseudomonal/anti-MRSA" drug if not recovered
Dose optimisation (PK/PD)	Use pharmacokinetic-pharmacodynamic targets (e.g. extended β-lactam infusions, AUC/MIC)
IV-to-oral conversion	Switch when patient stable and gut absorbing
Antibiotic time-out / shortest duration	Reassess at 48–72 h; use the shortest effective course (shorter courses select less resistance)
Diagnostic stewardship	Avoid culturing asymptomatic bacteriuria; restrict unnecessary tests to prevent inappropriate treatment

Strategy	What it involves
Guidelines, indication documentation, education	Local pathways, documenting indication, ongoing prescriber education

- **The "Four Moments of Antibiotic Decision-Making"** (a practical bedside frame): (1) *Does this patient have an infection that needs antibiotics?* (2) *Have appropriate cultures been taken before starting?* (3) *After a few days — can antibiotics be stopped, narrowed, or switched IV-to-oral?* (4) *What duration is truly necessary?*
- **ICU/VAP-specific algorithm (6 steps):** (1) start broad-spectrum empirically to cover MDR GNB/MRSA; (2) **stop** if infection becomes unlikely; (3) **narrow** once the organism is identified; (4) **optimise by PK/PD**; (5) **switch to monotherapy on days 3–5**; (6) **shorten duration** (a short, fixed course e.g. ~7–8 days for most VAP). Quantitative lower-respiratory cultures (BAL $\geq 10^4$ CFU/mL or tracheal aspirate $\geq 10^5$ CFU/mL) with a de-escalation algorithm increase antibiotic-free days without harming outcome.
- **Rapid diagnostics & biomarkers:** rapid molecular detection of organisms/resistance (multiplex PCR, MALDI-TOF) shortens time to appropriate therapy and to de-escalation; **procalcitonin-guided** cessation reduces antibiotic exposure in the ICU (*PRORATA* trial) and is a recognised adjunct.

Pillar 2 — Infection prevention and control (interrupt transmission)

- **Hand hygiene** before/after every patient contact — alcohol-based hand rub, but **soap-and-water (mechanical removal)** for *C. difficile* and norovirus (spores/non-enveloped virus resist alcohol).
- **Standard precautions** for all patients + **transmission-based precautions**: **contact** (gown + gloves) for MDROs and *C. difficile*; **droplet** and **airborne** (N95 + negative-pressure room, ≥12 air changes/h) as indicated.
- **Daily 2% chlorhexidine gluconate bathing** of ICU patients with central lines — standard of care to prevent bloodstream infection.
- **Environmental cleaning** of high-touch surfaces and shared equipment; **sporicidal (bleach)** cleaning and adjunctive **UV-C** for tenacious pathogens; dedicated disinfectants and screening of transfers for *C. auris*; **water-safety/management plans** (Legionella, NTM, MDR gram-negatives in drains).
- **Device-care bundles** (the single highest-yield ICU intervention) — see table — plus the cardinal rule: *insert devices only when essential and review the need for each device daily.*

Bundle	Key evidence-based elements
CLABSI	Hand hygiene; **maximal sterile barrier**; **chlorhexidine-alcohol** skin prep; **ultrasound-guided** insertion; prefer **subclavian** (femoral most infection-prone); all-inclusive kit + checklist; scrub-the-hub; disinfectant caps; chlorhexidine-impregnated dressings; daily chlorhexidine baths; daily review of line need
VAP	Avoid intubation (HFNO/NIV); **head-of-bed 30–45°**; daily oral care/tooth-brushing; aseptic respiratory-equipment care (no tap-water rinsing); **minimise sedation**, early mobilisation, early enteral feeding, daily extubation-readiness (spontaneous breathing trials)

Bundle	Key evidence-based elements
CAUTI	Catheterise only when strictly necessary; aseptic insertion + closed drainage; minimise manipulation; **daily review of need**; alternatives — bladder scan, condom/intermittent catheter
SSI	Treat infection pre-op; **prophylaxis within 1 h before incision and stop after closure**; clip (not shave) hair; chlorhexidine-alcohol antisepsis; nasal **mupirocin** decolonisation in *S. aureus* carriers for high-risk surgery

- **Active surveillance & cohorting:** screen high-risk transfers/long-term-care admissions for MDROs/*C. auris*, isolate pending results, cohort staff and patients during outbreaks; reduce colonisation pressure.
- **C. difficile control:** because antibiotic exposure is the chief cause, *stewardship is the first-line preventive measure* — restricting **fluoroquinolones and clindamycin** reduces incidence; add contact isolation, soap-and-water hand hygiene and bleach disinfection.
- **Selective digestive/oropharyngeal decontamination (SDD/SOD):** may reduce HAP and mortality, but routine use is *limited by concern over selecting resistance* and remains context-dependent.

Institutional, surveillance and One Health measures

- **Surveillance & tracking:** laboratory-based + automated electronic surveillance; mandatory reporting (e.g. NHSN), expressed as **standardised infection ratios**; produce a periodic **antibiogram** to guide empirical therapy to *local* susceptibility data.
- **Outbreak response:** molecular typing — **whole-genome sequencing** (gold standard) — to confirm clonality and trace plasmid-borne resistance genes; case definition, case-finding, control measures, communication.
- **Regional/interfacility communication** of MDRO status on transfer; **CDC five core actions** — (1) infection prevention & control, (2) tracking & data, (3) antibiotic use & access (stewardship), (4) vaccines/therapeutics/diagnostics, (5) environment & sanitation via the **One Health** approach (agriculture, animal antibiotic use, environmental reservoirs).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Two-pillar prevention framework":** a central box *Preventing AMR in the ICU* feeding two columns — **Antimicrobial Stewardship** (label: audit-and-feedback, formulary restriction, preauthorisation, de-escalation, PK/PD dosing, IV-to-oral, antibiotic time-out, shortest duration, diagnostic stewardship) and **Infection Prevention & Control** (label: hand hygiene, contact/droplet/airborne precautions, CLABSI/VAP/CAUTI/SSI bundles, chlorhexidine bathing, environmental + water safety, active surveillance/isolation) — both resting on a base bar labelled *Surveillance • Antibiogram • Outbreak investigation (WGS) • One Health*.
- **"Chain of transmission interrupted":** Reservoir (colonised patient/environment/device) → Hands of HCW / shared equipment → Susceptible patient; mark the break-points — *hand hygiene*, *contact precautions*, *environmental cleaning*, *device removal*.

Clinical / Diagnostic significance

- **Empirical-to-targeted transition:** appropriate early empirical cover saves lives in septic ICU patients, but must be paired with mandatory cultures *before* antibiotics and prompt **de-escalation** once susceptibilities return — this is where resistance is actually contained.
- **Local data drive choice:** the institutional antibiogram and individual risk factors (prior antibiotics, prior MDRO, length of stay) determine the empirical regimen; rapid diagnostics shorten the window of unnecessary broad-spectrum exposure.
- **Bundle compliance is auditable:** process measures (hand-hygiene compliance, line-insertion checklist adherence) and outcome measures (CLABSI/VAP/CAUTI rates, hospital-onset *C. difficile*) feed quality improvement and reimbursement.
- **Stewardship pays clinically:** demonstrated reductions in *C. difficile*, improved susceptibility patterns and lower cost without worse outcomes.

High-yield exam pointers

- AMR prevention in the ICU = **two pillars**: *Antimicrobial Stewardship* + *Infection Prevention & Control*, on a base of *surveillance/One Health*.
- **Three core ASP strategies:** prospective **audit + feedback**, **formulary restriction**, **preauthorisation**.
- **Four Moments of Antibiotic Decision-Making**; ASP goals = better care, less resistance, fewer adverse effects, lower cost.
- **VAP 6-step strategy:** start broad → stop if unlikely → narrow → PK/PD optimise → **monotherapy day 3–5** → **shorten duration**.
- **Shorter courses select less resistance;** de-escalate on cultures; consider **procalcitonin-guided** stop (*PRORATA*).
- **Device bundles** + *"insert only if essential, review daily"*; **daily 2% chlorhexidine baths** prevent CLABSI; **HOB 30–45°** for VAP.
- **Hand hygiene** is the single most effective IPC measure — but **soap-and-water for C. difficile/norovirus**; **contact precautions** for MDROs.

- **Stewardship is first-line prevention of C. difficile** — restrict **fluoroquinolones + clindamycin**.
- CDC **urgent** threats: CR-*Acinetobacter*, *C. auris*, *C. difficile*, **CRE**, drug-resistant gonorrhoea; carbapenemases **KPC/NDM/OXA-48**.
- **CDC five core actions + One Health**; outbreak typing by **whole-genome sequencing**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bacterial Resistance to Antimicrobial Agents" (mechanisms, CDC threats table & five core actions, One Health); "Treatment and Prophylaxis of Bacterial Infections" (antimicrobial stewardship strategies, ASP team, prophylaxis); "Infections Acquired in Health Care Facilities" (device bundles, transmission-based precautions, chlorhexidine bathing, surveillance, *C. difficile*/*C. auris*).
- **CMDT 2026** — "Common Problems in Infectious Diseases & Antimicrobial Therapy" (antimicrobial stewardship, *Four Moments of Antibiotic Decision-Making*, selective digestive decontamination).
- **Murray & Nadel's Textbook of Respiratory Medicine** — "Ventilator-Associated Pneumonia" (ICU 6-step antimicrobial management, quantitative-culture de-escalation, PK/PD, monotherapy on days 3–5, duration, procalcitonin/PRORATA, rapid diagnostics).
- *Coverage note:* the corpus covers stewardship and infection control fully; explicit ICU-specific stewardship detail is consolidated chiefly from the Murray VAP chapter (the general texts treat it more briefly, as the spec anticipated). Procalcitonin/PRORATA and short fixed VAP courses are standard, source-supported ICU practice.

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Progressive multifocal leucoencephalopathy

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Progressive multifocal leucoencephalopathy (**PML**) is a subacute, usually fatal **demyelinating disease of the central nervous system** caused by lytic reactivation of the **JC virus** (a human polyomavirus) in profoundly immunosuppressed patients. It is the **only known clinical manifestation of JC virus infection** and characteristically produces *multifocal*, *non-enhancing* white-matter lesions that coalesce over time. In Harrison's it is described chiefly as a **late opportunistic infection of AIDS** (seen in ~1–4% of AIDS patients) and, in the multiple sclerosis chapter, as the **principal serious risk of natalizumab** and certain other disease-modifying therapies (DMTs).

Etiology & Pathogenesis

- **Causative agent: JC virus**, a ubiquitous **human polyomavirus** (double-stranded DNA, non-enveloped). The eponym derives from the initials of the index patient (*John Cunningham*).
- **High background seroprevalence: ~80% of the general adult population** have antibodies to JC virus, indicating prior (usually childhood, asymptomatic) infection. The virus then remains **latent** (kidney/lymphoid tissue).
- **Restricted replication in health: <10% of healthy adults** show any evidence of ongoing viral replication — disease requires a permissive immunosuppressed state.

- **Reactivation:** Loss of immune surveillance permits viral reactivation, haematogenous spread to the CNS, and **lytic infection of oligodendrocytes**, producing demyelination.
- **Pathology:** Lesions begin as **small foci of demyelination in subcortical white matter** that progressively **coalesce**. The **cerebral hemispheres, cerebellum, and brainstem** may all be involved.
- **Why immunomodulators raise risk:** Natalizumab blocks the **α4β1 integrin (adhesion molecule)**, *preventing lymphocytes from binding endothelial cells and entering the CNS* — the resulting loss of intrathecal immune surveillance permits unchecked JC virus replication, the mechanistic basis of its PML risk.

Predisposing immunosuppressed states (who gets PML)

Setting	Key points (per source)
Advanced HIV/AIDS	A **late manifestation of AIDS**; occurs in **~1–4%** of AIDS patients; one of the few opportunistic infections that **continues to occur despite widespread ART**
Natalizumab (Tysabri) for MS	Anti-α4β1 integrin MAb; **major risk is PML (~0.4%)**; give only if **serum JC virus antibodies are absent** (~50% of patients); **repeat JCV antibody testing every 6 months** on treatment
Dimethyl/diroximel fumarate for MS	**Rare PML cases**, associated with persistent **lymphopenia**
Cladribine (Mavenclad) for MS	Lymphocytotoxic; infection risk **including PML**
Other (standard)	Haematological malignancy, transplant/chemotherapy, other potent immunosuppression — *see Coverage note*

Clinical features

- **Tempo:** Subacute, **protracted course** with **multifocal neurologic deficits**, *with or without* changes in mental status.
- **Focal signs: Hemiparesis**, **visual field defects** (hemianopia), **ataxia**, **aphasia**, and **sensory deficits** — reflecting the multifocal white-matter involvement.
- **Seizures:** Occur in **~20%** of patients.
- **Notable negatives: Headache, fever, nausea and vomiting are rarely seen** — their presence should **prompt a search for an alternative diagnosis** (e.g., toxoplasmosis, lymphoma).
- **Course:** Relentless progression; cognitive and focal deficits accumulate.

Investigations & Diagnosis

- **MRI brain (key investigation):**
  - **Multiple, NON-enhancing white-matter lesions** that may coalesce.
  - **Predilection for the occipital and parietal lobes.**
  - **T2-weighted: signal hyperintensity**; **T1-weighted: diminished (low) signal.**
  - Absence of mass effect and absence of enhancement help distinguish PML from enhancing/space-occupying lesions.

- **CSF JC virus DNA (PCR):** Diagnostic **sensitivity ~76%, specificity close to 100%** — a positive CSF JCV PCR in the right clinical/MRI context is effectively confirmatory.
- **Brain biopsy:** Reserved for atypical cases (definitive demonstration of demyelination with oligodendroglial inclusions) — *standard practice; see Coverage note*.
- **CD4 count / HIV viral load** in PML complicating HIV, as these carry prognostic weight (below).

Differential diagnosis (HIV CNS lesions)

Feature	PML	CNS toxoplasmosis	Primary CNS lymphoma
Enhancement	**Non-enhancing**	**Ring-enhancing** (eccentric *target sign*)	Enhancing (often homogeneous)
Number/site	Multifocal, **white matter**, occipito-parietal	Multiple, deep + grey–white junction/basal ganglia	Single or few, periventricular
Mass effect	Minimal/absent	Present (oedema)	Present
Confirmatory test	**CSF JCV DNA PCR**	Response to anti-toxoplasma Rx; serology	CSF EBV DNA; biopsy

Treatment & Prognosis

- **No specific antiviral therapy** exists for PML; agents such as **cidofovir have failed to show clear benefit**.
- **Cornerstone = restore immunity / remove the trigger:**
  - In HIV: **initiate/optimise ART** to reconstitute CD4 immunity.
  - In drug-induced PML: **stop the offending DMT** (and, for natalizumab, consider plasma exchange to accelerate drug clearance — *standard; see Coverage note*).
- **Immune reconstitution inflammatory syndrome (IRIS): Paradoxical worsening of PML** can follow ART initiation as an immune-reconstitution phenomenon — a key management caveat.
- **Prognosis (HIV-associated):**
  - **Pre-ART era:** most patients died **within 3–6 months** of symptom onset.
  - **With ART:** dramatically improved — **median survival ~2 years**, and survival **>15 years** has been reported; however, **only ~50%** of HIV-PML patients show neurologic improvement.
  - **Favourable predictors: baseline CD4+ count >100/µL** and ability to maintain **HIV viral load <500 copies/mL**. **Baseline HIV-1 viral load itself has no independent predictive value.**

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Axial T2/FLAIR MRI brain schematic (PML lesions).** Labels to mark: *Asymmetric subcortical white-matter hyperintensity*; *Parieto-occipital predilection*; *Coalescing demyelinating foci*; *Involves subcortical U-fibres*; *NON-enhancing on post-contrast T1*; *T1-hypointense / T2-hyperintense*; *No/minimal mass effect*; *Grey matter relatively spared*.
- **Pathogenesis flow diagram.** Boxes/arrows: *Latent JC virus (kidney/lymphoid tissue)* → *Severe immunosuppression (HIV with low CD4 / natalizumab / fumarate / cladribine)* → *Viral reactivation* → *Haematogenous spread to CNS* → *Lytic infection of oligodendrocytes* → *Multifocal demyelination* → *Progressive multifocal neurological deficits*.

Clinical / Diagnostic significance

- **AIDS-defining illness:** PML is an AIDS-defining opportunistic infection; its appearance signals **advanced immunosuppression** and warrants ART optimisation.
- **Pharmacovigilance for DMTs: JC virus antibody stratification** is mandatory before and during **natalizumab** therapy — JCV-seronegative patients are preferred candidates; rising JCV index, prior immunosuppressant use, and longer treatment duration raise risk.
- **"Non-enhancing white-matter lesions + focal deficits + immunosuppression"** is the classic triad that should trigger **CSF JCV PCR**.
- **Watch for IRIS** when starting ART in a patient with (or at risk of) PML — neurologic worsening may be inflammatory rather than progressive infection.
- **MRI + CSF JCV DNA PCR** can often avoid the need for brain biopsy.

High-yield exam pointers

- **JC virus = human polyomavirus**; **PML is its ONLY clinical manifestation**; **~80%** adults are seropositive.
- **Occurs in ~1–4% of AIDS patients**; a **late** AIDS manifestation; persists despite ART.
- **MRI: multiple NON-enhancing** white-matter lesions, **occipito-parietal**, **T2-hyperintense / T1-hypointense**.
- **CSF JC virus DNA PCR: sensitivity ~76%, specificity ~100%.**
- **~20% have seizures**; headache/fever/vomiting are **rare** (suggest another diagnosis).
- **No specific therapy; cidofovir ineffective** — treat by **immune reconstitution (ART) / stopping the culprit DMT**.
- **Natalizumab PML risk ~0.4%** — give only if **JCV antibody negative**; **retest q6 months**.
- **Prognosis:** pre-ART death in **3–6 months**; with ART median survival **~2 years**; better if **CD4 >100/µL** and **VL <500 copies/mL**.
- **ART can cause paradoxical worsening = PML-IRIS.**

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 208 "Human Immunodeficiency Virus Disease: AIDS and Related Disorders"** (JC virus/PML epidemiology, clinical features, MRI, CSF JCV PCR, ART/prognosis, IRIS) and **Ch 455 "Multiple Sclerosis"** (Table 455-6: natalizumab/fumarate/cladribine PML risk and JCV antibody stratification). **Coverage note (spec.gap = true):** Harrison 22e has **no dedicated PML chapter**; content is distributed across the HIV chapter (which cross-refers to Ch 142 on polyomaviruses, *not supplied here*) and the MS-therapeutics chapter. Items added as **universally accepted standard internal medicine but NOT explicitly stated in the two supplied chapters** are flagged in-text: the *John Cunningham* eponym expansion; **oligodendrocyte** as the lytically infected target cell; **brain biopsy** as the definitive test; **plasma exchange** to clear natalizumab; and non-HIV immunosuppressed settings (haematologic malignancy, transplant/chemotherapy). The differential-diagnosis comparison draws on toxoplasmosis (eccentric target sign, ring enhancement) and CNS lymphoma descriptions within Ch 208.

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Pyrexia of unknown origin (PUO)

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Pyrexia of unknown origin (PUO), more often termed *fever of unknown origin* (FUO), denotes a **prolonged febrile illness that defies diagnosis despite intensive, structured evaluation**. The term should be reserved for such illnesses — most fevers either resolve spontaneously or declare a cause once distinguishing features appear. FUO is not a single disease but a final common presentation of an atypical manifestation of a common disorder far more often than a rare exotic disease. The diagnostic challenge lies in disciplined pursuit of *potentially diagnostic clues* rather than indiscriminate testing.

Diagnostic criteria — classic vs current definition

- The original **Petersdorf and Beeson (1961)** definition: illness of **≥3 weeks' duration**, fever **≥38.3°C (≥101°F) on two occasions**, with diagnosis uncertain despite **1 week of inpatient evaluation**.
- Harrison's **current (modern) definition** retains time/temperature thresholds but mandates a standardised minimum workup and excludes the immunocompromised:

Criterion	Requirement
Temperature	Fever **≥38.3°C (≥101°F)** on **at least two occasions**
Duration	Illness of **at least 3 weeks**
Host	**No known immunocompromised state**
Investigation	Diagnosis uncertain **after thorough history, examination and the obligatory investigations** (see below)

- **Inflammation of unknown origin (IUO)** — identical to FUO *except the temperature criterion*: persistently raised CRP/ESR for ≥3 weeks in an immunocompetent patient with a **normal body temperature** and no explanation despite the same obligatory workup. IUO and FUO share the **same causes and the same workup**.
- For perspective, normal mean oral temperature is ~36.6°C; *fever* is a pyrogen-driven upward shift of the hypothalamic set point (mediated by pyrogenic cytokines **IL-1, IL-6, TNF**), distinct from **hyperthermia** (uncontrolled heat gain, set point unchanged, unresponsive to antipyretics). **Hyperpyrexia** = fever >41.5°C.

Classification — categories of FUO

The classic **Durack–Street four-category** scheme separates the immunocompetent "classic" patient from special hosts, each with a distinct differential and threshold (durations per CMDT 2026):

Category	Defining features
Classic FUO	≥3 weeks, fever ≥38.3°C, immunocompetent, undiagnosed after the obligatory workup
Hospital-associated (nosocomial) FUO	Fever in a hospitalised patient from a process **not present/incubating on admission**; cultures negative; undiagnosed despite appropriate evaluation (≥3 days, including ≥2 days culture incubation)
Neutropenic FUO	Fever with **<500 neutrophils/μL**; cultures negative; undiagnosed after **3 days** — *fungal and occult bacterial infection* dominate
HIV-associated FUO	Confirmed HIV, febrile **≥4 weeks as outpatient or ≥3 days as inpatient**; undiagnosed after 3 days (≥2 days incubation) — *mycobacterial/opportunistic infection* dominate

- Special scenarios with unique differentials: **FUO in solid-organ transplant recipients** (CMV, fungi, nocardiosis, *P. jirovecii*, mycobacteria) and **FUO in the returning traveller** (malaria, enteric fever, leishmaniasis, rickettsioses).

Etiology — broad categories

The five working categories (CMDT) and their geographic skew (Harrison):

Category	Key examples
Infections	**Extrapulmonary/miliary tuberculosis**, infective/culture-negative endocarditis, occult abscess (hepatic, splenic, subphrenic, pelvic, renal), diverticulitis, vertebral osteomyelitis/spondylodiscitis; brucellosis, **Q fever (Coxiella burnetii)**, **Whipple disease (Tropheryma whipplei)**, EBV/CMV, malaria, leishmaniasis, HIV seroconversion
Noninfectious inflammatory diseases (NIIDs)	**Adult-onset Still's disease**, large-vessel vasculitis / **giant cell arteritis**, polymyalgia rheumatica, SLE, polyarteritis nodosa, cryoglobulinemia, sarcoidosis; autoinflammatory syndromes (familial Mediterranean fever, **VEXAS**, Schnitzler's)
Malignancy	**Malignant lymphoma (most common neoplastic cause)**, leukaemia, renal cell carcinoma, hepatic tumours, **atrial myxoma**, Castleman disease
Miscellaneous	**Drug fever**, factitious/fraudulent fever, granulomatous hepatitis, subacute thyroiditis, recurrent pulmonary emboli, alcoholic hepatitis

Category	Key examples
Undiagnosed	~Half of cases (higher in Western cohorts — *"the FUO paradox"*); most resolve spontaneously

- **Geography matters:** infection (esp. **tuberculosis** — up to half of infective FUO) predominates in Asia/Middle-East; **NIIDs predominate in Western cohorts** (up to one-third). In adults >65 years, multisystem immune diseases (GCA, PMR, sarcoid, RA) cause 25–30%.
- **Eponym pearls:** *VEXAS* — somatic **UBA1** variants, elderly males, vacuoles in myeloid precursors. *Schnitzler's* — urticaria + bone pain + monoclonal gammopathy. *Marantic (nonbacterial thrombotic) endocarditis* — paraneoplastic. Common **drug-fever** culprits: allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, furosemide, sulfonamides, minocycline, vancomycin, β-lactams, isoniazid; fever subsides **within ~72 h** of stopping the drug.

Diagnostic approach — obligatory workup and PDC-driven strategy

- **Obligatory minimum investigations** (define the patient as true FUO): ESR **and** CRP; full blood count with differential and platelets; haemoglobin, electrolytes, creatinine, total protein, **ALP, ALT, AST, LDH, creatine kinase, ferritin**; **ANA and rheumatoid factor**; serum **protein electrophoresis**; urinalysis; **blood cultures (n = 3)**; urine culture; **chest radiograph**; **abdominal ultrasonography**; and **TST or IGRA**. (CMDT additionally lists HIV antibody/antigen and TSH.)
- **Hunt for Potentially Diagnostic Clues (PDCs)** — all localising signs, symptoms and abnormalities pointing to a diagnosis — through *repeated* history and examination. History: fever pattern/duration, drugs, travel (remote and recent), animal/occupational exposures, sexual and family history, country of origin. Examination: eyes/**fundoscopy**, lymph nodes, **temporal arteries**, liver, spleen, skin and mucosae, surgical scars.
- **Stop confounders early:** discontinue **antibiotics and glucocorticoids** before further testing (they mask cultures and shrink nodes); withdraw all drugs/supplements to exclude **drug fever**; exclude **factitious fever** (self-induced) and **fraudulent fever** (manipulated thermometer) by simultaneous multi-site temperature measurement and by noting **pulse–temperature dissociation**.
- **Targeted, PDC-guided testing only:** "screening" serologies/febrile agglutinins are low-yield and discouraged without a clue. Hold blood cultures long enough for fastidious **HACEK** organisms; use special media when *Legionella, Bartonella, Histoplasma* or nutritionally-variant streptococci are suspected. Headache → CSF examination (HSV-2, *Cryptococcus*, *M. tuberculosis*). For suspected **miliary TB**, **liver biopsy** for acid-fast smear, culture and PCR has the highest yield. **Cryoglobulins** are a useful low-cost screen.
- **Yield of invasive tests:** bone-marrow biopsy 15–25% (higher in HIV); liver biopsy 10–15% — pursue any abnormal finding aggressively (rash → skin biopsy; node → excision biopsy + culture).

Imaging — role of 18F-FDG-PET/CT

- **18F-FDG-PET/CT is the pivotal functional imaging test** when PDC-guided tests are unrevealing. FDG accumulates in high-glycolysis tissue — **malignant cells and activated leukocytes** — so it images infection, sterile inflammation **and** malignancy (an advantage in FUO, where all three are possible). It localises the metabolic focus to direct biopsy/culture.

- **Diagnostic yield ~50%** (Harrison meta-analyses); CMDT cites yields of **84–98%** for underlying cause. Perform it **during active inflammation** (raised CRP/ESR or while febrile) for best yield; **postpone glucocorticoids** until after the scan (they rapidly quench FDG uptake in vasculitis and lymphoma).
- **Alternatives** when PET/CT is unavailable: **67Ga-citrate scintigraphy** (yield ~21–54%) or **111In-/99mTc-labelled leukocyte scintigraphy** (~8–31%); whole-body MRI is a promising emerging option.
- **Giant cell arteritis** is found in up to **17%** of elderly FUO patients; PET/CT detects large-vessel involvement, but **temporal artery biopsy is still recommended in patients ≥55 years** (small-calibre temporal vessels and high cerebral FDG can confound PET).

Treatment, prognosis and the role of therapeutic trials

- **Treat the established cause** — empirical therapy is generally *avoided*; it can mask infection/lymphoma and abolish culture yield. **Empirical therapy is justified only when the patient is haemodynamically unstable, septic, neutropenic or deteriorating**, or with strong suspicion of TB or sight-threatening GCA.
- **Therapeutic trials** (used selectively): antituberculous therapy (reassess at **6 weeks** — no response argues against TB); NSAIDs (often dramatic in Still's disease); **colchicine** (prevents FMF and recurrent pericarditis attacks); glucocorticoids (impressive in **GCA/PMR**, but only after lymphoma/infection excluded); **IL-1 inhibition with anakinra** (recombinant IL-1Ra blocking IL-1α and IL-1β) for autoinflammatory FUO with serositis, high ferritin and high CRP.
- **Prognosis is favourable** in undiagnosed FUO: fever resolves spontaneously in ~75% of undiagnosed patients; long-term mortality is **≤8%**. A **normal PET/CT predicts spontaneous resolution**. A **second opinion at an FUO expert centre** yields a diagnosis in over half of previously unexplained cases.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Diagnostic algorithm for FUO** (flow chart): *Fever ≥38.3°C + illness ≥3 weeks + immunocompetent* → **History + examination + obligatory investigations** → *Stop antibiotics/glucocorticoids; exclude thermometer manipulation and drug fever* → branch: **PDCs present** → guided tests → diagnosis; **PDCs absent/misleading** → cryoglobulins + fundoscopy → **18F-FDG-PET/CT** → *Abnormal* → confirm by biopsy/culture; *Normal* → repeat history/examination, PDC-driven invasive testing → *Stable* → follow up for new PDCs / NSAID vs *Deteriorating* → further tests / therapeutic trial.
> - **Etiologic pie/box** with labels: **Infections, Noninfectious inflammatory diseases (NIIDs), Malignancy, Miscellaneous, Undiagnosed** — annotated with the geographic contrast (TB-rich Asia vs NIID-rich West).

Clinical / Diagnostic significance

- The single highest-value manoeuvre is the **repeated, meticulous history and examination** to extract PDCs — FUO is usually an atypical presentation of a *common* disease.

- **Tuberculosis (especially miliary/extrapulmonary)** is the most important treatable infectious cause in India and the tropics; a negative TST/IGRA does **not** exclude it.
- **Giant cell arteritis** must be actively sought in any elderly FUO with raised ESR/CRP, headache or visual symptoms — it is treatable and sight-threatening.
- Always re-examine for **endocarditis (including culture-negative/HACEK), occult abscess, lymphoma and drug fever** — the four "must-not-miss" recurring culprits.
- Discontinuing antibiotics/steroids and timing PET/CT to active inflammation materially change diagnostic yield.

High-yield exam pointers

- **Petersdorf–Beeson 1961:** ≥3 weeks, fever ≥38.3°C (101°F) ×2, undiagnosed after **1 week inpatient** evaluation.
- Modern definition adds a **mandatory minimum workup** and excludes the **immunocompromised**; **IUO** = FUO with a *normal temperature*.
- **Four categories:** classic, **nosocomial**, **neutropenic (<500/µL)**, **HIV-associated** (4 wks OP / 3 days IP).
- Five etiologic classes: **infection, malignancy, NIID/autoimmune, miscellaneous, undiagnosed (~50%)**.
- **Lymphoma** = commonest malignant cause; **TB/endocarditis** = commonest infective causes; **GCA/Still's/SLE/sarcoid** lead the NIIDs.
- **18F-FDG-PET/CT** is the key functional scan; do it during active inflammation; hold steroids until after.
- **Drug fever** resolves within **~72 h** of stopping the culprit; suspect with eosinophilia/DRESS.
- **Empirical therapy is the exception** (instability, neutropenia, suspected TB, GCA with visual loss); most undiagnosed FUO resolves spontaneously, mortality ≤8%.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Fever of Unknown Origin"; and "Fever" (definition, fever vs hyperthermia, pyrogenic cytokines).
- **CMDT 2026** — "Common Problems in Infectious Diseases & Antimicrobial Therapy: Fever of Unknown Origin" (categories, age/duration considerations, laboratory/imaging/biopsy yields, current management).
- *Coverage note:* The spec lists no dedicated subspecialty textbook for this topic; the Durack–Street four-category framework is named per standard internal-medicine teaching (Harrison 22e details the classic/IUO definitions and the structured PET/CT-based approach; CMDT 2026 supplies the explicit nosocomial/neutropenic/HIV thresholds). All numbers, eponyms and criteria were verified against these chapters.

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Short-course MDR-TB regimen

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Multidrug-resistant tuberculosis (MDR-TB) is disease caused by a strain of *M. tuberculosis* resistant at least to **isoniazid and rifampin**, the two most potent first-line bactericidal drugs; **rifampin-resistant TB (RR-TB)** is treated identically. A **short-course MDR-TB regimen** is an all-oral course of **6–9 months** that has now replaced the older 18–24-month, injectable-containing regimens. The flagship is the **6-month BPaLM regimen** (bedaquiline, pretomanid, linezolid, moxifloxacin), recommended by WHO since 2022 and incorporated into the 2024 guidance for MDR/RR-TB.

Resistance categories that frame the regimen choice

Term	Resistance pattern
RR-TB	Resistance to **rifampin** (managed as MDR)
MDR-TB	Resistance to **isoniazid + rifampin**
Pre-XDR-TB	MDR/RR-TB **plus** resistance to **any fluoroquinolone**
XDR-TB	MDR-TB + fluoroquinolone resistance + resistance to **≥1 other Group A drug** (bedaquiline or linezolid)

- India alone carries ~27% of the global MDR/RR-TB burden; resistance arises by spontaneous point mutations (*rpoB* → rifampin in 95%; *katG/inhA* → isoniazid; *gyrA/gyrB* → fluoroquinolones), and almost always follows effective **monotherapy** or poor adherence.

Rationale for a short-course, all-oral regimen

- **Traditional regimens were unacceptable:** ≥18–24 months, dominated by toxic injectable agents (**kanamycin, capreomycin, amikacin**) causing **ototoxicity and nephrotoxicity**, with poor tolerability, high default rates and cure in only ~50–60%.
- **Evidence base for shortening:** a 2018 individual-patient meta-analysis of >12,000 patients linked **better** outcomes to **linezolid, bedaquiline, clofazimine, carbapenems and later-generation fluoroquinolones**, and **worse** outcomes to kanamycin and capreomycin — which were therefore dropped.
- **Landmark trials:** the **STREAM-1** trial validated a 9–12-month shorter ("Bangladesh") regimen (~90% success); **Nix-TB** and **ZeNix** established **BPaL** (bedaquiline–pretomanid–linezolid, ~89% favourable outcomes) for highly resistant TB and showed **linezolid 600 mg** caused far fewer adverse events than 1200 mg; **TB-PRACTECAL** proved the 24-week **BPaLM** regimen **non-inferior** with **fewer serious adverse events** than the 9–20-month standard of care; **BEAT-Tuberculosis** validated **BDLLfxCfz**.
- **Programmatic advantages:** all-oral therapy removes painful injections, **lowers pill burden**, improves adherence and completion, shortens the period of infectiousness (interrupting transmission), is more **cost-effective**, and reduces amplification of further resistance.

Name the drugs and the duration of use

WHO/Harrison now endorse **four approaches** to MDR/RR-TB; all-oral regimens are preferred, and the choice depends on disease severity, drug-resistance pattern and prior treatment.

Regimen	Component drugs	Duration
BPaLM (preferred)	**B**edaquiline + **Pa** (pretomanid) + **L**inezolid 600 mg + **M**oxifloxacin	**6 months** (drop moxifloxacin → **BPaL** if fluoroquinolone resistance documented)
BDLLfxCfz	**B**edaquiline + **D**elamanid + **L**inezolid 600 mg + **Lfx**/levofloxacin + **Cfz**/clofazimine	**6 months** (Lfx or Cfz may be omitted per FQ-DST; usable in children & pregnancy)
9-month all-oral	**BLMZ**, or **BLLfxCfzZ**, or **BDLLfxZ**	**9 months** (when FQ-susceptible, no prior 2nd-line exposure)
Longer individualised	Group A (Lfx/Mfx, bedaquiline, linezolid) + ≥1 Group B (clofazimine, cycloserine/terizidone) ± Group C	**≥18–20 months** (XDR-TB / complex resistance)

Component drug detail (BPaLM):

- **Bedaquiline** — diarylquinoline; inhibits mycobacterial **ATP synthase**; dose **400 mg once daily ×2 weeks, then 200 mg thrice weekly** for ~6 months; CYP3A4-metabolised, very long t½ (>14 days); carries an FDA **black-box warning** (QT prolongation, mortality signal).
- **Pretomanid** — nitroimidazole **prodrug** inhibiting mycolic-acid synthesis; **200 mg once daily**; main risk **hepatotoxicity**.
- **Linezolid** — oxazolidinone binding the **50S ribosome**; **600 mg once daily** (better tolerated than 1200 mg); toxicities — **myelosuppression, optic and peripheral neuropathy, lactic acidosis, serotonin syndrome** (weak MAOI).
- **Moxifloxacin** — fluoroquinolone inhibiting **DNA gyrase/topoisomerase IV**; **400 mg once daily** in BPaLM; QT prolongation.
- (BDLLfxCfz adds **delamanid 100 mg twice daily** and **clofazimine** — a riminophenazine causing reversible **orange–brown skin/fluid discolouration**, t½ ~70 days.)

Pre-requisites before starting a short-course regimen

- **Confirmed RR/MDR-TB** by rapid molecular DST (e.g., **Xpert MTB/RIF**) — rifampin resistance at minimum.
- **Baseline fluoroquinolone DST** — mandatory; decides whether moxifloxacin/levofloxacin is retained (it directs BPaLM vs BPaL, and BDLLfxCfz composition).
- **No prior exposure (or <1 month)** to the regimen's novel drugs (bedaquiline, pretomanid, linezolid for BPaLM; bedaquiline, delamanid, linezolid for BDLLfxCfz) — unless susceptibility is confirmed.
- **Eligible age & disease form:** BPaLM for patients **≥14 years**, all forms **except** disseminated, CNS and osteoarticular TB (BDLLfxCfz extends to children and pregnant/breastfeeding women).

- **Baseline cardiac assessment: ECG/QTc** and serum electrolytes (K^+, Mg^{2+}, Ca^{2+}) — patients on QT-prolonging drugs (bedaquiline, delamanid, clofazimine, fluoroquinolones) need on-treatment ECG monitoring.
- **Baseline organ-function screen: LFTs** (hepatotoxic drugs), **full blood count** (linezolid marrow suppression), **visual acuity & colour vision** (linezolid optic neuritis), renal function, **HIV test** and **pregnancy test**.
- **Informed consent** and enrolment in **active TB drug-safety monitoring (aDSM)**.
- **Adherence support** — directly observed therapy (DOT) or **video-observed therapy (VOT)**, social/nutritional support, plus pyridoxine where neuropathy risk is high.

Contraindications and cautions

- **Pregnancy and breastfeeding** — a contraindication to **BPaLM** (pretomanid safety data incomplete); use **BDLLfxCfz** or a bedaquiline-based 9-month/longer regimen instead (avoid thioamides, bedaquiline and delamanid where data are lacking in pregnancy).
- **Disseminated, CNS (meningeal) and osteoarticular TB** — excluded from BPaLM; require longer, individualised therapy.
- **QTc >500 ms or a history of ventricular arrhythmia** — do **not** give the QT-prolonging agents (bedaquiline, delamanid, clofazimine, fluoroquinolones).
- **Significant prior exposure (>1 month)** to, or documented resistance to, the regimen's core drugs.
- **Age <14 years** for BPaLM (choose a child-appropriate regimen).
- **Severe drug intolerance/allergy** to a core agent, and clinically significant **drug–drug interactions** (e.g., strong CYP3A4 inducers lowering bedaquiline, serotonergic drugs with linezolid).
- Injectable agents **kanamycin and capreomycin must not be used**; amikacin is reserved (≥18 years, with audiometry) only when oral options fail.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Resistance ladder (vertical steps):** label *RR-TB (rifampin-R) → MDR-TB (isoniazid + rifampin-R) → Pre-XDR (MDR + fluoroquinolone-R) → XDR (MDR + FQ-R + bedaquiline/linezolid-R)*.
- **BPaLM 6-month timeline (horizontal bar):** labels — *Baseline (Day 0): DST + FQ-DST, ECG/QTc, LFT, CBC, vision, HIV, pregnancy test*; four parallel drug bars — *Bedaquiline 400 mg OD ×2 wk → 200 mg thrice-weekly*, *Pretomanid 200 mg OD*, *Linezolid 600 mg OD*, *Moxifloxacin 400 mg OD (omit if FQ-resistant → BPaL)*; bracket *26 weeks (extend if culture-positive at month 4)*; footer *Monthly monitoring: sputum culture, ECG, CBC, vision & neuro review*.

Clinical / Diagnostic significance

- **Universal upfront DST**, especially for rifampin and fluoroquinolones, is the single most important determinant of regimen selection and prevents inadvertent under-treatment.
- **Sputum culture (liquid)** is the standard for monitoring; Xpert MTB/RIF and serial chest X-rays are **not** suitable for response monitoring (they detect non-viable bacilli / lag behind).

- **QTc surveillance** during treatment is essential because several agents are additively cardiotoxic; correct hypokalaemia/hypomagnesaemia.
- **Linezolid** demands monthly **FBC, vision and neurological review**; dose reduction or interruption mitigates marrow suppression and optic/peripheral neuropathy.
- Persistent culture positivity at month 4 (or extensive cavitation) flags slow responders who may need **regimen extension or re-evaluation for amplified resistance** and surgery in localised disease.

High-yield exam pointers

- **MDR-TB = resistance to at least isoniazid + rifampin**; **XDR = MDR + fluoroquinolone + a second Group A drug** (bedaquiline/linezolid).
- **BPaLM = Bedaquiline + Pretomanid + Linezolid (600 mg) + Moxifloxacin for 6 months** — the preferred short-course regimen; becomes **BPaL** if fluoroquinolone-resistant.
- **Bedaquiline 400 mg OD ×2 wk then 200 mg thrice-weekly; linezolid 600 mg OD; pretomanid 200 mg OD; moxifloxacin 400 mg OD.**
- **Pre-requisites:** confirmed RR/MDR-TB, baseline FQ-DST, no prior drug exposure, age ≥14, baseline ECG/LFT/CBC/vision, informed consent, aDSM.
- **Contraindications:** pregnancy/breastfeeding (BPaLM), CNS/osteoarticular/disseminated TB, QTc >500 ms, prior exposure/resistance, age <14.
- **All-oral and injectable-free** — kanamycin/capreomycin abandoned for worse outcomes and toxicity.
- **Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid** (always in longer regimens); **Group B = clofazimine, cycloserine/terizidone.**
- Treatment success with short-course all-oral regimens approaches **~89–90%** (Nix-TB/ZeNix/TB-PRACTECAL).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Tuberculosis" (drug-resistant TB definitions, the four WHO approaches, BPaLM/BDLLfxCfz/9-month regimens, Group A/B/C drugs, pre-requisites, contraindications and monitoring) and "Antimycobacterial Agents" (drug mechanisms, doses, adverse effects; STREAM-1, Nix-TB, ZeNix, TB-PRACTECAL trial detail).
- **CMDT 2026** — "Pulmonary Disorders" (current management of drug-resistant TB; isoniazid- and pyrazinamide-monoresistant regimens; bedaquiline–pretomanid–linezolid reference).

Coverage note: The corpus fully supports the regimens, drugs, doses, pre-requisites and contraindications above. The specific WHO operational rule that BPaLM may be **extended from 26 to 39 weeks** in patients still culture-positive at month 4 is standard WHO programmatic guidance and is stated here as such, as the precise extension figure is not given verbatim in the chapters read.

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Rhino-orbital-cerebral mucormycosis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Mucormycosis is a group of life-threatening, highly angioinvasive and relentlessly progressive infections caused by fungi of the order **Mucorales** (subphylum *Mucoromycotina*). The **rhino-orbital-cerebral (ROCM)** form is the most common presentation worldwide and classically affects patients with **uncontrolled diabetes mellitus, especially diabetic ketoacidosis (DKA)**. It begins in the paranasal sinuses and spreads contiguously/haematogenously to the orbit and brain, producing the characteristic black necrotic eschar and cavernous-sinus thrombosis. Mortality remains high; outcome depends on early polyene therapy, aggressive surgical debridement and rapid reversal of the predisposing state.

Etiology and Predisposing Factors

- The Mucorales comprise **seven families** that cause human disease. ***Rhizopus oryzae*** and ***R. delemar*** (family Mucoraceae) are by far the most common causes. *Apophysomyces elegans* is an important agent **in India**, and *Mucor irregularis* in China.
- Mucormycosis incidence is **higher in India than most other countries even before the COVID-19 pandemic**; during the pandemic it occurred commonly as a co-infection in hospitalised COVID-19 patients, driven by high-dose corticosteroids combined with the high background prevalence of diabetes.

Family	Representative genera/species
Mucoraceae	*Rhizopus oryzae, R. delemar, R. microsporus, Rhizomucor, Mucor, Actinomucor*
Lichtheimiaceae	*Lichtheimia* (formerly *Mycocladus/Absidia*)
Cunninghamellaceae	*Cunninghamella*
Saksenaceae	*Saksenaea, Apophysomyces*
Mortierellaceae, Thamnidiaceae, Syncephalastraceae	*Mortierella, Cokeromyces, Syncephalastrum*

- **Key predisposing factors:** uncontrolled diabetes mellitus / **DKA** (→ ROCM specifically); defects in phagocytic function (**neutropenia**, high-dose **corticosteroids**); **elevated free iron** (e.g., deferoxamine therapy in iron-overloaded dialysis patients); solid-organ or **haematopoietic stem-cell transplant (HSCT)**; haematological malignancy.
- Patients on **itraconazole or voriconazole prophylaxis** may be at increased risk; breakthrough disease is also reported with posaconazole, isavuconazole or echinocandin prophylaxis.
- *Important caveat:* the **majority of diabetics presenting with mucormycosis are NOT acidotic**, and many have **no prior diagnosis of diabetes** — presentation may be the first recognition of hyperglycaemia (often unmasked by recent glucocorticoids).

Pathogenesis — the Iron / GRP78 / CotH Axis

- The Mucorales are ubiquitous environmental fungi; infection follows inhalation of spores into the sinuses in a susceptible host.

- **Free iron is the central virulence determinant.** In **DKA**, acidosis causes **dissociation of iron from sequestering proteins**, enhancing fungal survival and virulence. The ketoacid **β-hydroxybutyrate** upregulates host and fungal receptors mediating adherence and tissue penetration.
- **Deferoxamine** acts as a fungal **xenosiderophore** — it chelates iron for the host but delivers it directly to the Mucorales, historically causing rapidly fatal disseminated disease.
- Even without acidosis, **hyperglycaemia** promotes infection by ≥4 mechanisms: (1) **hyperglycation of iron-sequestering proteins** (disrupts iron sequestration); (2) **upregulation of GRP78**, a mammalian receptor that binds Mucorales and enables tissue penetration; (3) poorly characterised **defects in phagocyte function**; (4) enhanced expression of **CotH**, a Mucorales-specific invasin that mediates host-cell invasion by binding GRP78.
- The hallmark is **angioinvasion → vascular thrombosis → tissue infarction and necrosis**, which also impairs antifungal drug delivery to the infected site.

Clinical Features and Stage-wise Progression of ROCM

- **Patients with diabetes/DKA typically develop the rhino-orbital-cerebral form** and only rarely pulmonary or disseminated disease.
- **Early symptoms are non-specific:** eye or facial pain, **facial numbness**, followed by **conjunctival suffusion**, periocular swelling and **blurry vision**.
- Periorbital skin takes on a **dusky, subacute appearance** — in contrast to the acute, bright-red periocular changes of **bacterial orbital cellulitis**.
- **Fever may be absent in up to half** of cases; the WBC count is usually elevated as long as marrow function is intact.
- **Sino-orbital spread:** untreated infection spreads from the **ethmoid sinus → orbit**, causing compromise of extraocular-muscle function, **proptosis** and **chemosis**.
- **Intracranial / cavernous-sinus spread:** from the orbit the fungus extends contiguously or haematogenously to the **frontal lobe**, and via venous drainage to the **cavernous sinus**. **Contralateral eye involvement with bilateral proptosis, chemosis, vision loss and ophthalmoplegia is ominous and suggests cavernous-sinus thrombosis.**
- **Local tissue evolution:** infected tissue may look **normal** initially (hence "blind" biopsy of normal-appearing sinus is warranted when suspicion is high) → **erythematous (± oedema) → violaceous → black necrotic eschar**. Extension into the mouth produces painful necrotic ulceration of the **hard palate** — a *late* finding indicating extensive, well-established disease.
- *Note:* progression is **variable, not always fulminant** — death may occur in days, or progression may take months, depending on host immunity, inoculum and species virulence.

Diagnosis

- **A high index of suspicion is essential** — autopsy series show **up to half of cases are diagnosed only post-mortem**.
- **Definitive diagnosis:** positive culture from a **sterile site** (needle aspirate, tissue biopsy, pleural fluid) **or histopathological evidence of invasive disease**. **Biopsy with histopathology is the most sensitive and specific modality.**

- **Characteristic histology:** broad/**wide (≥6–30 µm)**, thick-walled, **ribbon-like, aseptate (pauciseptate) hyphae** that **branch at right angles (≈90°)**. Best stained with **PAS or H&E**; **methenamine silver may not stain optimally**.

Feature	Mucorales	Aspergillus / Fusarium / Scedosporium
Septation	Aseptate / pauciseptate	Septate
Hyphal width	Broad, ribbon-like (6–30 µm)	Thin
Branching angle	Wide, ~90° (right angle)	Acute (~45°)

- **Culture caveats:** positive in **<50%** of cases — long filamentous hyphae are killed by tissue **homogenisation**, so alert the lab and place **minced tissue sections** (not homogenate) on media; incubate at both **room temperature and 37°C**. Mucorales are not fastidious and grow within **48–96 h**. Species identification requires culture (not histology).
- **Imaging:** sinusitis on CT/MRI is often **indistinguishable from bacterial sinusitis**, and bony erosion into the orbit is **rarely seen on CT even when clinically present**. **MRI is more sensitive (~80%)** for orbital and CNS disease. Imaging routinely **underestimates** extent — high-risk patients should undergo **endoscopy and/or surgical exploration with biopsy**.
- **PCR** of Mucorales-specific targets is useful but **not FDA-approved**. Because therapy must often start empirically, **begin a lipid polyene as soon as suspicion is reasonable** while confirmation is awaited.

Differential Diagnosis

- **Other invasive moulds:** aspergillosis, scedosporiosis, fusariosis, dematiaceous (brown-pigmented) fungi — distinguishing them matters because **polyenes treat Mucorales whereas expanded-spectrum triazoles treat most septate moulds**, and **voriconazole actually exacerbates mucormycosis**.
- **Entomophthoromycoses** (*Basidiobolus, Conidiobolus*) — histologically similar but distinguished by culture; also treated with polyenes, so urgent differentiation is unnecessary.
- **Bacterial orbital cellulitis / cavernous-sinus thrombosis** (most commonly *Staphylococcus aureus*, also streptococci and gram-negatives).
- ***Klebsiella rhinoscleromatis*** (indolent facial rhinoscleroma).
- ***Tolosa-Hunt syndrome*** — painful ophthalmoplegia, ptosis, headache and cavernous-sinus inflammation; **lack of progression** helps distinguish it from mucormycosis.

Treatment

- **Four pillars of management:** (1) **early initiation** of antifungal therapy; (2) **surgical debridement** of all necrotic tissue when feasible; (3) **rapid reversal of predisposing factors**; (4) **treat the underlying malignancy without waiting** to finish antifungals.
- **Surgery:** because thrombosis/necrosis impairs drug penetration, **debridement is an independent predictor of favourable outcome**; intra-operative **frozen sections** help delineate infected margins. Use a *moderated* approach — debride to the extent it is safe.

- **Reverse the host defect:** correct **hyperglycaemia and acidosis** (sodium bicarbonate improved survival in DKA mice), **taper corticosteroids**, and **avoid iron** — use a **conservative RBC-transfusion** policy (haemolysis liberates free iron).

Line	Drug	Dose	Notes
First-line	**Liposomal AmB (LAmB)**	5–10 mg/kg/day	Preferred for **brain** disease — best CNS penetration; consider 7.5–10 mg/kg/day for CNS, but no benefit above 10 mg/kg/day (autoinduction lowers levels)
First-line	AmB lipid complex (ABLC)	5 mg/kg/day	Less nephrotoxic than deoxycholate; possibly less effective than LAmB for CNS
First-line	AmB deoxycholate	1.0–1.5 mg/kg/day	Cheap, FDA-approved, but highly toxic and **poor CNS penetration**
Second-line / salvage	**Isavuconazole**	200 mg (372 mg isavuconazonium sulfate) load q8h ×6, then once daily	FDA-approved; rational empirical choice when septate-mould vs Mucorales is unresolved
Second-line / salvage	Posaconazole	200 mg four times daily	Salvage only; lower blood levels than isavuconazole
Combination	**Echinocandin + lipid polyene**	Standard echinocandin doses	Synergy in murine disease; retrospective benefit in ROCM. **Do NOT escalate echinocandin ≥3 mg/kg/day** (paradoxical loss of benefit)

- **Primary therapy must be a polyene** except perhaps in mild, surgically excised, isolated suprafascial cutaneous disease in an immunocompetent host.
- **Deferasirox** is fungicidal *in vitro* and synergistic with LAmB in DKA mice; however human trial evidence is limited (see Coverage note).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Coronal section of face/skull showing ROCM spread** — Labels: *ethmoid/maxillary sinus (primary focus), nasal turbinate with black eschar, orbit with proptosis & chemosis, extraocular muscles, optic nerve, cavernous sinus (thrombosis), internal carotid artery, frontal lobe extension, hard-palate necrotic ulcer.*
- **Histopathology of Mucorales** — Labels: *broad ribbon-like aseptate hypha (6–30 μm), right-angle (90°) branching, thrombosed blood vessel with intravascular hyphae (angioinvasion), surrounding tissue infarction.*

Clinical / Diagnostic significance

- In any **diabetic with sinusitis + facial/orbital pain, numbness, or proptosis**, suspect ROCM and act emergently — delay is lethal.
- **Hyperglycaemia with new sinusitis and possible orbital extension** warrants suspicion even with **no known history of diabetes**.

- **Bilateral proptosis/ophthalmoplegia = cavernous-sinus thrombosis**, a neurosurgical/ophthalmic emergency.
- Diagnostic workup: urgent **ENT endoscopy + biopsy/KOH + histopathology + fungal culture**, **MRI brain/orbit/sinuses**, glycaemic and acid-base assessment.
- **Never give voriconazole** if mucormycosis is in the differential — it worsens disease.
- Management is **multidisciplinary** (Internal medicine/Endocrine, ENT, Ophthalmology, Neurosurgery, Microbiology) with combined medical + surgical therapy.

High-yield exam pointers

- **ROCM = most common form worldwide; diabetes/DKA is the classic host;** India has disproportionately high incidence (further amplified by COVID-19 + steroids).
- ***Rhizopus oryzae/R. delemar*** = commonest agents; **aseptate, broad, ribbon-like hyphae, right-angle branching.**
- Central mechanism = **free iron + GRP78/CotH-mediated angioinvasion**; **deferoxamine** is a risk factor (xenosiderophore).
- Hallmark sign = **black necrotic eschar** (nasal/palatal); periorbital skin is **dusky**, not bright-red.
- **MRI > CT** for orbital/CNS extent; **culture positive in <50%** — alert lab, do not homogenise tissue; **PCR not FDA-approved**.
- **First-line = liposomal amphotericin B 5–10 mg/kg/day + early surgical debridement + control of diabetes/acidosis/iron**.
- **Isavuconazole and posaconazole** are second-line/salvage; **avoid voriconazole**.
- Disseminated disease mortality **>90%**; mucormycosis-related **necrotising fasciitis ~80%**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 224 "Mucormycosis"** (Spellberg & Ibrahim), incl. Tables 224-1 (taxonomy) and 224-2 (antifungal options) and Fig. 224-1 (histopathology).

Coverage note: The provided chapter text is **truncated at the start of the adjunctive-deferasirox phase-2 trial sentence**, so the final human trial outcome (the *DEFEAT-Mucor*-type result showing no benefit/possible harm of adjunctive deferasirox) and any concluding outcome/mortality figures for ROCM specifically were not in the supplied text and are therefore stated only as far as the text supports. **Hyperbaric oxygen** as adjunctive therapy is *not* mentioned in the provided text and has been deliberately omitted to avoid fabrication.

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Strongyloides hyperinfection syndrome

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Strongyloides stercoralis* is a soil-transmitted intestinal nematode that is **unique among helminths** (along with *Capillaria*) in its ability to complete its entire life cycle and replicate within the human host through **autoinfection**, allowing infection to persist silently for decades. **Hyperinfection syndrome** is the dangerous acceleration of this autoinfection cycle, with massive multiplication of filariform larvae within the normal migratory route (gut → lungs), triggered by impaired cell-mediated immunity. When larvae spread beyond this route to organs such as the CNS, liver, kidney, skin and peritoneum, the condition is termed **disseminated strongyloidiasis**. It carries a very high mortality (approaching 100% untreated, ~25% even when treated) and is most often unmasked by **glucocorticoid therapy**.

Life cycle & pathophysiology (basis of hyperinfection)

- **Acquisition:** filariform larvae in faecally-contaminated soil penetrate skin/mucosa → bloodstream → lungs → ascend bronchial tree → swallowed → mature into adult worms embedded in proximal small-bowel mucosa.
- The minute (1–2 mm) **parthenogenetic adult females** produce eggs that hatch in the mucosa into **rhabditiform larvae** (~250 µm, short buccal cavity).
- **Autoinfection:** some rhabditiform larvae transform *within the bowel* into invasive **filariform larvae** (~450 µm) that penetrate the colonic wall or perianal skin and re-enter the circulation — perpetuating internal reinfection without fresh exogenous exposure.
- This autoinfection cycle is normally **restrained by intact cell-mediated (Th2) immunity and eosinophils**. When this restraint fails, larval numbers amplify exponentially → **hyperinfection**, and disrupted gut mucosa allows **translocation of enteric gram-negative bacteria** → bacteraemia/sepsis.

Risk factors / Predisposing conditions

Category	Specific predisposing factors
Drugs (greatest risk)	**High-dose / prolonged corticosteroids** (the single most important trigger); other immunosuppressants — calcineurin inhibitors, chemotherapy, biologics
Viral / retroviral	**HTLV-1 infection** (classic, strong association — shifts immunity away from protective Th2); AIDS/HIV
Haematological / malignancy	Haematologic malignancies (lymphoma, leukaemia); cytotoxic chemotherapy
Transplantation	Solid-organ and haematopoietic stem-cell transplantation (donor-derived transmission described)
Host / nutritional	Malnutrition, **alcohol use disorder**, diabetes, chronic debilitating illness, hypogammaglobulinaemia
Epidemiological exposure	Residence in / travel to **Southeast Asia, sub-Saharan Africa, Brazil**, endemic SE United States; immigrants, refugees, military personnel — *even decades earlier* (latent autoinfection)

- **Exam pearl:** Strongyloides hyperinfection is the classic helminth disease **precipitated by steroids** — eosinophilia is *not* protective once steroids blunt the immune response, and (importantly) eosinophilia is often **suppressed by the very steroids** that precipitate the syndrome.

Clinical presentation

Uncomplicated (chronic) strongyloidiasis — often asymptomatic or:

- **Cutaneous:** recurrent **urticaria** (often buttocks); **larva currens** — a *pathognomonic*, pruritic, raised, serpiginous track that advances rapidly (up to **10 cm/h**).
- **GI:** mid-epigastric pain mimicking peptic ulcer (aggravated by food), nausea, watery diarrhoea, bloating, occult GI bleeding, weight loss.
- **Eosinophilia** that fluctuates over time; pulmonary symptoms rare.

Hyperinfection / disseminated disease — overwhelming, multi-system and often fulminant:

System	Manifestations
Gastrointestinal	Severe colitis/enteritis, malabsorption, paralytic ileus, **intestinal obstruction, perforation, massive GI haemorrhage**
Pulmonary	Pneumonitis, cough, wheeze, **haemoptysis**, diffuse infiltrates/ARDS, respiratory failure; larvae/eggs in sputum
Bloodstream	**Recurrent gram-negative bacteraemia / polymicrobial sepsis** from enteric flora translocation — a frequent presenting feature
CNS	**Gram-negative (E. coli/enteric) meningitis**, brain abscess; larvae may be seen in CSF
Skin	Widespread purpuric/petechial eruption, **"thumbprint" periumbilical purpura** from migrating larvae
Other	Hepatic, renal, peritoneal involvement; progression to shock and death

- **Red flag combination:** an immunosuppressed (especially steroid-treated) patient with **recurrent gram-negative sepsis or enteric meningitis + unexplained ileus/abdominal signs + pulmonary infiltrates**, particularly with a remote tropical exposure, is hyperinfection until proven otherwise.

Diagnosis / Investigations

- **Stool microscopy** — demonstrates motile **rhabditiform larvae** (not eggs); short buccal cavity distinguishes them from hookworm larvae. *Single stool sensitivity is low (~30%; detects only ~one-third of uncomplicated cases)* → request **serial (3–7) samples**.
- **Concentration / culture techniques** — **agar-plate culture** and Baermann concentration markedly raise sensitivity.
- **Duodenal sampling** — aspiration or biopsy of duodenojejunal contents (string test) when stools repeatedly negative.
- **Serology (ELISA)** — sensitive (~**90% sensitivity/specificity**, CDC assay) for *uncomplicated/chronic* infection; cross-reacts with other helminths. **Indicated to screen before immunosuppression / transplantation**, especially with eosinophilia or endemic exposure.
- **PCR / molecular assays** — increasing sensitivity and species specificity.

- **In hyperinfection:** larval burden is huge, so a **single stool exam is usually positive**; **filariform larvae** are readily found in **stool, sputum, BAL fluid, CSF and surgical drainage fluid** — i.e. sample the migration sites.
- **Supportive:** eosinophilia + mild anaemia in chronic disease; **eosinophilia is frequently ABSENT in hyperinfection (poor prognostic sign)**; hypoproteinaemia, deranged LFTs, and diffuse pulmonary infiltrates on imaging; blood cultures growing **enteric gram-negative organisms**.

Treatment

- **Drug of choice — Ivermectin**, more effective than albendazole:
  - *Uncomplicated:* **ivermectin 200 µg/kg/day orally for 1–2 days**.
  - *Alternative:* albendazole 400 mg orally twice daily for 3 days (less effective).
- **Hyperinfection / disseminated disease:**
  - **Prolonged ivermectin** continued daily **until at least 14 days after stool/sputum become and remain larva-negative**.
  - In immunocompromised hosts, **repeat the ivermectin course ~2 weeks after the initial treatment**; with ongoing immunosuppression, **regular suppressive dosing (e.g. monthly ivermectin)** may be needed.
  - When oral route impossible (ileus): ivermectin has been given **per rectum** or **parenterally** (veterinary preparation under single-patient expanded-access protocols).
- **Adjuncts:** broad-spectrum antibiotics for concurrent gram-negative sepsis/meningitis; supportive care for ARDS, ileus, fluid/electrolyte derangement; **taper/withdraw glucocorticoids and other immunosuppression** wherever feasible.
- **Even asymptomatic infection must be treated** because of the lifelong risk of fatal hyperinfection — eradication is the goal (monitor falling eosinophil count and antibody titre as response markers).

Prevention / screening (high-yield):

- **Screen all at-risk patients (serology ± stool) BEFORE starting corticosteroids, chemotherapy, biologics, or transplantation**, especially with any history — even remote — of residence in an endemic area.
- **Presumptive ivermectin treatment** is warranted in seropositive (or strongly exposed) patients even when stool examination is negative.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Life cycle of *Strongyloides stercoralis*** (labels): *filariform larva penetrates skin → bloodstream → lungs / alveoli → ascends trachea, swallowed → adult female in small-bowel mucosa (parthenogenesis) → eggs hatch → rhabditiform larva (~250 µm)*; branch the three fates — **(a) Direct/Indirect free-living cycle in soil**, **(b) Autoinfection** (rhabditiform → filariform → perianal skin/colonic wall → recirculate), and **(c) Hyperinfection/Dissemination** (with immunosuppression → massive filariform larvae → **lungs, CNS, liver, kidney, skin + gram-negative sepsis**).
- **Diagram 2 — "Autoinfection → Hyperinfection → Dissemination" arrow ladder**, annotated with the immune trigger (**steroids / HTLV-1 / impaired CMI**) at the step where control is lost.

Clinical / Diagnostic significance

- Classic **"steroid-unmasked" parasitosis** — always exclude/treat Strongyloides before immunosuppressing a patient from an endemic area.
- **Recurrent enteric gram-negative bacteraemia or *E. coli* meningitis** in an immunosuppressed host should prompt a search for Strongyloides as the conduit.
- **Eosinophilia is paradoxically a good sign** (intact immunity); its absence in a deteriorating immunosuppressed patient is ominous.
- Untreated dissemination is **near-uniformly fatal** — early empirical ivermectin saves lives when suspicion is high.

High-yield exam pointers

- **Autoinfection** makes Strongyloides the helminth that can persist **for decades** and the only common one to cause **fatal hyperinfection**.
- **Greatest single risk factor = corticosteroids**; strongest infective co-factor = **HTLV-1**.
- **Larva currens** (10 cm/h serpiginous track) is *pathognomonic*; **periumbilical "thumbprint" purpura** suggests dissemination.
- Stool ova-and-parasite finds **larvae, not eggs**; **single stool ~30% sensitive** → do serial stools + **agar-plate culture**; **serology (ELISA ~90%)** for screening.
- **Hyperinfection:** larvae in **sputum/BAL/CSF**; **single stool usually positive**; **eosinophilia often absent**.
- **Ivermectin 200 µg/kg/day** is drug of choice; in dissemination continue **≥2 weeks after larvae clear** and **repeat course** in the immunosuppressed.
- **Screen + treat before immunosuppression / transplant**; treat even asymptomatic carriers.
- Mortality: **~100% untreated, ~25% treated** — outcome hinges on early recognition.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Intestinal Nematode Infections" (Strongyloidiasis section: life cycle, autoinfection/hyperinfection/dissemination, larva currens, HTLV-1 and glucocorticoid risk, diagnosis, ivermectin treatment).
- **CMDT 2026** — "Protozoal & Helminthic Infections" (Strongyloidiasis: risk factors, mortality figures ~100%/25%, ELISA sensitivity, screening before immunosuppression, ivermectin regimens for hyperinfection).

Coverage note: The corpus has no dedicated infectious-disease subspecialty textbook in the spec (specialty_books empty); depth is therefore drawn from Harrison 22e + CMDT 2026, which together cover the topic comprehensively. The "thumbprint periumbilical purpura" sign is universally-accepted standard ID teaching included for completeness though not verbatim in the two cited chapters.

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CD4 count in management of HIV infection

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — The **CD4+ T lymphocyte** is the principal target cell of HIV and the central pivot of immune competence; the **absolute CD4 count** (cells/µL) is therefore the single most widely used marker for *staging*, *prognosis* and *guiding opportunistic-infection (OI) prophylaxis* in HIV. HIV preferentially infects and depletes CD4+ helper T cells (gp120 binds the 55-kDa CD4 molecule plus a co-receptor, CCR5 or CXCR4), so the count is a direct readout of the degree of immunodeficiency. It is complementary to, not a substitute for, the **plasma HIV RNA (viral load)** — the count measures *immune damage already done*, the viral load measures *active replication and treatment response*.

CD4 cell biology — what the count actually measures

- CD4 is a glycoprotein on **helper (Th) T lymphocytes**, also on monocytes/macrophages and dendritic cells; it is the primary HIV receptor.
- In an untreated patient the count falls at an **average of ~50 cells/µL per year**; when it crosses **<200/µL** the immunodeficiency is severe enough to expose the patient to OIs and AIDS-defining neoplasms.
- The count thus serves four management roles: (1) **stage** the disease, (2) **risk-stratify** for specific OIs, (3) decide **start/stop of OI prophylaxis**, and (4) **monitor immune reconstitution** on antiretroviral therapy (ART).

CD4-based CDC staging and the AIDS-defining threshold

The CDC (MMWR 2014) classifies HIV by CD4 count (count takes precedence; percentage used only if count missing) for persons aged ≥6 years:

Stage	CD4 count (cells/µL)	CD4 percentage
Stage 1	≥500	≥26%

Stage	CD4 count (cells/μL)	CD4 percentage
Stage 2	200–499	14–25%
Stage 3 (AIDS)	<200	<14%

- A diagnosis of **AIDS** is made in any person ≥6 years with HIV and a **CD4 <200/μL (Stage 3)** *or* a CD4 percentage <14%, *or* who develops an **AIDS-defining (stage-3) opportunistic illness** regardless of count.
- The **200/μL** cut-off is evidence-based: cohort studies show AIDS develops within ~3 years in **>80%** of untreated persons whose counts fall below this level.

CD4 count and the spectrum of opportunistic disease

The CD4 count predicts *which* complications are likely, allowing a focused differential at any given count:

Approx. CD4 (cells/μL)	Characteristic complications
>500	Acute retroviral syndrome, persistent generalised lymphadenopathy; later — **herpes zoster, vaginal candidiasis, oral hairy leukoplakia, Kaposi sarcoma**
200–500	Bacterial pneumonia, pulmonary TB, mucocutaneous candidiasis, ITP
<200	***Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis, cryptococcosis, coccidioidomycosis, cryptosporidiosis**
<50	**Disseminated *Mycobacterium avium* complex (MAC), CMV retinitis, CNS lymphoma, disseminated histoplasmosis**

- This graded relationship (Harrison Fig. 208-32; CMDT Fig. 36-1) is the basis for using the count to anticipate, prevent and empirically treat OIs.

CD4 thresholds for opportunistic-infection prophylaxis (start / stop)

Decisions on prophylaxis are based on **CD4 count, recent viral load and prior OI history** (NIH/CDC/IDSA guidelines):

Pathogen	Start primary prophylaxis	First-choice agent	Stop (immune reconstitution)
***P. jirovecii* (PCP)**	CD4 **<200/μL**, CD4 <14%, oropharyngeal candidiasis, or prior PCP	**TMP-SMX** 1 DS tab daily	CD4 **>200/μL for ≥3 months** on ART
Toxoplasma gondii	Toxoplasma **IgG-positive** and CD4 **<100/μL**	**TMP-SMX** 1 DS tab daily	CD4 **>200/μL** + HIV RNA suppressed ≥3 months
***M. avium* complex**	CD4 **<50/μL** *only if ART not initiated* (rarely needed now)	**Azithromycin** 1200 mg weekly	Once on fully suppressive ART
Cryptococcus / CMV	Secondary (post-disease) prophylaxis only	Fluconazole / valganciclovir	CD4 >100/μL for ≥6 months + suppression

Pathogen	Start primary prophylaxis	First-choice agent	Stop (immune reconstitution)
Histoplasma (endemic)	Prior disease or CD4 <150/μL with high risk	Itraconazole 200 mg	CD4 >150/μL ≥6 months on ART

- **Key teaching point:** a single TMP-SMX DS tablet covers **both PCP and toxoplasmosis**, so the practical rule is — start co-trimoxazole when **CD4 <200/μL** and continue until immune reconstitution.
- Prophylaxis is *safely discontinued* once ART raises the CD4 above the starting threshold (and viral load is suppressed) — prophylaxis decisions are dynamic, driven by the **trend** of the CD4.

Role of CD4 in initiating and monitoring ART

- **When to start ART:** Current DHHS guidance recommends **ART for *everyone* with HIV, as soon as possible after diagnosis, regardless of CD4 count or viral load** — the count no longer gates *whether* to treat, but still informs *timing and urgency*.
- **Urgency by CD4:** With **advanced disease (CD4 <50/μL)** ART should be started as soon as possible. When an OI is diagnosed concurrently and **CD4 ≥50/μL**, a **2–4 week delay** may be considered (treating the OI first) to reduce the severity of immune reconstitution inflammatory syndrome (IRIS) — relevant especially to **TB and cryptococcal meningitis**.
- **Expected response to ART:** a rapid **≥1-log (10-fold) fall in HIV RNA within 1–2 months**, suppression to **<50 copies/mL by ~6 months**, and a **CD4 rise of ~100–150 cells/μL** over the same period.
- **Monitoring frequency (CMDT Table 36-5):** CD4 **every 3–6 months**; this can be reduced to **every 12 months** once viral load is suppressed on ART for 2 years with CD4 **>300/μL**, and routine CD4 monitoring becomes **optional/unnecessary** once CD4 is consistently **>350–500/μL** with sustained virologic suppression. Thereafter **viral load** is the chief monitoring tool.
- **IRIS** (Table 208-12): paradoxical worsening or unmasking of an OI weeks–months after starting ART; most common when ART is begun at **CD4 <50/μL** with a precipitous drop in viral load, classically with TB.

Limitations and pitfalls of CD4 interpretation

- Subject to **diurnal variation**, transient depression with intercurrent illness or recent vaccination, and **inter-/intra-laboratory variability** — therefore the **trend matters more than a single value**.
- The **CD4 percentage** is more stable; **<14%** ≈ CD4 <200/μL, and a percentage of **~15%** ≈ **200 cells/μL**.
- After **splenectomy** the absolute count is unreliable (artefactual lymphocytosis) — use the **CD4 percentage**.
- The CD4 count says nothing about viral replication; **viral load is the more accurate marker of activity and ART response**, providing prognostic information independent of the count.
- Patients immunised when CD4 was **<100/μL** should be **re-immunised** once the count recovers to **>200/μL** for an adequate response; live vaccines are avoided at CD4 <200/μL.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"CD4 staircase" — CD4 count vs opportunistic disease:** Draw a vertical CD4 axis (cells/μL) marked at **500, 200, 50**. Place labelled boxes at each level — **>500:** herpes zoster, oral hairy leukoplakia, vaginal candidiasis, Kaposi sarcoma; **<200:** PCP, toxoplasmosis, cryptococcosis, coccidioidomycosis, cryptosporidiosis; **<50:** disseminated MAC, CMV retinitis, CNS lymphoma, histoplasmosis. Add a dashed line at **200 = "AIDS / start PCP prophylaxis."**
- **Natural-history curve:** time on X-axis; plot **falling CD4** against **rising/plateauing HIV RNA**, labels — *acute retroviral syndrome*, *clinical latency (~10 yrs, decline ~50/μL/yr)*, *symptomatic/AIDS (<200/μL)*.

Clinical / Diagnostic significance

- Establishes **stage and prognosis**, and identifies the patient who has progressed to **AIDS** even when asymptomatic.
- Directs **OI prophylaxis** (start and stop) and shapes the **empirical differential** when a person with HIV presents acutely (e.g., headache + CD4 <100 → think cryptococcal meningitis/CNS toxoplasmosis).
- Confirms **immune reconstitution** on ART (rising CD4) and flags risk of **IRIS** when baseline CD4 is very low.
- A baseline CD4 is part of the initial work-up alongside HIV RNA, genotypic resistance testing, CBC/chemistry, hepatitis and toxoplasma serology, and TB screening.

High-yield exam pointers

- **AIDS = CD4 <200/μL (or <14%) OR an AIDS-defining illness** in a person with HIV.
- CDC stages: **1 ≥500, 2 = 200–499, 3 <200** cells/μL.
- Untreated CD4 declines ~**50 cells/μL per year**; median time to AIDS ~10 years.
- **PCP prophylaxis at <200**, **toxoplasmosis (IgG+) at <100**, **MAC at <50** (only if ART deferred) — TMP-SMX covers PCP *and* toxoplasma.
- Stop PCP prophylaxis when CD4 **>200/μL for ≥3 months** on ART.
- **ART is for everyone regardless of CD4** — CD4 now guides *timing/urgency*, not eligibility; start ASAP if CD4 <50.
- Expect a **CD4 rise of ~100–150/μL** in the first months of effective ART.
- **IRIS** is most frequent when ART starts at **CD4 <50/μL**, classically with TB/cryptococcus.
- Use **CD4 percentage** (≈15% = 200/μL) when the absolute count is unreliable (post-splenectomy, acute illness).
- **Trend > single value**; viral load, not CD4, is the marker of treatment response.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (CDC CD4 staging Table 208-2; CD4–opportunistic-disease relationship; NIH/CDC/IDSA 2024 OI prophylaxis thresholds Table 208-11; DHHS principles of ART/when-to-start; IRIS characteristics Table 208-12).
- **CMDT 2026** — "HIV Infection & AIDS" (CD4 as prognostic/prophylaxis marker and its limitations; CD4–OI Figure 36-1; prophylaxis thresholds; health-care maintenance and CD4 monitoring frequency Table 36-5).

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Seroconversion illness in HIV

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Seroconversion illness* (the **acute retroviral syndrome / acute HIV syndrome / primary HIV infection**) is the symptomatic, self-limiting acute viral illness that appears in the interval between acquisition of HIV and the appearance of detectable anti-HIV antibody. It develops **~3–6 weeks after primary infection** in an estimated **50–70%** of newly infected individuals, coincides with the **burst of high-level plasma viremia** and wide dissemination/seeding of lymphoid tissue, and clinically resembles **acute infectious mononucleosis**. Recognising it is a high-stakes opportunity: the patient is intensely infectious, standard antibody tests may still be negative, and early diagnosis permits immediate antiretroviral therapy (ART).

Pathogenesis & timing (why the illness occurs)

- After mucosal/parenteral entry there is a brief **"eclipse" phase** (virus replicating locally, not yet detectable in plasma); virus is then carried to draining lymph nodes and other lymphoid compartments rich in **CD4+ T-cell targets**, producing a **burst of high-level plasma viremia**.
- The symptomatic illness coincides with this **peak viremia** and the seeding of lymphoid organs; symptoms subside as the **HIV-specific immune response** (CD8+ CTL, then antibody/ADCC) develops and viremia is curtailed toward the viral **"set-point."**
- **Immunologic perturbations:** initial fall in total lymphocytes and both CD4+ and CD8+ subsets; later a **transient selective expansion of CD8+ T cells** producing **inversion of the CD4:CD8 ratio**. CD4+ counts usually remain mildly depressed afterward.
- The magnitude of the initial viremic burst does **not** reliably correlate with subsequent rate of disease progression; however, **~10%** of patients manifest a **fulminant** immunologic/clinical course after primary infection.
- **Opportunistic infections can occur even during this acute phase**, reflecting the transient profound immunodeficiency at peak viremia.
- Symptomatic seroconversion severe enough to seek medical attention has been **suggested to indicate increased risk of an accelerated course**, though this remains debated; primary infection (with or without an acute syndrome) is typically followed by **clinical latency / smouldering low-level disease activity**.

Clinical features

The picture is that of a non-specific acute viral syndrome ("mononucleosis-like"), typically lasting **one to several weeks** and resolving spontaneously. *Clinical findings in the acute HIV syndrome (Harrison Table 208-10):*

System	Manifestations
General	Fever, pharyngitis, **lymphadenopathy** (~70%), headache/retro-orbital pain, arthralgia/myalgia, lethargy/malaise, anorexia, weight loss
Dermatologic	**Erythematous maculopapular rash** (face/trunk), **mucocutaneous ulceration** (oral, anal, genital)
Gastrointestinal	Nausea, vomiting, diarrhoea
Neurologic	Aseptic **meningitis**, **encephalitis**, peripheral neuropathy, myelopathy, Guillain-Barré–like illness

- The combination of **fever + pharyngitis + generalised lymphadenopathy + maculopapular rash + painful mucocutaneous (oral/genital) ulcers** is the most suggestive cluster and distinguishes it from EBV/CMV mononucleosis (in which ulcers and rash without ampicillin are uncommon).
- Fever, rash, pharyngitis and myalgia are reported **less frequently in those infected by injection drug use** than by sexual contact.
- Most recover spontaneously, often left with only a mildly depressed CD4+ count; the illness is then followed by a prolonged **clinical latency** (median time to AIDS ~10 years untreated; average CD4 decline ~50/μL per year).

Laboratory diagnosis — the window period & marker kinetics

The central diagnostic problem is that **antibodies appear only ~3–12 weeks after infection**, so antibody-only tests may be falsely negative during seroconversion. Markers become detectable in a characteristic order:

Marker	Approx. time to detectability	Diagnostic role
HIV-1 RNA (NAT / viral load)	Earliest (≈10 days; after the eclipse phase)	Confirms acute infection when antibody is negative
p24 antigen	Days–~2 weeks (before antibody)	Component of the 4th-generation combo assay
Anti-HIV antibody	~3–12 weeks (4th-gen detects in 99% by ~6 weeks; median ~2 weeks)	Basis of screening/confirmatory assays

- **Fiebig staging** describes the evolution of acute infection from **stage I (HIV RNA positive alone)** through to **stage VI (HIV RNA + full Western blot positive)**, charting the sequential appearance of RNA → p24 → antibody bands.
- **Recommended initial test:** a **fourth-generation HIV-1/2 antigen/antibody combination immunoassay** (detects HIV-1 & HIV-2 antibody **plus p24 antigen**) — narrows the window versus older antibody-only EIA.
- **CDC testing algorithm:** reactive 4th-gen combo → **HIV-1/HIV-2 antibody differentiation immunoassay** (e.g., *Bio-Rad Geenius*). If the differentiation assay is **negative or indeterminate**

but a NAT (HIV-1 RNA) is positive → diagnosis of acute HIV-1 infection. A combo-reactive specimen with repeatedly negative differentiation and **undetectable NAT** is presumed **false-positive** (e.g., recent influenza vaccination, autoantibodies, pregnancy-related alloantibodies).

- **Caveat:** low-level viremia **<1000 copies/mL** on NAT may be a false positive — interpret cautiously.
- The screening EIA is highly sensitive (**>99.5%**) but imperfectly specific in low-risk populations, so a reactive screen **always** needs a more specific confirmatory step before a diagnosis is given. The older stand-alone **Western blot** has been superseded in the algorithm by the antibody **differentiation assay** plus **NAT**.
- **Supportive non-specific findings:** lymphopenia (and other cytopenias), transient atypical lymphocytosis, raised transaminases/ESR — reinforcing the mononucleosis-like character.

Differential diagnosis

- **Epstein–Barr virus** and **CMV** infectious mononucleosis; **acute toxoplasmosis**; **acute viral hepatitis**; **secondary syphilis**; **rubella/measles/parvovirus/enteroviral** exanthems; **streptococcal pharyngitis**; **acute aseptic meningitis** of other viral cause; and drug reactions.
- A high index of suspicion plus a careful sexual/exposure history is essential, because the antibody screen may still be negative — *a negative antibody test does not exclude acute HIV*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Natural history curve (Pantaleo–Fauci graph):** X-axis = time (weeks → years); **left Y-axis = CD4+ T-cell count (cells/μL)**, **right Y-axis = HIV RNA copies/mL**. Label: *Primary infection → Acute HIV syndrome (wide dissemination of virus; seeding of lymphoid organs)* with **peak plasma viremia** and **CD4 nadir**, then **partial CD4 rebound + fall of viremia to set-point**, *Clinical latency*, *Constitutional symptoms*, *Opportunistic diseases*, *Death*.
- **Diagnostic window / marker-kinetics timeline:** X-axis = days–weeks from infection; plot sequential appearance of **HIV RNA → p24 antigen → anti-HIV antibody**, mark the **eclipse phase** and **window period**, and annotate **Fiebig stages I–VI**.

Clinical / Diagnostic significance

- **Extreme transmissibility:** peak plasma (and genital) viral load during seroconversion makes onward transmission highly efficient — a key driver of epidemic spread; diagnosis enables counselling, partner notification and **treatment-as-prevention (U=U)**.
- **Treat immediately:** current guidance is to **start ART as soon as possible in everyone, including acute HIV infection, regardless of CD4 count** — rationale includes earlier viral suppression, blunting immune damage from the outset, limiting seeding of the latent reservoir, and reducing transmission.
- Obtain baseline **CD4 count, plasma HIV RNA (viral load), genotypic resistance testing**, and screen for co-infections (**RPR/VDRL, hepatitis B and C, other STIs**) before/at ART initiation.
- Distinguish from **post-exposure prophylaxis (PEP)** scenarios: a person presenting with acute retroviral syndrome already has established infection (treat as such), not a candidate for PEP.

- Pitfall to avoid in exams and wards: **do not rely on a single antibody EIA** in a recently exposed symptomatic patient — add **p24/NAT**.

High-yield exam pointers

- Synonyms: **acute retroviral syndrome = acute HIV syndrome = primary HIV infection = seroconversion illness.**
- Occurs in **~50–70%** of infections, **~3–6 weeks** post-exposure; lasts **1 to several weeks**; **mononucleosis-like.**
- Classic cluster: **fever + pharyngitis + lymphadenopathy (~70%) + maculopapular rash + painful muco-cutaneous (oral/genital) ulcers**; may include **aseptic meningitis**.
- **Window period:** antibodies appear **~3–12 weeks**; **HIV RNA is the earliest marker**, then **p24 antigen**, then antibody.
- **First-line test = 4th-generation Ag/Ab combo immunoassay** (Ab + **p24**); confirm with **HIV-1/2 differentiation assay**; **antibody-negative + NAT-positive = acute HIV.**
- **Fiebig stages I–VI** track RNA → p24 → Western-blot positivity.
- Immunology: transient **CD4 fall**, **CD8 expansion**, **CD4:CD8 inversion**; **~10%** have a fulminant course.
- **Management = start ART immediately regardless of CD4**; baseline CD4, viral load, resistance genotype, STI/hepatitis screen.
- **A negative HIV antibody test does NOT exclude acute infection** — pursue p24/NAT if clinically suspected.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (Acute HIV Infection; Clinical Manifestations; Table 208-10 *Clinical Findings in the Acute HIV Syndrome*; Fig. 208-33 *The Acute HIV Syndrome*; Laboratory Diagnosis — 4th-generation EIA, p24 antigen, NAT, CDC algorithm Fig. 208-31).
- **CMDT 2026** — "HIV Infection & AIDS" (laboratory testing algorithm and window-period kinetics, Table 36-2; recommendation to start ART in all, including acute infection).

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Systemic protozoal infections

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Protozoa are microscopic single-celled eukaryotic parasites. *Systemic* (blood-and-tissue) protozoa are those that invade the bloodstream and deep organs rather than remaining confined to the gut lumen, producing disseminated, often life-threatening disease. Their defining feature is the capacity (like bacteria) to **multiply within the human host** and to evade immunity either by **antigenic variation** (*Trypanosoma brucei*) or by **intracellular survival** (*Plasmodium, Babesia, Leishmania, Toxoplasma, Trypanosoma cruzi*). A naïve patient suffering a first infection is usually the most severely affected, because partial immunity later limits parasite numbers; immunocompromised hosts (especially PLWH) are prone to dissemination, and several of these infections are **AIDS-defining**.

Classification of systemic (blood & tissue) protozoa

Organism	Disease	Vector / mode	Key target / hallmark
Plasmodium (6 species; esp. *P. falciparum*)	Malaria	Female *Anopheles* mosquito	Erythrocytes; cyclical fever, cerebral malaria
Babesia	Babesiosis	*Ixodid* (hard) ticks	Erythrocytes; severe in asplenia
Trypanosoma cruzi	Chagas disease	Reduviid (triatomine) bug faeces	Cardiomyopathy, megaoesophagus/megacolon
T. brucei gambiense / rhodesiense	African trypanosomiasis (sleeping sickness)	Tsetse fly (*Glossina*)	Chancre, CNS invasion
Leishmania (>20 species)	Visceral / cutaneous / mucocutaneous leishmaniasis	Sandfly (*Phlebotomus*)	Intracellular amastigotes in macrophages
Toxoplasma gondii	Toxoplasmosis	Cat-faeces oocysts, tissue cysts, transplacental	Brain (ring-enhancing lesions), eye, fetus
Naegleria, Acanthamoeba, Balamuthia	Amebic meningoencephalitis	Free-living, fresh/brackish water, soil	CNS — almost universally fatal

- Three immune-evasion mechanisms underpin systemic spread: **antigenic variation**, **intracellular sequestration**, and **endothelial cytoadherence** (*P. falciparum*).
- Immunocompromise predisposes to disseminated infection with *Leishmania, Toxoplasma, Cryptosporidium* and *T. cruzi*.

Malaria (Plasmodium)

- Six *Plasmodium* species infect humans; the classically described are **P. falciparum, P. vivax, P. ovale, P. malariae** and the zoonotic **P. knowlesi**. *P. falciparum* dominates sub-Saharan Africa, causing >80% of infections and ~90% of malarial deaths.

- *P. falciparum* is uniquely dangerous because it **invades erythrocytes of all ages** (very high parasitaemia), **cytoadheres to vascular endothelium** (sequestration → organ damage), and is most prone to **drug resistance**. *P. vivax/ovale* invade only reticulocytes (lower parasitaemia) and form dormant liver **hypnozoites** causing relapse.

Feature	P. falciparum	P. vivax / ovale
RBC preference	All ages	Reticulocytes (vivax needs Duffy antigen)
Parasitaemia	Very high	Low (seldom >2%)
Relapse (hypnozoite)	No	Yes — needs primaquine
Severe disease	Common	Uncommon

- **Severe falciparum malaria (Table 231-2):** cerebral malaria (unarousable coma >30 min post-convulsion, GCS <11), severe anaemia (Hb <5 g/dL), acidosis (lactate ≥5 mmol/L, "respiratory distress"), acute kidney injury (creatinine >265 µmol/L), noncardiogenic pulmonary oedema/ARDS, hypoglycaemia (<2.2 mmol/L; aggravated by quinine), shock, DIC/bleeding, **blackwater fever** (massive haemoglobinuria), and **hyperparasitaemia** (>5% in nonimmune, >10% in any patient).
- **Diagnosis:** Giemsa-stained **thick and thin blood films** remain the gold standard — thick film is sensitive (detects ~0.001% parasitaemia) and quantifies the parasite count, thin film allows species identification. **Rapid antigen tests** (PfHRP2-based dipsticks) are simple and sensitive but do not quantify parasitaemia and can be missed by *pfhrp2* deletions.
- **Treatment:** Uncomplicated falciparum malaria → an oral **artemisinin-based combination therapy (ACT)** (artemisinin derivative + a longer-acting partner drug). *P. vivax/ovale/malariae* and *P. knowlesi* → chloroquine (or ACT) plus, for vivax/ovale, **primaquine** for radical cure of liver hypnozoites (screen for G6PD deficiency first).
- **Severe malaria** → immediate parenteral **artesunate 2.4 mg/kg IV stat, repeated at 12 h and 24 h, then daily**; IV artesunate reduced mortality by ~22.5% versus quinine in African children. *Pfkelch13* mutations confer artemisinin resistance (SE Asia, now East Africa).

Leishmaniasis

- Caused by >20 species of **obligate intracellular** *Leishmania*, transmitted by sandflies; the parasite lives as non-flagellate **amastigotes** inside macrophages and as flagellate promastigotes in the vector. Three clinical syndromes: **visceral (VL)**, **cutaneous (CL)** and **mucocutaneous/mucosal (ML)**.
- **Visceral leishmaniasis (kala-azar, "black fever"):** an AIDS-defining illness; presents with prolonged fever, **massive splenomegaly** (the cardinal feature), hepatomegaly, lymphadenopathy, weight loss, darkening of skin and hypergammaglobulinaemia/pancytopenia. >90% of global VL occurs in **India, Bangladesh, Sudan, Ethiopia and Brazil**.
- **Diagnosis:** demonstration of amastigotes in **splenic, bone-marrow or lymph-node aspirate smears**; serology with the **rK39** antigen (rapid point-of-care test, though it stays positive for years after cure).

- **Treatment: Pentavalent antimony** (sodium stibogluconate / meglumine antimoniate) remains the drug of choice in most regions, **but antimony resistance is widespread in Bihar (India)**, where **liposomal/deoxycholate amphotericin B** or oral **miltefosine** (the first effective oral antileishmanial; teratogenic) is preferred. Combination regimens (e.g., single-dose liposomal amphotericin B followed by miltefosine or paromomycin) are used.
- **Post-kala-azar dermal leishmaniasis (PKDL)** follows VL on the Indian subcontinent as nodular/macular skin infiltration and is a parasite reservoir. **Mucocutaneous (espundia)** disease (New World *L. (Viannia) braziliensis*) destroys the nasal septum and palate and does not heal spontaneously.

Toxoplasmosis

- *Toxoplasma gondii* is an **obligate intracellular** parasite acquired by ingesting **oocysts** (cat faeces–contaminated food/water), **tissue cysts** (undercooked meat) or **transplacentally**. **Tachyzoites** cause acute, invasive disease; latent **bradyzoite tissue cysts** persist lifelong, predominantly in the CNS.
- **Immunocompetent host:** usually asymptomatic, or a self-limited infectious-mononucleosis–like illness; ocular disease (chorioretinitis) may occur.
- **Immunocompromised host (AIDS, transplant):** reactivation of latent cysts produces **toxoplasmic encephalitis** — multiple **ring-enhancing lesions** on contrast CT/MRI (the leading cause of focal brain lesions in advanced HIV); fatal unless treated.
- **Congenital toxoplasmosis:** from primary maternal infection; severity is greatest with early-gestation infection (visual, hearing and cognitive impairment), while late-infected infants may appear normal but develop **chorioretinitis** decades later.
- **Treatment: pyrimethamine + sulfadiazine + leucovorin (folinic acid)** is first-line for toxoplasmic encephalitis (typically ≥6 weeks); **clindamycin** substitutes for sulfadiazine (or TMP-SMX when pyrimethamine is unavailable). In pregnancy, **spiramycin** is used to prevent transmission before 18 weeks; pyrimethamine/sulfadiazine/folinic acid is used after seroconversion later in pregnancy.

Other systemic protozoa — trypanosomiasis, babesiosis, free-living amebae

- **Chagas disease (*T. cruzi*):** transmitted in reduviid-bug faeces in Latin America; also via transfusion, transplantation and mother-to-child. After acute parasitaemia, the parasite multiplies intracellularly (amastigotes) in muscle and ganglion cells; a minority later develop chronic **cardiomyopathy** and **megaoesophagus/megacolon**.
- **African trypanosomiasis (sleeping sickness):** tsetse-fly–borne; a painful **chancre** at the bite is a clue. **T. b. gambiense** (West/Central Africa) causes chronic low-grade parasitaemia with late CNS invasion over months–years; **T. b. rhodesiense** (East Africa) causes high parasitaemia with early CNS invasion and death within weeks. Antigenic variation drives recurrent waves of parasitaemia.
- **Babesiosis:** *Babesia* infects erythrocytes (ixodid-tick borne, NE/Midwest USA); ranges from a nonspecific febrile illness to severe haemolytic disease in **asplenic** patients. Standard therapy is **atovaquone plus azithromycin**.

- **Free-living amebic CNS infection:** *Naegleria fowleri* (warm fresh water/hot springs) causes fulminant, usually fatal **primary amebic meningoencephalitis (PAM)** — pyogenic-looking CSF with motile trophozoites; *Acanthamoeba* and *Balamuthia mandrillaris* cause indolent **granulomatous amebic encephalitis (GAE)** with a space-occupying lesion, chiefly in the immunocompromised; *Acanthamoeba* also causes **keratitis** (corneal trauma, contact-lens wearers). **Miltefosine**-containing combinations are recommended despite a poor prognosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Plasmodium life cycle (mosquito–human):** label *sporozoites*, *hepatocyte (exo-erythrocytic schizont / hypnozoite)*, *merozoites*, *ring trophozoite*, *schizont*, *gametocytes*, *female Anopheles mosquito*.
- **Classification flow-box "Systemic protozoa":** two columns — *Blood protozoa* (Plasmodium, Babesia, Trypanosoma) and *Tissue protozoa* (Leishmania, Toxoplasma, free-living amebae) — each labelled with vector and target organ.

Clinical / Diagnostic significance

- **Travel/exposure history is pivotal:** malaria must be the first consideration in any febrile returned traveller or immigrant from an endemic area; locally acquired malaria has re-emerged in parts of the USA.
- **Microscopy of stained blood/aspirate smears** is the unifying diagnostic tool (malaria — thick/thin films; VL — splenic/marrow amastigotes; African trypanosomiasis — bloodstream trypomastigotes).
- **Imaging:** contrast CT/MRI for toxoplasmic encephalitis (multiple ring-enhancing lesions) and amebic GAE (space-occupying lesion).
- **Asplenia and HIV/immunosuppression** convert several of these from mild to fulminant or AIDS-defining infections — a key management pearl.
- Severe falciparum malaria is a **medical emergency** requiring parenteral artesunate, glucose monitoring (hypoglycaemia), and watch for concomitant bacteraemia at high parasitaemia.

High-yield exam pointers

- Systemic protozoa **multiply within the host** and evade immunity by **antigenic variation** (*T. brucei*) or **intracellular survival** (*Plasmodium, Leishmania, Toxoplasma*).
- *P. falciparum* = highest mortality; invades all RBCs, cytoadherence/sequestration → **cerebral malaria, blackwater fever, ARDS, AKI, hypoglycaemia**.
- **Severe malaria** → IV **artesunate 2.4 mg/kg at 0, 12, 24 h then daily**; vivax/ovale relapse → **primaquine** (check G6PD).
- **VL = kala-azar**; cardinal sign **massive splenomegaly**; dx by **rK39** + splenic/marrow amastigotes; **antimony resistant in Bihar** → amphotericin B / miltefosine.
- **Toxoplasmic encephalitis** = commonest cause of **ring-enhancing brain lesions in AIDS**; Rx **pyrimethamine + sulfadiazine + folinic acid**; **spiramycin** in early pregnancy.
- **Chagas** (reduviid bug) → cardiomyopathy + megaoesophagus; **African sleeping sickness** (tsetse fly) → chancre + CNS disease.

- **Naegleria** → fatal PAM (warm freshwater); **Acanthamoeba/Balamuthia** → GAE + keratitis.
- AIDS-defining systemic protozoa: **visceral leishmaniasis, toxoplasmosis, cryptosporidiosis, disseminated *T. cruzi***.

> **SOURCE & COVERAGE**
>
> Harrison 22e — Ch 228 "Introduction to Parasitic Infections" (primary); supplemented by Ch 230 "Amebiasis and Infection with Free-Living Amebae", Ch 231 "Malaria", Ch 233 "Leishmaniasis", and Ch 235 "Toxoplasma Infections". **Coverage note:** Ch 234 (Trypanosomiasis) text was not provided; the Chagas and African-trypanosomiasis content above is grounded in the Ch 228 overview only — specific antitrypanosomal drug regimens (e.g., benznidazole/nifurtimox, suramin/pentamidine/melarsoprol/eflornithine/fexinidazole) are standard textbook therapy but were not verifiable against the supplied chapters and are therefore omitted from the drug tables. The "six *Plasmodium* species" figure is from Ch 228; Ch 231 tabulates the five classical species (with *P. ovale* now split into two subspecies).

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Viral encephalitis in India

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Encephalitis is inflammation of the brain *parenchyma* caused most often by a virus (occasionally by a primary autoimmune process), and is distinguished from meningitis by the presence of altered consciousness, behavioural change, focal neurological deficits and/or seizures. When the meninges are co-involved the term *meningoencephalitis* is used. In India the aetiologic spectrum is distinctive: **herpes simplex virus** dominates sporadic adult cases, while **Japanese encephalitis virus** is the single largest cause of epidemic encephalitis, and several India-relevant emerging agents (**Nipah, Chandipura, dengue, chikungunya, West Nile, Kyasanur Forest disease**) round out the picture. The clinical importance lies in separating the *one treatable cause (HSV)* from the many supportively-managed arboviruses, since empirical acyclovir saves lives.

Aetiologic framework relevant to India

- **Sporadic, year-round, all ages:** herpesviruses — HSV-1 (commonest sporadic cause), VZV, EBV, CMV (immunocompromised).
- **Epidemic / seasonal arboviral (monsoon & post-monsoon):** Japanese encephalitis virus (JEV), West Nile virus (WNV), dengue (DENV 1–4), chikungunya virus (CHIKV) — all mosquito-borne.
- **Emerging zoonotic / regional outbreaks:** Nipah virus (Kerala, West Bengal), Chandipura virus (central/western India, paediatric), Kyasanur Forest disease virus (Karnataka, tick-borne).
- **Post-infectious / chronic:** measles → subacute sclerosing panencephalitis (SSPE); rubella → progressive rubella panencephalitis.
- **Other neurotropic:** rabies virus (encephalitic/paralytic), enteroviruses (EV-A71, EV-D68 → acute flaccid myelitis).

Tabulation — pathogen, vector/reservoir, characteristic presentation and management

Pathogen (family)	Vector / reservoir / epidemiology in India	Characteristic clinical presentation	Diagnosis	Management
Herpes simplex virus-1 (Herpesviridae)	None — sporadic, all seasons; commonest cause of sporadic fatal encephalitis	Acute febrile illness with *inferomedial frontotemporal* signs — olfactory/gustatory hallucinations, anosmia, bizarre behaviour, memory loss, aphasia, focal seizures	CSF lymphocytic pleocytosis ± RBCs; **CSF HSV PCR (sens ~96%, spec ~99%)**; MRI T2/FLAIR temporal-lobe signal; EEG periodic temporal sharp-slow complexes (2–3 s)	**IV acyclovir 10 mg/kg q8h × 21 days** (neonates 20 mg/kg q8h); start empirically in all suspected viral encephalitis
Japanese encephalitis virus (Flaviviridae)	*Culex tritaeniorhynchus* mosquito; amplifiers = pigs + ardeid wading birds (herons); rice-field belt; monsoon/post-monsoon; children mainly	Largely subclinical; ~1% develop encephalitis — high fever, reduced sensorium, *parkinsonian/dystonic movement disorder*, seizures, acute flaccid paralysis; CFR ~20–30%	CSF lymphocytic pleocytosis; **anti-JEV IgM (MAC-ELISA) in CSF/serum**; MRI *thalamic*, substantia nigra & basal-ganglia lesions	Supportive (ICP, seizures, ventilation); **no specific antiviral**; vaccine-preventable (SA14-14-2 live-attenuated; inactivated Vero/IXIARO)
Nipah virus (Paramyxoviridae, *Henipavirus*)	*Pteropus* fruit bats; date-palm sap, pig intermediate host; person-to-person & nosocomial spread; Kerala/W. Bengal outbreaks	Influenza-like prodrome → rapidly progressive encephalitis with reduced consciousness, brainstem signs, segmental myoclonus, dystonia; respiratory illness; **CFR 67–92%**; late relapse (3.4–7.5%)	ELISA (serum & CSF) and **RT-PCR of urine/respiratory secretions (not blood)**	Supportive; ribavirin used (unproven); strict barrier/contact-droplet isolation; outbreak containment
Chandipura virus (Rhabdoviridae)	Sandflies & mosquitoes; reservoir hedgehogs; central/western India; children; recurrent outbreaks	Rapid influenza-like onset (fever, vomiting, abdominal pain) → altered sensorium & seizures within hours; **CFR ~45–80%**; *virus/cells often NOT detectable in CSF*	RT-PCR/serology; CSF typically bland	Supportive intensive care only; high early mortality
Dengue virus 1–4 (Flaviviridae)	*Aedes aegypti*; hyperendemic across India	Usually "break-bone fever"; neurological forms = dengue encephalopathy/encephalitis, reduced sensorium, seizures (often with thrombocytopenia, plasma leak)	NS1 antigen / RT-PCR (acute); IgM ELISA (convalescent); leukopenia, thrombocytopenia, raised AST	Supportive fluid management; avoid aspirin/NSAIDs (bleeding); no specific antiviral

Pathogen (family)	Vector / reservoir / epidemiology in India	Characteristic clinical presentation	Diagnosis	Management
Chikungunya virus (Togaviridae, *Alphavirus*)	*Aedes aegypti / Ae. albopictus*	Fever with severe migratory small-joint polyarthritis & rash; uncommon neuroinvasive disease (meningoencephalitis), esp. neonates/elderly	RT-PCR (acute) / IgM serology	Paracetamol + NSAIDs for arthralgia; supportive; FDA-approved live-attenuated vaccine exists
West Nile virus (Flaviviridae)	*Culex* mosquitoes; birds reservoir	Mostly subclinical; <1% neuroinvasive — encephalitis, meningitis, *poliomyelitis-like acute flaccid paralysis*, movement disorders	**CSF WNV IgM** (best test; reaches 70–80% by day 7); MRI thalamus/basal ganglia/brainstem	Supportive only; no proven antiviral
Varicella-zoster virus (Herpesviridae)	Reactivation; immunocompromised	Encephalitis via *CNS vasculopathy* — multifocal ischaemic/haemorrhagic infarcts; ± preceding zoster	CSF VZV PCR **and** CSF IgM (complementary)	IV acyclovir; consider adjunctive glucocorticoid (unproven)
Measles virus → SSPE (Paramyxoviridae)	Past measles in early childhood; latency 6–8 yr	Progressive cognitive decline, myoclonus, seizures, spasticity in 5–15 yr olds	EEG periodic high-voltage complexes (3–8 s); markedly raised CSF anti-measles antibody/oligoclonal bands	No definitive cure; isoprinosine ± intrathecal IFN-α; prevent via measles vaccination
Kyasanur Forest disease virus (Flaviviridae)	*Haemaphysalis* ticks; monkeys; Karnataka (Western Ghats)	Biphasic — haemorrhagic febrile illness then, in a minority, a second phase of *meningoencephalitis*	RT-PCR / IgM serology	Supportive; **inactivated KFD vaccine used in India** for prevention
Rabies virus (Rhabdoviridae)	Dog bite (commonest in India); bats	*Furious* rabies — hydrophobia, aerophobia, autonomic storm; *paralytic (dumb)* — ascending paralysis; near-100% fatal	Antigen in brain/nuchal skin biopsy; PCR of saliva/CSF	No effective therapy once symptomatic; **prevention = post-exposure prophylaxis** (wound care, vaccine, RIG)

Key India-specific entities — expanded points

- **HSV-1 encephalitis** is the *only* common viral encephalitis with effective specific therapy. NMDA-receptor antibodies appear in up to 25% of recovered patients and may cause relapse/worsening weeks later — this requires immunotherapy, not antiviral escalation.

- **Japanese encephalitis** is the most significant viral encephalitis of Asia (~68,000 cases and ~13,600–20,400 deaths/year). India runs a JE vaccination programme in endemic districts; pig/bird amplification and irrigated rice ecology drive transmission. A *parkinsonian movement disorder with bilateral thalamic MRI lesions* is the exam hallmark.
- **Nipah** is the highest-lethality entity (CFR up to ~92%) — recognise the date-palm-sap and fruit-bat exposure history, brainstem/myoclonic signs, and the public-health imperative of isolation and contact tracing.
- **Chandipura** is a peculiarly *Indian paediatric* rhabdoviral encephalitis with explosive course and high mortality, in which CSF is characteristically unremarkable for virus.

General diagnostic approach

- **CSF (mandatory unless raised ICP):** lymphocytic pleocytosis (>5 cells/μL in >95%), mildly raised protein, *normal glucose*; collect ≥20 mL, freeze 5–10 mL for PCR/metagenomics.
- **CSF PCR** is the primary test for HSV, VZV, CMV, EBV, HHV-6, enteroviruses; **arboviral diagnosis rests on virus-specific IgM** (CSF/serum, MAC-ELISA) since viraemia is transient.
- **Neuroimaging:** MRI temporal lobes → HSV; bilateral thalami/basal ganglia → flaviviruses (JE, WNV); deep-grey/brainstem → arboviral.
- **EEG:** periodic lateralised temporal complexes → HSV; SSPE periodic bursts.
- **Metagenomic next-generation sequencing (mNGS)** of CSF for obscure/immunocompromised cases.

Principles of management

- **Empirical IV acyclovir** in every patient with suspected viral encephalitis (especially with focal features) *while awaiting PCR* — discontinue if HSV excluded.
- **Supportive ICU care:** ICP monitoring, fluid restriction (avoid hypotonic fluids, watch SIADH), fever suppression, standard anticonvulsants, airway/ventilatory support, prophylaxis against aspiration, DVT and pressure ulcers.
- **Pathogen-specific:** CMV — ganciclovir + foscarnet; arboviruses (JE, WNV, dengue, chikungunya, Chandipura, Nipah) — supportive only.
- **Prevention is decisive:** JE vaccine (endemic districts), KFD vaccine (Karnataka), measles vaccine (prevents SSPE), rabies PEP, and vector control (mosquito-source reduction, repellents/DEET, bed-nets, full-sleeve clothing).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled axial MRI brain panels:** (1) *HSV* — asymmetric T2/FLAIR hyperintensity of right temporal lobe (label: temporal lobe, insula, cingulate gyrus); (2) *Japanese encephalitis* — bilateral thalamic T2/FLAIR lesions (label: thalamus, substantia nigra, basal ganglia).
- **Transmission-cycle schematic for JE:** label *Culex tritaeniorhynchus mosquito → amplifying hosts (pig, ardeid wading bird/heron) → dead-end host (human)*, with rice-field habitat.

Clinical / Diagnostic significance

- The clinical priority is *not to miss treatable HSV*; a negative early (≤72 h) HSV CSF PCR does not exclude it — repeat in 1–3 days if suspicion is high.
- *Movement disorder + bilateral thalamic lesions* in an endemic child = JE until proven otherwise; *bat/date-palm-sap exposure with brainstem signs and respiratory failure* = Nipah (isolate immediately).
- Hypoglycorrhachia or persisting CSF neutrophilia should redirect toward bacterial, tuberculous, fungal or amoebic causes (*Naegleria*, *Balamuthia*).
- Autoimmune encephalitis (anti-NMDA-R, LGI1, CASPR2) is the key non-infective mimic and may follow HSV encephalitis.

High-yield exam pointers

- **HSV-1 = commonest sporadic; JEV = commonest epidemic** viral encephalitis in India.
- **Acyclovir 10 mg/kg IV q8h × 21 days** — memorise dose; start empirically, do not wait for PCR.
- **JE:** *Culex tritaeniorhynchus*; pig + ardeid-bird amplifiers; parkinsonism; bilateral thalamic MRI; anti-JEV IgM diagnostic; SA14-14-2 / IXIARO vaccines.
- **Nipah:** Henipavirus, *Pteropus* bats, date-palm sap, CFR 67–92%, PCR of urine/respiratory secretions (not blood), barrier nursing.
- **Chandipura:** Indian rhabdovirus, children, sandfly-borne, CFR 45–80%, CSF often bland.
- **WNV diagnosis = CSF IgM** (not PCR); **KFD = Karnataka, Haemaphysalis tick, vaccine available**.
- Arboviral encephalitides (JE, WNV, dengue, chikungunya, Chandipura, Nipah) → **supportive treatment only**; prevention via vaccine + vector control.
- **SSPE = late measles complication**, periodic EEG, raised CSF anti-measles antibody, preventable by vaccination.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Encephalitis" (HSV dosing, CSF/PCR/MRI/EEG, SSPE, differential diagnosis) and "Arthropod-Borne and Rodent-Borne Virus Infections" (Japanese encephalitis, West Nile, dengue, chikungunya, Chandipura, Kyasanur Forest disease epidemiology and presentation); "Common Viral Respiratory Infections"/Hendra–Nipah section (Henipavirus biology).
- CMDT 2026 — "Viral & Rickettsial Infections" (Japanese encephalitis essentials, diagnosis, vaccines and prognosis; Nipah virus clinical features, CFR, diagnostic ELISA/PCR; supportive management).

Coverage note: The spec flags India-specific epidemiology as thin, and this is accurate — Harrison/CMDT confirm the pathogens, vectors, presentations and management used above, but do **not** give India-state-wise incidence figures or the Indian national JE/AES surveillance data; those administrative specifics are outside the corpus and have not been fabricated. Chandipura, Nipah-India and KFD are corpus-supported as Indian entities. Rabies is included as a universally-accepted neurotropic viral encephalitis though it is conventionally discussed separately.

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Toxoplasmosis

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Toxoplasmosis is a zoonosis caused by the obligate intracellular coccidian protozoan *Toxoplasma gondii*. The **cat (Felidae)** is the *definitive host* in which the sexual cycle and oocyst formation occur, while humans and other warm-blooded animals are *intermediate hosts*. Up to a third of the world's population is latently infected. Acute acquired infection is asymptomatic in 80–90% of immunocompetent persons, but the parasite persists lifelong as tissue cysts; the major clinical burden falls on three groups — the **immunocompromised** (reactivation encephalitis), the **fetus/newborn** (congenital toxoplasmosis), and persons with **ocular disease** (chorioretinitis).

Etiology, Life Cycle & Transmission

- **Organism & forms:** *T. gondii* exists in three forms — the rapidly dividing invasive **tachyzoite** (infects all nucleated cells except RBCs; causes tissue damage), the slow-replicating **bradyzoite** within **tissue cysts** (persist in CNS, skeletal/cardiac muscle, retina — the chronic/latent stage), and the environmentally hardy **oocyst** (sexual-stage product shed only in cat faeces, sporulating to 8 sporozoites after 2–3 days in air).
- **Life cycle:** The **enteroepithelial (sexual) cycle** occurs only in the cat intestine, producing unsporulated oocysts in faeces; an acutely infected cat may excrete up to **100 million oocysts/day**. In intermediate hosts the **asexual cycle** proceeds — ingested cysts/oocysts release organisms that transform into tachyzoites, disseminate, and ultimately encyst as bradyzoites (tissue cysts appear 7–10 days after infection).
- **Routes of transmission:**

- **Oral (commonest):** ingestion of **tissue cysts** in raw/undercooked meat (lamb, pork, beef, venison) or **sporulated oocysts** from soil/water/food contaminated by cat faeces; also unpasteurised goat milk, untreated water, raw shellfish (filter-feeders concentrate oocysts).
- **Transplacental** (tachyzoites) → congenital toxoplasmosis.
- **Blood transfusion / solid-organ or haematopoietic stem-cell transplantation** (donor → seronegative recipient).
- Rarely **laboratory accident** (needlestick, infected tissue).

- **Genotypes:** Northern-hemisphere strains are predominantly 3 clonal genotypes; **South/Central American strains are more virulent**, atypical, and cause severe ocular and even sepsis-like disease in immunocompetent hosts — a travel history is diagnostically important.

Pathogenesis, Pathology & Immune Response

- Released bradyzoites/sporozoites invade gut epithelium → transform into **tachyzoites** → disseminate as free organisms or inside phagocytes ("**Trojan horse**") to lymph node, muscle, myocardium, retina, placenta and **CNS**. Hallmark lesion: **cell death and focal necrosis with surrounding mononuclear inflammation**.
- **Control is mainly cell-mediated:** a strong **TH1 response** with **IL-12 and IFN-γ** (plus $CD4^+$ and cytolytic $CD8^+$ T cells, activated macrophages) contains the parasite; humoral antibody is parasiticidal with complement (basis of the *Sabin-Feldman dye test*).
- In the **immunocompromised or fetal host**, failure of T-cell immunity (notably $CD8^+$ loss) permits unchecked tachyzoite spread → **necrotizing encephalitis, pneumonitis, myocarditis**. Reactivation in AIDS is almost always from **spontaneous rupture of latent cysts** in the brain when **$CD4^+$ count <100/μL**.
- **Pathology by site:** lymph node — *follicular hyperplasia with clusters of epithelioid histiocytes encroaching on germinal centres* (Piringer-Kuchinka pattern); CNS — necrotizing encephalitis with microglial nodules and cyst-bearing necrotic borders; eye — necrotizing retinochoroiditis; *T. gondii is the commonest cause of posterior uveitis in immunocompetent persons*.

Clinical Manifestations (Four Syndromes)

Syndrome	Host	Key features
1. Acute acquired	Immunocompetent	80–90% asymptomatic. Commonest sign = **bilateral, non-tender cervical lymphadenopathy** (also suboccipital, supraclavicular); mononucleosis-like illness — fever (<40°C), malaise, headache, sore throat, myalgia, atypical lymphocytosis. Self-limited over weeks–months; rarely pneumonitis, myocarditis, polymyositis, encephalitis (virulent strains)
2. Congenital	Fetus / newborn	Follows **primary maternal infection in pregnancy**. Transmission rises with gestational age (~15% 1st trimester → ~65% 3rd) but **severity falls** — early infection → abortion, stillbirth, severe disease; late → usually asymptomatic at birth. Classic *Sabin tetrad*: **hydrocephalus, intracranial (diffuse) calcifications, chorioretinitis, and convulsions**; also microcephaly, intellectual disability, strabismus

Syndrome	Host	Key features
3. Ocular	Any (congenital or acquired)	**Retinochoroiditis** — blurred vision, scotoma, photophobia, eye pain; fundus shows **yellow-white cotton-like patches with overlying vitritis** ("*headlight in the fog*"), healing to pigmented scars. Causes ~35% of chorioretinitis in US/Europe; recurrent flares, esp. South-American strains
4. Reactivation in immunocompromised	AIDS, transplant, immunosuppressed	**Toxoplasmic encephalitis (TE)** is the principal CNS opportunistic infection in AIDS — subacute fever, headache, altered mental status (75%), focal deficits/hemiparesis, seizures (33%); sites = **basal ganglia, corticomedullary junction, brainstem**. Also pneumonitis (mimics PJP), myocarditis, chorioretinitis. >95% of TE in AIDS is reactivation, typically at **$CD4^+$ <100/µL**

Diagnosis

- **Serology (mainstay in immunocompetent):** Acute infection suggested by **simultaneous IgM + IgG**, seroconversion, or a 4-fold (≥16-fold) titre rise. IgG (Sabin-Feldman **dye test**, IFA, ELISA) appears at 2–3 weeks, peaks 6–8 weeks, persists for life. IgM (double-sandwich IgM-ELISA, **IgM-ISAGA**) rises early but may **persist >1 year** — a positive IgM alone does not prove recent infection. **IgG avidity testing** (high avidity = infection >3–4 months ago) helps date infection in pregnancy. Circulating **IgA** favours acute/congenital infection.
- **Molecular: PCR** is the mainstay for detecting organism in **amniotic fluid** (congenital — replaced fetal blood sampling), CSF, blood, aqueous/vitreous humour, BAL. Highly specific but variably sensitive — a **negative PCR does not exclude** toxoplasmosis.
- **Histology / isolation:** demonstration of **tachyzoites** in tissue/fluid = acute infection; isolated **cysts** indicate only past/latent infection. Lymph-node biopsy shows the characteristic reactive pattern.
- **Immunocompromised (TE):** based on **clinical picture + positive IgG (IgM usually negative) + neuroimaging**. **CT/MRI** show **multiple ring-enhancing lesions** at the basal ganglia and corticomedullary junction; MRI is most sensitive. Predictive value of a typical picture in a seropositive AIDS patient is ~80%. A favourable **empirical therapeutic trial** (>50% improve by day 3, >90% by day 7) is diagnostic; non-response or a **solitary lesion** suggests **primary CNS lymphoma** (EBV-positive CSF PCR) and warrants **stereotactic brain biopsy**.
- **Congenital/newborn:** persistence of IgG beyond 12 months, or positive **IgM/IgA after the first week of life**, is diagnostic; assess eyes, brain (imaging) and CSF as up to 25% are seronegative at birth.
- **Ocular:** typical retinal lesion + positive serum IgG; intra-ocular antibody production (**Goldmann-Witmer coefficient**) or ocular-fluid PCR/Western blot in atypical cases.

Treatment & Prophylaxis

- **Mechanism note:** anti-*Toxoplasma* drugs act only on **tachyzoites** — they control disease but **do not eradicate tissue cysts**. **Folinic acid (leucovorin)** is added to counter pyrimethamine marrow toxicity (NOT folic acid).

Setting	Regimen (from source)
Immunocompromised / TE (acute)	**Pyrimethamine** (200 mg load, then 50 mg/d if <60 kg, 75 mg/d if >60 kg) + **sulfadiazine** (1000 mg qid <60 kg; 1500 mg qid >60 kg) + **leucovorin** 10–25 mg/d, minimum **6 weeks**. Sulfa intolerance → **clindamycin** 600 mg qid. Resource-poor / pyrimethamine unavailable → **TMP-SMX** (5 mg/kg TMP + 25 mg/kg SMX bid)
Ocular (immunocompetent)	Pyrimethamine + sulfadiazine **or** clindamycin × **6 weeks**, ± **prednisone**; treat sight-threatening lesions (macula/optic disc)
Acute lymphadenopathy (immunocompetent)	Usually **no therapy**; treat only if severe/persistent or visceral (2–4 weeks)
Pregnancy	**Spiramycin** 1 g tid until delivery for early acute infection (does **not** cross placenta; cuts transmission ~60%). After **18 weeks** or documented fetal infection → **pyrimethamine + sulfadiazine + folinic acid** (pyrimethamine avoided in 1st trimester — teratogenic)
Congenital (neonate)	Pyrimethamine 1 mg/kg + sulfadiazine 100 mg/kg + folinic acid for **1 year**; prednisone 1 mg/kg/d if indicated
Primary prophylaxis (AIDS)	If seropositive and **$CD4^+$ <100/µL** → **TMP-SMX 1 double-strength tab daily** (also prevents PJP). Alternatives: dapsone-pyrimethamine, atovaquone ± pyrimethamine. **Stop** when $CD4^+$ >200/µL for ≥3 months
Secondary prophylaxis (maintenance)	Pyrimethamine + sulfadiazine (or clindamycin/TMP-SMX) + leucovorin until immune reconstitution; **stop** when $CD4^+$ >200/µL for ≥6 months on ART (with repeat MRI)

Prevention

- **Cook meat** to a safe internal temperature (≈63–66°C; ground meat/poultry higher) and rest; **freezing to −20°C** kills tissue cysts.
- Wash hands, fruits and vegetables; avoid raw shellfish and unpasteurised milk.
- **Cat-litter precautions:** change the litter box **daily** (fresh oocysts are non-infective for ~48 h before sporulation), preferably by a non-pregnant, HIV-negative person; wear gloves for gardening; keep cats indoors and feed only cooked/commercial food.
- Screen **donor and recipient** serology before transplantation; counsel seronegative pregnant and immunocompromised persons. Some countries screen pregnant women (France, Austria) and/or newborns (Denmark, Massachusetts).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Life cycle of *Toxoplasma gondii*** (circular): label **Definitive host (cat)** → **enteroepithelial/sexual cycle** → **unsporulated oocyst in faeces** → **sporulated oocyst (8 sporozoites)** in soil/water; **Intermediate hosts** (human, sheep, pig, rodent, birds) → **tachyzoites** (acute, infect all nucleated cells) → **tissue cysts with bradyzoites** in CNS/muscle/retina; arrows for **undercooked meat** and **transplacental** routes to humans.
- **MRI brain in toxoplasmic encephalitis:** label **multiple ring-enhancing lesions**, **basal ganglia**, **corticomedullary junction**, **surrounding vasogenic oedema**.

Clinical / Diagnostic significance

- *T. gondii* is the **commonest cause of focal brain lesions / mass lesions in AIDS** — empirical anti-toxoplasma therapy with imaging follow-up is standard; failure to improve points to CNS lymphoma.
- A **solitary** ring-enhancing lesion or **negative Toxoplasma IgG** in an AIDS patient argues against TE and toward lymphoma/other diagnoses → consider early biopsy.
- In **pregnancy**, the IgM/IgG plus **avidity** panel and **amniotic-fluid PCR** guide the choice between spiramycin and pyrimethamine-based therapy and decisions on continuation of pregnancy.
- **Ocular toxoplasmosis** is the leading infectious cause of posterior uveitis; recurrence and macular involvement threaten vision.
- **Antiretroviral therapy** (immune reconstitution to $CD4^+$ >200/μL) is the key to discontinuing both primary and secondary prophylaxis.

High-yield exam pointers

- **Cat = definitive host**; oocysts shed **only** in cat faeces; humans = intermediate host.
- Three forms: **tachyzoite** (acute, all nucleated cells, spares RBCs), **bradyzoite/tissue cyst** (latent), **oocyst** (sexual stage, environmental).
- **Sabin-Feldman dye test** = reference IgG serology; **IgM-ISAGA** and **avidity** date infection; **PCR of amniotic fluid** for congenital diagnosis.
- **Sabin classic tetrad** of congenital disease: **hydrocephalus, intracranial calcification, chorioretinitis, convulsions**; transmission ↑ but severity ↓ with later gestation.
- **TE in AIDS** at **$CD4^+$ <100/μL**: **multiple ring-enhancing** basal-ganglia/corticomedullary lesions; >90% respond to empirical therapy by day 7.
- **Pyrimethamine + sulfadiazine + leucovorin** = standard; **clindamycin** if sulfa-intolerant; **TMP-SMX** alternative and the prophylactic agent of choice (covers PJP too).
- **Spiramycin** = drug of choice in early pregnancy (doesn't cross placenta); **avoid pyrimethamine in the 1st trimester**.
- Primary prophylaxis: **TMP-SMX** at **$CD4^+$ <100/μL**; stop at **$CD4^+$ >200/μL ×3 months** (primary) or **×6 months** (secondary).
- Drugs kill **tachyzoites only** — never eradicate cysts; add **folinic acid (leucovorin)**, not folic acid.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Toxoplasma Infections" (etiology, life cycle, transmission, pathogenesis, immune response, clinical syndromes, serologic/PCR/imaging diagnosis, treatment doses, AIDS prophylaxis thresholds, prevention).
- **CMDT 2026** — "Protozoal & Helminthic Infections: Toxoplasmosis" (four clinical syndromes, current serologic/PCR algorithm, drug regimens, spiramycin in pregnancy, chemoprophylaxis) and HIV chapter for TE prophylaxis.
- *Coverage note:* The **Sabin classic tetrad** (hydrocephalus, intracranial calcification, chorioretinitis, convulsions) is universally accepted standard internal medicine; Harrison lists the component features (hydrocephalus, microcephaly, intellectual disability, chorioretinitis, epilepsy) without naming the eponymous tetrad. The *Goldmann-Witmer coefficient* and *Piringer-Kuchinka* lymph-node pattern are named per standard usage; Harrison/CMDT describe the underlying tests/histology.

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Cholera — treatment and prevention

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Cholera is an acute, toxin-mediated diarrhoeal disease caused by *Vibrio cholerae* serogroup **O1** or **O139** (the serogroups with epidemic potential) that can, within hours, produce profound, rapidly progressive dehydration and death. The severe form is termed **cholera gravis**. Death results almost entirely from **hypovolaemic shock** and metabolic acidosis driven by massive secretory (rice-water) stool loss; consequently, prompt, aggressive fluid and electrolyte repletion converts a historically lethal illness into a self-limited one. Management therefore rests on two pillars — *rehydration* (the cornerstone) and *adjunctive antibiotics/zinc* — while prevention combines water-sanitation-hygiene (WASH) measures with oral cholera vaccination.

Principles of treatment — rehydration is paramount

- **Goal:** rapidly restore euvolaemia, then maintain hydration by replacing ongoing losses until diarrhoea stops. Treatment intensity is guided by the **degree of dehydration** (Table below) and the patient's age/weight.
- **Oral rehydration solution (ORS)** is the mainstay for mild–moderate dehydration. It exploits the **hexose–Na^+ co-transport mechanism**: glucose (or galactose) is actively transported across the gut mucosa, dragging Na^+ with it; Cl^- and water follow passively. *This transport pathway remains intact even when cholera toxin is active*, which is why ORS works despite ongoing toxin-driven secretion.
- **WHO reduced ("low")-osmolarity ORS** is now recommended for dehydrating diarrhoea of any cause. Composition (mmol/L): **Na^+ 75, K^+ 20, Cl^- 65, citrate 10, glucose 75 — total osmolarity 245 mOsm/L**. Each sachet (added to 1 L safe water) contains NaCl 2.6 g, trisodium citrate dihydrate 2.9 g, KCl 1.5 g and anhydrous glucose 13.5 g.

- **Homemade ORS** (when sachets unavailable): 0.5 teaspoon (½ small spoonful) table salt + 6 level teaspoons table sugar in 1 L of safe water; supplement potassium via **bananas or green coconut water**.
- **Rice-based ORS is considered superior to standard ORS** specifically in cholera. ORS may be given by **nasogastric tube** if the patient cannot drink.
- **Continue feeding/breast-feeding** during treatment; encourage potassium-rich intake.

Dehydration assessment and fluid prescription

Degree	Key clinical findings	Fluid loss	Treatment
None/ mild	Thirst only	<5% body wt	ORS to replace losses (e.g. ≥10 y: ½–1 cup, max 1 L/d)
Moderate	Thirst, postural hypotension, weakness, tachycardia, ↓skin turgor, dry mouth, no tears	5–10% body wt	ORS *ad libitum*, up to max 2 L/d (give within first 4 h; weight-based volumes)
Severe	Lethargy/unconsciousness ("floppiness"), weak/absent pulse, inability to drink, sunken eyes/fontanelles	>10% body wt	**IV fluids** (see below)

- **Severe dehydration → IV resuscitation.** Use **Ringer's lactate** (best commercial choice because profound acidosis, pH <7.2, is common; if unavailable, normal saline). It *must* be supplemented with **potassium**, preferably given orally.
- **Volume schedule (WHO):** give **100 mL/kg in the first 3 h** (first **6 h** in children <12 months) — start rapidly then slow down — for a **total of 200 mL/kg in the first 24 h**. Continue until the patient is awake, can ingest ORS, and no longer has a weak pulse.
- Alternatively framed: in severely dehydrated patients (>10% body wt) the **total deficit can be replaced within the first 3–4 h, with half in the first hour**. **Transient muscle cramps and tetany are common** during rapid repletion.
- Thereafter switch to **oral therapy**, matching intake to output. Patients with continued large-volume diarrhoea may need prolonged IV fluids.
- **Hypokalaemia** can be severe but responds to K^+ (IV or oral). *Where monitoring staff are inadequate, the oral route for both rehydration and potassium is safer than IV.*

Composition of cholera stool vs. replacement fluid

Fluid (mmol/L)	Na^+	K^+	Cl^-	Base
Adult cholera stool	135	15	100	45
Child cholera stool	100	25	90	30
Ringer's lactate	130	4*	109	28

*Ringer's lactate is relatively K^+- and base-poor versus stool, which is why additional potassium (oral preferred)** is mandatory to replace stool losses.

Adjunctive antibiotics and zinc

- Antibiotics are **not necessary for cure**, but an agent to which the organism is susceptible **shortens the duration and volume of fluid loss and hastens clearance of the organism from stool**. Hence give to patients with **moderate or severe dehydration**.

Class / drug	Adult dose	Paediatric dose
Azithromycin (macrolide; agent of choice)	Single **1-g** oral dose	Single **20 mg/kg** dose
Erythromycin (macrolide)	250 mg PO QID × 3 days	12.5 mg/kg/dose QID × 3 days
Doxycycline (tetracycline)	Single **300-mg** dose (non-pregnant)	>8 y: single 4–6 mg/kg dose
Tetracycline	500 mg PO QID × 3 days (non-pregnant)	>8 y: 12.5 mg/kg/dose QID × 3 days
Ciprofloxacin (fluoroquinolone)	500 mg PO BID × 3 days	15 mg/kg BID × 3 days

- **Resistance caveats:** macrolides (azithromycin/erythromycin) are the **agents of choice**; resistance to **tetracyclines is widespread**, and **fluoroquinolone resistance is increasing** — use these only where susceptibility is confirmed.
- **Zinc** reduces the volume and severity of diarrhoea in young children, including cholera: **<6 months → 10 mg/day for 10 days; 6 to <60 months → 20 mg oral zinc/day for 10 days**.

Prevention — sanitation, surveillance and vaccines

- **General/public-health measures:** provision of **safe water** and **sanitary disposal of faeces**, **improved nutrition**, and care with **food preparation and storage** in the household significantly reduce incidence. Prevent spread by **infected or asymptomatic carriers** moving from endemic to non-endemic regions (the probable route of the 2010 Haiti outbreak).
- **Oral cholera vaccines (OCV)** — two types developed to maximise mucosal immunity: **oral killed** vaccines and **live attenuated** vaccines.
- **Three oral KILLED vaccines are WHO-prequalified:**
  - **BivWC (Shanchol; Shantha Biotechnics, Hyderabad, India)** — both biotypes/serotypes of *V. cholerae* O1 **and** O139, *without* supplemental cholera toxin B (CTB) subunit; manufacture being terminated.
  - **Euvichol / Euvichol-Plus (Eubiologics, Seoul, South Korea)** — currently supplies the vast majority of global control-programme vaccine.
  - **WC-rBS (Dukoral; Valneva, Sweden)** — both biotypes/serotypes of *V. cholerae* O1 **supplemented with 1 mg recombinant CTB subunit** per dose.
- **Killed-vaccine schedule/efficacy:** given as a **2- or 3-dose regimen, doses ~14 days apart**, providing **~60–85% protection** for the first few months. **Boosters:** WC-rBS after 2 years (≥6 y) or 6 months (children 2–5 y); BivWC gave **~60% protection over 5 years** in a Kolkata study (~40% in children ≤5 y). Even a **single dose** confers some outbreak protection (40% all / 63% severe cholera over 6 months) but **no protection in children <5 y** with one dose. **Herd immunity** is predicted once coverage **>50%**; killed vaccines are **safe in high-HIV-prevalence populations**.

- **Live attenuated vaccine: CVD 103-HgR (Vaxchora; Emergent BioSolutions)** — derived from a classic strain that **lacks the cholera-toxin genes**; **FDA-approved for travellers** (ages **2–64 y**) but **not WHO-prequalified**. Single oral dose; **90% and 80% efficacious** against severe cholera at 10 and 90 days post-vaccination in volunteer challenge.
- **Global strategy:** the **Global Task Force on Cholera Control (GTFCC)** strategy (launched 2017, WHO secretariat) aims to **cut cholera deaths by 90% and eliminate cholera in up to 20 countries by 2030**, integrating **WASH programmes + vaccination** and a **Global Vaccine Stockpile** (used mainly for *reactive*, often single-dose, campaigns owing to shortages).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Hexose–Na^+ co-transport / basis of ORS.** Label: intestinal villus enterocyte; **SGLT1 glucose–Na^+ co-transporter** on apical membrane; **glucose**; **Na^+**; **Cl^- and H_2O following passively**; Na^+/K^+-ATPase on basolateral membrane; note "*pathway intact despite cholera toxin*." Contrast with adjacent crypt cell showing cholera-toxin → ↑cAMP → Cl^-/water secretion (the diarrhoea).
- **Diagram 2 — Fluid-management flowchart by dehydration severity.** Boxes labelled: **Assess dehydration → None-mild (ORS) / Moderate (ORS up to 2 L) / Severe (IV Ringer's lactate 100 mL/kg in 3 h, total 200 mL/kg/24 h + oral K^+) → transition to maintenance ORS**, with the endpoint "awake, drinking, normal pulse."

Clinical / Diagnostic significance

- **Diagnosis:** suspect in any patient ≥5 y with acute watery diarrhoea in/near an endemic area, or with severe dehydration. Confirm by stool **dark-field microscopy** (darting motility, immobilised by specific antiserum), culture on **TCBS** or **TTG agar**, **Cary-Blair** transport / **alkaline-peptone water** enrichment, or **point-of-care antigen dipstick** in the field.
- **Labs reflect volume/electrolyte loss:** raised haematocrit (haemoconcentration), prerenal azotaemia, **bicarbonate <15 mmol/L** with a high **anion gap** acidosis, arterial **pH ~7.2**, and usually normal $Na^+/K^+/Cl^-$ — guiding the Ringer's lactate + potassium choice.
- **Management pearl:** complications (acute tubular necrosis, shock) are *purely* a consequence of dehydration and are **averted by adequate fluid/electrolyte therapy** — the disease is then self-limited over a few days.

High-yield exam pointers

- **Rehydration is the single most important intervention; death is from hypovolaemic shock.**
- WHO low-osmolarity ORS = **245 mOsm/L** (Na 75, K 20, Cl 65, citrate 10, glucose 75).
- Severe case = **Ringer's lactate, 100 mL/kg in 3 h (6 h if <12 mo), 200 mL/kg in 24 h**, plus **oral potassium**.
- **Rice-based ORS > standard ORS** in cholera; ORS works via **glucose–Na^+ co-transport** (intact despite toxin).
- Antibiotics are **adjunctive** (reduce stool volume/duration, hasten clearance) for **moderate/severe** dehydration — **azithromycin 1 g single dose** is first choice; tetracycline/FQ resistance rising.
- **Zinc:** 10 mg/day (<6 mo) or 20 mg/day (6–<60 mo) for **10 days** in children.

- **Three WHO-prequalified killed OCVs:** Shanchol (BivWC), Euvichol/Euvichol-Plus, Dukoral (WC-rBS, +CTB); live attenuated = **Vaxchora (CVD 103-HgR)**.
- **GTFCC 2017 goal:** 90% fewer deaths and elimination in up to 20 countries by **2030** via WASH + vaccine.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 173 "Cholera and Other Vibrioses"** (Waldor & Ryan); Tables 173-1 to 173-4 (dehydration assessment, treatment by severity, ORS and stool/IV electrolyte composition). All drug doses, ORS/Ringer's compositions, vaccine names and efficacy figures are taken directly from this chapter. *Coverage note:* the chapter fully covers this topic; SGLT1 is named in the diagram per universally accepted physiology (Harrison cites the "hexose–Na^+ co-transport" mechanism without naming the transporter).

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Tropical pulmonary eosinophilia

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Tropical pulmonary eosinophilia (**TPE**) is a distinct *hyper-responsive* syndrome that develops in a minority of individuals infected with the lymphatic-dwelling filarial nematodes **Wuchereria bancrofti** and **Brugia malayi**. It is characterised by paroxysmal nocturnal cough and wheeze, diffuse pulmonary infiltrates, intense peripheral blood eosinophilia (>3000/μL), markedly elevated serum IgE and antifilarial antibody, and a dramatic response to diethylcarbamazine (DEC). It is best understood as an *occult (amicrofilaraemic) filariasis* in which microfilariae are cleared from blood and trapped in the lungs, where they provoke an exuberant allergic-inflammatory reaction.

Etiology & Epidemiology

- **Causative parasites:** the lymphatic-dwelling filariae **W. bancrofti** and **B. malayi** — the same species that cause lymphatic filariasis. TPE is therefore one end of the clinical spectrum of bancroftian/brugian filariasis.
- **Vectors:** *Culex* mosquitoes (urban) and *Anopheles*/*Aedes* (rural) transmit W. bancrofti; *Mansonia* and *Anopheles* transmit B. malayi. Infective L3 larvae are deposited on skin during the mosquito bite.
- **Microfilarial periodicity:** both species are predominantly **nocturnally periodic** — microfilariae are scarce in peripheral blood by day and surge at night, which correlates with the characteristic *nocturnal* respiratory symptoms of TPE.
- **Adult worms** reside in afferent lymphatics or lymph nodes and may remain viable for **more than two decades**, providing a chronic antigenic stimulus.
- **Geography:** most cases reported from **India, Pakistan, Sri Lanka, Brazil, Guyana and Southeast Asia**. A history of residence in a filaria-endemic region is near-universal.
- **Trend:** the incidence of TPE has *declined over the past decade*, probably reflecting global mass drug administration (MDA) for elimination of lymphatic filariasis.

Pathogenesis & Pathology

- TPE represents a state of **immunological hyper-responsiveness** to the filarial parasite rather than uncontrolled infection.
- **Microfilariae and parasite antigens are rapidly cleared from the bloodstream by the lungs** — this *pulmonary sequestration* explains the cardinal paradox of TPE: blood is characteristically **amicrofilaraemic** despite active filarial infection.
- Clinical symptoms result from **allergic and inflammatory (hypersensitivity) reactions** elicited by the trapped/cleared parasites within the lung.
- A **prominent, eosinophil-enriched intra-alveolar infiltrate** develops; degranulating eosinophils release **cytotoxic, proinflammatory eosinophil granule proteins** that mediate much of the tissue damage (eosinophilic alveolitis).
- In some patients, trapping of microfilariae in other reticuloendothelial organs causes **hepatomegaly, splenomegaly or lymphadenopathy**.
- **If untreated**, the chronic eosinophilic inflammation progresses to **interstitial fibrosis** and irreversible, progressive pulmonary damage.

Clinical Features

- **History:** residence in / travel to a filaria-endemic area.
- **Respiratory: paroxysmal cough and wheezing**, classically **nocturnal** (paralleling the nocturnal periodicity of microfilariae); dyspnoea; may mimic bronchial asthma.
- **Constitutional: weight loss, low-grade fever, malaise**.
- **Lymphoreticular: lymphadenopathy**; sometimes hepatosplenomegaly.
- **Hallmark laboratory clue: pronounced blood eosinophilia (>3000 eosinophils/μL)**.
- Symptoms are subacute–chronic and, untreated, can persist for months with progressive pulmonary impairment.

Investigations & Diagnostic Criteria

- **Peripheral blood eosinophilia** >3000/μL (often very high).
- **Serum IgE:** total IgE markedly elevated (Harrison quotes **4–40 KIU/mL**); **antifilarial antibody titres markedly raised** — both are characteristic.
- **Absence of microfilariae in peripheral blood** (occult filariasis) — a key feature distinguishing TPE from classical microfilaraemic filariasis.
- **Chest imaging (X-ray / CT):** may be normal, but generally shows **increased bronchovascular markings**; **diffuse miliary lesions or mottled opacities** may be seen in the **middle and lower lung fields**.
- **Pulmonary function tests: restrictive** abnormalities in most cases, with **obstructive** defects in about half; reduced diffusion capacity reflects interstitial involvement.
- **BAL:** eosinophilic alveolitis (intra-alveolar eosinophil-rich infiltrate).
- **Therapeutic trial:** prompt clinical and haematological response to **DEC** strongly supports the diagnosis.

The composite diagnostic picture: endemic-area residence + nocturnal cough/wheeze + extreme eosinophilia (>3000/μL) + very high IgE & antifilarial antibody + characteristic radiology + restrictive PFT + rapid response to DEC.

Differential Diagnosis

TPE is one of the **pulmonary infiltrates with eosinophilia (PIE)** syndromes and must be distinguished from the conditions Harrison lists below.

Condition	Distinguishing pointers
Bronchial asthma	Allergic; lower-grade eosinophilia; no antifilarial antibody; no endemic exposure
Löffler's syndrome	Transient, migratory infiltrates from larval transit (e.g. *Ascaris*); self-limited
Allergic bronchopulmonary aspergillosis (ABPA)	Central bronchiectasis, *Aspergillus*-specific IgE/precipitins, mucoid impaction
EGPA / Churg-Strauss (allergic granulomatosis with polyangiitis)	Asthma + eosinophilia + vasculitis; ANCA in a proportion; multi-organ involvement
Other systemic vasculitides	Notably **polyarteritis (periarteritis) nodosa**
Chronic eosinophilic pneumonia	"Photographic-negative" peripheral infiltrates; idiopathic; steroid-responsive
Hypereosinophilic syndromes (HESs)	Persistent eosinophilia >1500/μL with multi-organ damage; no filarial serology

PIE classification (Harrison Ch 299) for framing the answer:

Group	Examples
Primary pulmonary eosinophilic disorders	Acute eosinophilic pneumonia; Chronic eosinophilic pneumonia; EGPA (Churg-Strauss); Hypereosinophilic syndrome
Known-cause / secondary (TPE belongs here)	Asthma & eosinophilic bronchitis; ABPA; drug/toxin reaction; **Infection — parasitic/helminthic disease (includes TPE)**; non-parasitic infection

Treatment

- **Diethylcarbamazine (DEC)** is the drug of choice: **4–6 mg/kg daily for 14 days** (note this is a longer course than the standard active-filariasis regimen).
- **Symptoms usually resolve within 3–7 days** of starting therapy — the rapid response is both confirmatory and therapeutic.
- **Relapse occurs in ~12–25% of cases** (sometimes after an interval of several years) and **requires re-treatment**.
- **Goal:** early, complete treatment prevents progression to **interstitial fibrosis** and chronic restrictive lung disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Filarial life cycle highlighting pulmonary trapping in TPE** — labels: *Mosquito vector (Culex / Anopheles) → Infective L3 larvae deposited on skin → Adult worms in lymphatics / lymph nodes → Microfilariae released into blood (nocturnal periodicity) → Microfilariae & antigens cleared and TRAPPED in the lung → Eosinophil-enriched intra-alveolar infiltrate (eosinophilic alveolitis) → Hypersensitivity reaction / high IgE & antifilarial antibody → Untreated → interstitial fibrosis.*
- **Schematic chest X-ray of TPE** — labels: *Increased bronchovascular markings, diffuse miliary / mottled opacities in mid & lower zones, bilateral involvement, (may be normal in some cases).*

Clinical / Diagnostic significance

- TPE is an important, **eminently treatable** cause of chronic cough, wheeze and pulmonary infiltrates in patients from the Indian subcontinent — readily mistaken for refractory asthma or miliary tuberculosis.
- The **triad of extreme eosinophilia (>3000/µL), very high IgE/antifilarial antibody, and amicrofilaraemia** in an endemic-area resident is highly suggestive and should prompt a DEC trial.
- **Early diagnosis prevents irreversible interstitial fibrosis**; relapse mandates follow-up and re-treatment.
- Conceptually links to public-health filariasis control: falling TPE incidence mirrors the success of WHO MDA programmes.

High-yield exam pointers

- TPE = **occult/amicrofilaraemic filariasis** caused by **W. bancrofti & B. malayi**; microfilariae are **cleared and trapped in the lungs** (absent in peripheral blood).
- **Classic clue triad:** nocturnal paroxysmal cough/wheeze + eosinophilia **>3000/µL** + markedly raised **IgE & antifilarial antibody**.
- Symptoms are **nocturnal** because of the **nocturnal periodicity** of microfilariae.
- **CXR:** increased bronchovascular markings; mid/lower-zone miliary or mottled opacities; **may be normal**. **PFT:** restrictive in most, obstructive in half.
- Endemic in **India, Pakistan, Sri Lanka, Brazil, Guyana, SE Asia**; incidence falling with MDA.
- **DEC 4–6 mg/kg/day × 14 days**; response in **3–7 days**; **relapse 12–25%** needs re-treatment.
- Untreated → **interstitial fibrosis** and progressive restrictive lung disease.
- It is a **secondary (known-cause) PIE** — i.e. pulmonary infiltrates with eosinophilia due to a **parasitic/helminthic infection**.
- Pathology = **eosinophilic alveolitis**: cytotoxic eosinophil granule proteins drive the lung injury.
- Differentiate from **asthma, Löffler's syndrome, ABPA, EGPA (Churg-Strauss), chronic eosinophilic pneumonia, HES**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 240 "Filarial and Related Infections"** (TPE epidemiology, pathology, clinical features, differential and DEC treatment; lymphatic filariasis etiology/vectors/periodicity) and **Ch 299 "Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia"** (PIE classification framing). *Coverage note:* Ch 299 does not name TPE explicitly but lists "Infection — parasitic/helminthic disease" among secondary PIE syndromes; the male predominance and young-adult (2nd–4th decade) preponderance often cited for TPE are not stated in the provided chapters and are given as standard textbook context only.

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Tropical splenomegaly

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — *Tropical splenomegaly* in internal-medicine usage refers to **Hyperreactive Malarial Splenomegaly (HMS)**, formerly called *Tropical Splenomegaly Syndrome (TSS)*. It is a **chronic complication of malaria** seen in long-term residents of malaria-endemic tropical regions, in whom an **aberrant, exaggerated immunologic response to repeated malarial infection** produces *massive splenomegaly*, hepatomegaly, marked **serum IgM** elevation and high malarial-antibody titres, with **anemia and hypersplenism**. It is a clinically important and *reversible* cause of massive splenomegaly that must be separated from haematologic malignancy.

Etiology & epidemiology

- **Cause:** chronic or repeated malarial infection in a genetically/immunologically predisposed host. Chronic malaria characteristically produces **hypergammaglobulinaemia, a normochromic normocytic anaemia, and (in some) splenomegaly**.
- **Host:** *residents of malaria-endemic areas in tropical countries* who mount an **abnormal immunologic response** to repeated infection — not a feature of acute single-episode malaria.
- **Geography:** holoendemic malarious belts of sub-Saharan Africa, Papua New Guinea, South-East Asia, the Indian subcontinent and Amazonia. Harrison notes that *in some tropical countries (e.g., New Guinea) the incidence of palpable splenomegaly may reach 60%* — emphasising that, in the tropics, a palpable spleen does not automatically equate with disease.
- **Implicated species:** *Plasmodium falciparum* and *P. malariae* are classically responsible (the (in Africa) peripheral B-cell lymphocytosis and chronic antigenic drive).

Pathogenesis (an immunologic, not a parasitic, disease)

The driving event is **uncontrolled, polyclonal B-cell over-production of IgM** in response to recurrent malarial antigen, with loss of normal T-cell suppressor control:

- Chronic infection → **marked elevation of serum IgM and malarial antibody titres**.
- Production of **cytotoxic IgM antibodies against CD8+ (suppressor) T lymphocytes** and antibodies to **CD5+ T lymphocytes**, with a resultant **increase in the CD4+ : CD8+ ratio**.

- Loss of suppressor-T-cell restraint → **uninhibited B-cell production of IgM** → formation of **cryoglobulins** (IgM aggregates and immune complexes).
- These immune complexes are cleared by the reticulo-endothelial (RE) system, stimulating **lymphoid hyperplasia and clearance ("work") hypertrophy** of the spleen → progressive **massive splenomegaly**. **Hepatic sinusoidal lymphocytosis** is characteristic, and (in Africa) a **peripheral B-cell lymphocytosis** occurs.
- The same RE/lymphoid hyperplasia mechanism that enlarges the spleen drives **hypersplenism** (pooling and destruction of blood cells in congested, enlarged cords) → anaemia and pancytopenia.

This places HMS within the **"increased demand for splenic function / immune-and-RE hyperplasia"** mechanistic group of splenomegaly (Harrison Table 70-2), alongside other parasitic causes (leishmaniasis, trypanosomiasis).

Clinical features

- **Massive splenomegaly** — the dominant sign; the patient presents with an **abdominal mass** or a **"dragging" sensation** in the abdomen.
- **Occasional sharp abdominal pain** suggesting **perisplenitis** (capsular inflammation); massive enlargement may also cause early satiety and LUQ heaviness.
- **Hepatomegaly** is usually present alongside the splenomegaly.
- **Anaemia** and **some degree of pancytopenia (hypersplenism)** — fatigue, pallor, bleeding tendency.
- **Recurrent respiratory and skin infections** are common, and **many patients die of overwhelming sepsis** — the leading cause of death.
- Constitutional features (insidious onset over months–years); unlike acute malaria there is usually **no high parasitaemia** — in many cases **malaria parasites cannot be found on peripheral-blood smears by microscopy**.

Diagnosis: criteria & investigations

- **Peripheral smear:** often **negative for parasites** (low-grade/absent parasitaemia) — a negative film does NOT exclude HMS.
- **Serum immunoglobulins: markedly raised polyclonal IgM**; **high malarial antibody titres**.
- **Full blood count:** features of **hypersplenism** — splenomegaly with cytopenia(s), a **normal or hyperplastic bone marrow**, and response to splenectomy; anaemia ± leuko-/thrombocytopenia.
- **Liver/spleen histology: hepatic sinusoidal lymphocytosis** (a hallmark on liver biopsy); reactive lymphoid hyperplasia in the spleen.
- **Imaging — confirm and size the spleen: ultrasonography is the procedure of choice** (normal max cephalo-caudad diameter ≤13 cm; normal spleen <250 g and impalpable). The spleen is **"massively enlarged" when palpable >8 cm below the left costal margin or weighs ≥1000 g**. Bedside assessment uses **palpation** (bimanual / ballottement / *Middleton* manoeuvre) and **percussion** (*Nixon, Castell, Traube's space*).

- **Therapeutic test: clinical and immunologic response (spleen regression, fall in IgM) to sustained antimalarial therapy** is itself a key diagnostic criterion and helps separate HMS from lymphoma.
- ***Fakunle diagnostic criteria* (standard tropical-medicine criteria — see Coverage note):** *Major* — (1) gross splenomegaly (≥10 cm below costal margin) with no other local cause; (2) serum IgM ≥2 SD above the local mean; (3) high malarial antibody titres; (4) clinical and immunologic response to antimalarial therapy. *Minor* — hepatic sinusoidal lymphocytosis, hypersplenism, normal-to-exaggerated lymphocyte responses, and familial clustering.

Differential diagnosis (causes of massive / tropical splenomegaly)

HMS must be distinguished from other causes of a *massive* spleen, especially haematologic malignancy (some HMS cases have been *mistaken for haematologic malignancy*):

Category	Conditions to exclude
Tropical infective	Visceral leishmaniasis (*kala-azar*), hepatic **schistosomiasis**, chronic malaria itself, trypanosomiasis
Haematologic malignancy	**Chronic myeloid leukaemia**, **myelofibrosis with myeloid metaplasia**, **hairy-cell leukaemia**, **chronic lymphocytic leukaemia / lymphomas**, polycythaemia vera
Infiltrative / storage	**Gaucher's disease**, amyloidosis, sarcoidosis, diffuse splenic haemangiomatosis
Congestive (portal HTN)	Cirrhosis, portal/splenic vein obstruction, *"Banti's disease"*, schistosomal periportal fibrosis
Immune	Autoimmune haemolytic anaemia, Felty's syndrome, SLE

Key separators: in HMS the smear is usually parasite-negative, IgM is very high, hepatic sinusoidal lymphocytosis is present, and the spleen **regresses on antimalarials** — features that argue against leishmaniasis (bone-marrow/splenic LD bodies), CML (Philadelphia chromosome, granulocytosis), and lymphoma (lymph-node/tissue biopsy).

Management & prognosis

- **Endemic-area residents: antimalarial chemoprophylaxis** (sustained/prolonged) — *results are usually good*, with gradual spleen regression and fall in IgM. Compliance over months is essential; relapse follows withdrawal.
- **Non-endemic settings (travellers/migrants): antimalarial treatment** is advised.
- **Standard regimens (textbook practice — see Coverage note):** long-term **proguanil** or **chloroquine** prophylaxis are the conventional agents; therapy is continued for a prolonged period with serial spleen-size and IgM monitoring.
- **Supportive:** treat anaemia/cytopenias of hypersplenism; aggressively investigate and treat intercurrent infection — **overwhelming sepsis is the chief killer**.
- **Splenectomy** is generally avoided (it does not treat the underlying immune disorder and adds lifelong infection risk); it is reserved for refractory hypersplenism/symptomatic massive splenomegaly, with appropriate pre-operative vaccination.

- **Prognosis / caveat:** in cases **refractory to therapy, clonal lymphoproliferation may develop and can evolve into a malignant lymphoproliferative disorder** — long-term follow-up is mandatory.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Spleen microanatomy (basis of culling/pitting & work hypertrophy).** Labels: *splenic artery → central arteriole*, **white pulp** (B-cell follicle with germinal centre, marginal zone, peri-arteriolar T-cell sheath), **red pulp** (*pulp cords*, *pulp sinuses*), *sinusoidal slits/pores*, *reticulo-endothelial (macrophage) cells*, *splenic venous system*.
- **Diagram 2 — Pathogenesis flow of HMS.** Labels: *Repeated malarial infection → polyclonal B-cell activation (↑IgM, cryoglobulins, immune complexes) → anti-CD8 cytotoxic IgM → loss of suppressor T cells → ↑CD4:CD8 ratio → RE / lymphoid hyperplasia & clearance activity →* **massive splenomegaly + hepatomegaly + hypersplenism (anaemia, pancytopenia)**.

Clinical / Diagnostic significance

- A **reversible, treatable cause of massive splenomegaly** in the tropics — early recognition averts unnecessary splenectomy or chemotherapy for a misdiagnosed "lymphoma."
- The **parasite-negative smear with very high IgM and antimalarial-responsive splenomegaly** is the diagnostic signature.
- Demonstrates the spleen's **immune/RE "work hypertrophy"** physiology and the concept of **hypersplenism** (splenomegaly + cytopenia + hyperplastic marrow + response to splenectomy).
- Carries a real risk of **progression to clonal lymphoproliferative disease**, mandating surveillance.

High-yield exam pointers

- *Tropical splenomegaly* = *Hyperreactive Malarial Splenomegaly (HMS)* = old *Tropical Splenomegaly Syndrome*; it is a **chronic complication of malaria** (*P. falciparum / P. malariae*).
- It is an **immunologic disorder**, NOT high parasitaemia — **smear is often parasite-negative**.
- Hallmarks: **massive splenomegaly + hepatomegaly + very high serum IgM + high malarial antibody titres + hepatic sinusoidal lymphocytosis** (+ peripheral B-cell lymphocytosis in Africa).
- Immunology: **cytotoxic IgM vs CD8+ T cells, anti-CD5+ T-cell antibodies, ↑CD4:CD8 ratio, cryoglobulins**.
- Presents as an **abdominal "dragging" mass ± perisplenitic pain**, with **anaemia + pancytopenia (hypersplenism)**; **death is usually from overwhelming sepsis**.
- **Massive spleen** = palpable **>8 cm below the costal margin or ≥1000 g**; **ultrasound** is the imaging of choice; normal spleen **<250 g, ≤13 cm**.
- Treatment = **prolonged antimalarial chemoprophylaxis/treatment** (good response in endemic areas); **avoid splenectomy**.
- Refractory cases may undergo **clonal lymphoproliferation → malignant lymphoproliferative disorder**.
- Remember the tropical massive-splenomegaly DDx: **kala-azar, schistosomiasis, CML, myelofibrosis, lymphoma/CLL, Gaucher's**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 231 "Malaria"** (Chronic Complications of Malaria → *Hyperreactive Malarial Splenomegaly*: aetiology, immunopathogenesis, clinical features, treatment, lymphoma risk) and **Ch 70 "Enlargement of Lymph Nodes and Spleen"** (spleen structure/function, mechanisms of splenomegaly Table 70-2, massive-splenomegaly criteria and differential Table 70-3, hypersplenism, examination and imaging). **Coverage note (spec gap = true):** Harrison covers HMS only briefly within the Malaria chapter. Points **not explicitly in the provided Harrison text** but added as standard, universally-accepted tropical-medicine teaching, and flagged here: the **named *Fakunle diagnostic criteria***, the specific prophylactic drugs (**proguanil / chloroquine**) and the **≥10 cm spleen / IgM ≥2 SD** thresholds, the role/avoidance of **splenectomy**, and the detailed geographic distribution. All disease mechanisms, the IgM/CD8/CD5/CD4:CD8 immunology, clinical features, lymphoma risk, the "massively enlarged" definition (>8 cm / ≥1000 g) and the splenomegaly differential are directly grounded in the two cited chapters.

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Viral meningitis

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Viral meningitis is an acute inflammation of the leptomeninges and subarachnoid space (SAS) caused by viral infection, producing headache, fever and meningeal irritation **without** the profound alteration of consciousness, seizures, or focal deficits that characterise encephalitis. It is the commonest cause of the **"aseptic meningitis syndrome"** — a clinical-laboratory picture of meningeal inflammation (CSF lymphocytic pleocytosis, normal glucose, negative routine bacterial Gram's stain and culture) — and is, in the immunocompetent adult, a generally **benign, self-limiting** illness. *Enteroviruses* account for the great majority of identified cases.

Etiology

- A specific viral cause is now identifiable in **60–90%** of cases using CSF PCR, culture and serology; CSF *cultures* alone are positive in only 30–70%, and about two-thirds of culture-negative "aseptic" cases yield a virus on **CSF PCR**.
- **Most important / common agents:** *Enteroviruses* (coxsackieviruses, echoviruses, numbered enteroviruses), *varicella-zoster virus (VZV)*, *herpes simplex virus* (**HSV-2 > HSV-1**), *HIV*, and *arboviruses* (notably West Nile virus, WNV).
- **Less common:** HSV-1, human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), *lymphocytic choriomeningitis virus (LCMV)*, mumps, Epstein-Barr virus (EBV), Zika and other non-WNV arboviruses.
- **Enteroviruses cause >85%** of cases in which an agent is identified — the single dominant cause.

Clinical manifestations

- **Cardinal features:** headache (almost invariable — frontal/retro-orbital, with **photophobia** and pain on eye movement), fever, and **nuchal rigidity** (often mild, only at the limit of neck anteflexion).
- **Constitutional:** malaise, myalgia, anorexia, nausea/vomiting, abdominal pain, diarrhoea; mild lethargy or drowsiness is common.
- **Red flags pointing AWAY from simple viral meningitis (suggest encephalitis or alternative diagnosis):** *stupor, coma, marked confusion*, **seizures**, **focal neurological signs**, or neuroimaging evidence of parenchymal involvement. These are NOT features of pure viral meningitis.
- **Etiological clues on examination** — search for exanthems, *hand-foot-mouth disease*, *herpangina*, pleurodynia, myopericarditis and haemorrhagic conjunctivitis (enterovirus); genital vesicles (HSV-2); chickenpox/shingles rash (VZV); parotitis/orchitis (mumps); cranial nerve palsies, especially **V, VII, VIII** (HIV).

Epidemiology

- Estimated incidence ≥ **75,000 cases/year** in the United States (not a nationally reportable disease).
- In temperate climates there is a marked **summer–autumn (non-winter) predominance**, reflecting the seasonality of *enterovirus* and *arbovirus* infection; peak monthly incidence ~1 case/100,000.
- **Seasonal/host clues:** enteroviruses — summer/fall, children <15 yr; arboviruses — summer/early fall, geographic clusters; **mumps** — late winter/early spring, males (M:F **3:1**); **LCMV** — late fall/winter, exposure to house mice (*Mus musculus*), pet/laboratory rodents or their excreta.

CSF and laboratory diagnosis

- **CSF examination is the single most important test.** Typical viral profile:

Parameter	Viral (aseptic) meningitis	Contrast: pyogenic bacterial
Opening pressure	Normal/mildly raised (100–350 mmH_2O)	>180 mmH_2O (often markedly)
Cell type	**Lymphocytic** pleocytosis	Polymorphonuclear (PMN)
Cell count	Typically **25–500/µL** (occasionally thousands with LCMV/mumps)	100–10,000/µL
Glucose	**Normal**	Low (<2.2 mmol/L; CSF/serum <0.4)
Protein	Normal/mildly raised (**0.2–0.8 g/L**)	High (>0.45 g/L)
Gram's stain	Negative	Positive in >60%

- **Exceptions to remember:** PMNs may *predominate in the first 48 h*, especially **echovirus 9, WNV, eastern equine encephalitis virus, and mumps** — a PMN pleocytosis occurs in ~**45% of WNV meningitis** and may persist a week before shifting to lymphocytes. PMN pleocytosis with low glucose also occurs with CMV in the immunocompromised.

- **Hypoglycorrhachia (low CSF glucose)** is atypical but occurs in **10–30%** of mumps and LCMV cases (rarely echovirus/enterovirus, HSV-2, VZV). A lymphocytic pleocytosis *with low glucose* should still raise **TB, fungal, Listeria, or neoplastic** meningitis.
- **CSF PCR — diagnostic procedure of choice** for enteroviral and HSV CNS infection; far more sensitive than culture. Enteroviral **RT-PCR** sensitivity >95%, highest within 48 h, falling rapidly after day 5. The **FilmArray Meningitis/Encephalitis multiplex panel** detects HSV-1, HSV-2, enteroviruses, VZV, HHV-6 and human Parechovirus — but **NOT** CMV, WNV, LCMV or EBV.
- **Serology:** mainstay for **arboviruses (WNV)** — demonstration of **virus-specific IgM in CSF** or seroconversion (CSF WNV IgM more sensitive [>80% in neuroinvasive disease] than CSF RT-PCR ~70%); serology less useful for high-seroprevalence herpesviruses.
- **Viral culture** of CSF is generally poor-yield; ancillary isolation — enterovirus/adenovirus in stool; arbovirus/enterovirus/LCMV in blood; mumps/CMV in urine; enterovirus/mumps/adenovirus in throat washings. Stool enterovirus shedding persists weeks and is *not by itself diagnostic*.
- **Other tests:** full blood count, liver/renal function, ESR, C-reactive protein, electrolytes, glucose, amylase/lipase (mumps). **Neuroimaging (MRI > CT)** is not mandatory in uncomplicated cases but is indicated for altered consciousness, seizures, focal signs, atypical CSF, or immunocompromise. CSF **oligoclonal bands** can occur.

Specific viral etiologies — exam pearls

- **Enteroviruses** — >85% of identified cases; benign outside the neonatal period; supportive treatment, recovery without sequelae. Chronic/severe infection in neonates and the **hypo-/agammaglobulinaemic**.
- **HSV** — second to enteroviruses overall (**~5%** of cases, higher in adults / non-summer). In adults uncomplicated meningitis is mostly **HSV-2**, whereas **HSV-1 causes ~90% of HSV encephalitis**. Meningitis occurs in **~25–35% of women and ~10–15% of men** at primary genital herpes; ~20% develop recurrent attacks. Most **recurrent ("benign lymphocytic") aseptic meningitis — including cases formerly called *Mollaret's meningitis* — is due to HSV** (diagnosed by CSF PCR; cultures often negative).
- **VZV** — suspect with concurrent chickenpox/shingles, but increasingly recognised **without rash**; frequency 3–20% across series.
- **Arboviruses (WNV, St. Louis, California group)** — geographic/seasonal clusters; avian deaths can be sentinel for WNV; diagnosis by CSF IgM.
- **Mumps** — parotitis/orchitis/oophoritis/raised lipase-amylase; clinical meningitis in 10–30% of parotitis; pleocytosis can exceed 1000/μL; incidence fell >95% after vaccination.
- **HIV** — aseptic meningitis in 5–10% at primary (seroconversion) infection; **cranial nerve V, VII, VIII palsies** are more frequent than with other viruses.
- **LCMV** — rodent exposure; leukopenia, thrombocytopenia, abnormal LFTs; may show marked pleocytosis and hypoglycorrhachia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Meningeal anatomy / lumbar puncture site (labelled):** scalp — skull — **dura mater** — **arachnoid mater** — **subarachnoid space (CSF, site of inflammation)** — **pia mater** — cerebral cortex; plus a spine schematic marking the **L3–L4 / L4–L5 interspace** for LP below the conus medullaris.
- **CSF interpretation flow-box (labelled):** "Meningeal signs → LP" → branch A *Lymphocytes + normal glucose + negative Gram's stain* = **VIRAL/aseptic** → CSF PCR / WNV IgM; branch B *PMN + low glucose + positive Gram's* = **bacterial**; branch C *Lymphocytes + low glucose* = **TB / fungal / Listeria / neoplastic**.

Clinical / Diagnostic significance

- **Differential diagnosis is the crux** — exclude mimics of aseptic meningitis: untreated/partially-treated bacterial meningitis; early TB, fungal or *T. pallidum* (neurosyphilis); *Mycoplasma, Listeria, Brucella, Coxiella, Leptospira, Rickettsia*; parameningeal foci; neoplastic meningitis; and non-infectious inflammatory disease (drug-induced hypersensitivity meningitis, SLE, sarcoidosis, Behçet's, uveomeningitic syndromes).
- **Distinguishing bacterial from aseptic:** CSF protein >0.5 g/L and **serum procalcitonin >0.5 ng/mL** (sensitivity/specificity ~89%) favour bacterial; the validated **Bacterial Meningitis Score** predicts very low bacterial probability (NPV 99.7%) when *all* of — negative CSF Gram's stain, CSF neutrophils <1000/μL, CSF protein <80 mg/dL, peripheral ANC <10,000/μL, and no seizures — are met.
- **Treatment is principally supportive:** analgesics, antipyretics, antiemetics, fluid/electrolyte care. Empirical antibacterial (± aciclovir) cover is continued until bacterial meningitis is excluded.
- **Specific antiviral therapy** (benefit data limited): **IV aciclovir 15–30 mg/kg/day in 3 divided doses** for seriously ill HSV/VZV (and severe EBV) cases, stepping down to oral **aciclovir 800 mg five times daily**, **famciclovir 500 mg tid**, or **valaciclovir 1000 mg tid** for a total **7–14 days**; mild cases — oral agents alone. *No proven specific therapy* for arboviral (e.g., WNV) disease. **HIV** meningitis → antiretroviral therapy. Per CMDT, antiviral therapy for aseptic meningitis in immunocompetent hosts is of *uncertain benefit* (self-limiting), and long-term oral **valaciclovir prophylaxis does NOT prevent recurrent HSV-2 aseptic meningitis**.
- **Special hosts:** patients with deficient humoral immunity (e.g., **X-linked agammaglobulinaemia**) should receive **immunoglobulin (IM γ-globulin or IVIg)**; intraventricular Ig (Ommaya reservoir) has been used for refractory chronic enteroviral meningitis.
- **Admission criteria:** immunocompetent patients with a classic CSF profile and no red flags may be managed at home with follow-up; **hospitalise** the immunocompromised and any with altered consciousness, seizures, focal signs, or atypical CSF.
- **Prevention:** vaccination prevents meningitis from **poliovirus, mumps, measles, rubella and varicella**; the recombinant zoster vaccine (Shingrix) is recommended for VZV prevention.

High-yield exam pointers

- **Aseptic meningitis** = lymphocytic pleocytosis + normal glucose + negative routine bacterial Gram's stain/culture; **viral causes are the commonest**.
- **Enteroviruses cause >85%** of identified viral meningitis; **summer–autumn** peak; children.
- **CSF PCR (RT-PCR) is the test of choice**; enteroviral RT-PCR best within **48 h**, declines after day 5.
- **HSV-2** = leading cause of recurrent / **Mollaret's** aseptic meningitis; **HSV-1 = encephalitis**.
- **Early PMN predominance** can occur with **echovirus 9, WNV, EEE, mumps**; ~45% of WNV meningitis has CSF neutrophilia.
- **Low CSF glucose** in viral meningitis suggests **mumps or LCMV** (10–30%) — but always reconsider TB/fungal/Listeria.
- **Arbovirus (WNV)** diagnosis = **CSF virus-specific IgM** (more sensitive than CSF RT-PCR).
- Profound coma, seizures or focal deficits → think **encephalitis**, not pure meningitis.
- Treatment is **supportive**; aciclovir for HSV/VZV; **IVIg** for agammaglobulinaemia; antiretrovirals for HIV. **Prognosis in adults is excellent.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Meningitis" (Viral Meningitis section: clinical manifestations, etiology, CSF/PCR/serology, specific viral etiologies, treatment, prognosis; comparison data from the Bacterial Meningitis section of the same chapter).
- **CMDT 2026** — "Viral & Rickettsial Infections" (enteroviral syndromes; antiviral/valaciclovir-prophylaxis caveat for HSV-2 aseptic meningitis) and "Nervous System Disorders" (current management framing).

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Antimicrobial susceptibility testing

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Antimicrobial susceptibility testing (AST)* comprises the standardised in-vitro laboratory methods that quantify the activity of an antimicrobial agent against a bacterial isolate, expressed chiefly as the **minimal inhibitory concentration (MIC)** — the lowest drug concentration that inhibits visible growth of a microorganism under standardised laboratory conditions. AST converts a raw MIC into a clinically actionable category — *susceptible (S), intermediate (I), or resistant (R)* — by comparison with regulatory **breakpoints**, and thereby guides directed (pathogen-targeted) therapy, defines local resistance for the **antibiogram**, and underpins pharmacokinetic–pharmacodynamic (PK/PD) dosing. Methods are broadly **diffusion-based**, **dilution-based (quantitative)**, **automated/rapid phenotypic**, **specialised** (bactericidal/synergy), and **molecular/genotypic**.

Core endpoints the laboratory measures

- **MIC** — lowest concentration inhibiting growth with a standardised inoculum and growth conditions; the central quantitative endpoint, reported in µg/mL (e.g., vancomycin MIC of 2 µg/mL flags reduced susceptibility in *S. aureus*).
- **Minimal bactericidal concentration (MBC)** — lowest concentration that **kills ≥99.9% (≥3 $\log_{10}$)** of the original inoculum; distinguishes bactericidal from bacteriostatic action.
- **Breakpoint** — the MIC value(s) set by advisory bodies (**CLSI**, **EUCAST**) that partition isolates into S/I/R; derived from MIC distributions of clinical isolates, drug PK/delivery to the infection site, and clinical-trial outcome data. "Susceptible" predicts likely response to an appropriately dosed drug; "resistant" predicts poor/no response.
- **Bacteriostatic vs bactericidal** — inhibition of growth vs killing; bactericidal agents are preferred where host defences are impaired or limited (neutropenia, **meningitis**, **endocarditis**).
- **Tolerance** — organism inhibited but not killed (failure to activate autolysins); operationally an **MBC/MIC ratio ≥32**.
- **Postantibiotic effect (PAE)** — delayed regrowth of surviving bacteria after drug exposure (prominent with aminoglycosides), supporting extended-interval dosing.

Diffusion methods (qualitative / semi-quantitative)

- **Disk diffusion (Kirby–Bauer)** — standard inoculum (turbidity matched to the **0.5 McFarland** standard) is lawn-spread on **Mueller–Hinton agar**; antibiotic-impregnated paper disks are applied; after **16–18 h at 35 °C** the **zone of inhibition diameter (mm)** is measured and interpreted as S/I/R against CLSI/EUCAST tables. Cheap, flexible, the workhorse of most laboratories; gives a category, **not** a numeric MIC.
- **Gradient diffusion (E-test / *epsilometer*)** — a plastic strip carrying a predefined exponential antibiotic gradient is laid on inoculated agar; an elliptical inhibition zone forms and the **MIC is read where the ellipse intersects the strip**. Combines the simplicity of diffusion with a quantitative MIC; useful for fastidious organisms and for confirming key MICs (e.g., penicillin/pneumococcus, vancomycin/staphylococci).

- **D-test (double-disk approximation)** — erythromycin and clindamycin disks placed adjacently; flattening ("D" shape) of the clindamycin zone reveals **inducible clindamycin (MLS_B) resistance**.

Dilution (quantitative) methods — the reference for MIC and MBC

- **Broth dilution** — antibiotic prepared in **doubling (two-fold) serial dilutions** in Mueller–Hinton broth; each tube/well inoculated to a standard density (~5×10^5 CFU/mL); the **MIC is the lowest concentration with no visible turbidity** after overnight incubation.
  - *Macrodilution* uses tubes (labour-intensive); *microdilution* uses **96-well microtitre plates** and is the practical reference standard, allowing many drug/dilution combinations per plate.
- **Agar dilution** — antibiotic incorporated into agar plates at doubling dilutions; multiple isolates spot-inoculated onto each plate; MIC = lowest concentration inhibiting visible growth. Efficient when many isolates are tested against one drug (reference method for some organisms, e.g., *N. gonorrhoeae*).
- **MBC determination** — aliquots from the clear (no-growth) broth-dilution tubes are subcultured to drug-free agar; colony counts identify the lowest concentration giving **≥99.9% kill** = MBC; the **MBC/MIC ratio** defines tolerance.

Method	Output	Quantitative MIC?	Typical use
Disk diffusion (Kirby–Bauer)	Zone diameter → S/I/R	No	Routine first-line testing
E-test (gradient strip)	MIC (µg/mL)	Yes	Confirm key/borderline MICs, fastidious organisms
Broth microdilution	MIC (µg/mL)	Yes	Reference standard MIC
Agar dilution	MIC (µg/mL)	Yes	Reference for many isolates / one drug
Automated (VITEK 2, Phoenix, MicroScan)	MIC + S/I/R, hours	Yes	High-throughput routine labs

Automated, specialised and bactericidal methods

- **Automated systems** — *VITEK 2*, *BD Phoenix*, *MicroScan* use micro-volume broth-microdilution cards/panels with **turbidimetric/colorimetric growth monitoring** and software interpretation, delivering identification + MIC in hours; the basis of most clinical antibiograms.
- **Serum bactericidal titre (*Schlichter test*)** — highest dilution of the patient's serum (during therapy) that kills the infecting organism; historically used to gauge adequacy of therapy in endocarditis/osteomyelitis.
- **Synergy testing** —
  - *Checkerboard titration* → **fractional inhibitory concentration (FIC) index**: **≤0.5 = synergy**, >0.5–4 = indifference/additivity, >4 = antagonism.
  - *Time–kill curves* → a **≥2 $\log_{10}$ (≥100-fold)** greater kill by the combination vs the most active single agent defines synergy; also profiles bactericidal kinetics and PAE.

- **β-lactamase detection** — chromogenic **nitrocefin** test gives a rapid colour change with β-lactamase-producing organisms (e.g., *H. influenzae*, gonococci, staphylococci).
- **Screening / breakpoint agars** — e.g., oxacillin/cefoxitin screen for MRSA, vancomycin-screen agar; **population analysis profiling** detects **heteroresistant VISA (hVISA)**, which is *not detectable by routine susceptibility testing*.

Molecular / genotypic methods (detect resistance determinants)

- **Targeted nucleic-acid amplification (PCR/NAAT)** for resistance genes — **mecA** (methicillin resistance in *S. aureus*), **vanA/vanB** (VRE), **bla_KPC / NDM / OXA-48** carbapenemases, **bla_CTX-M** (ESBL).
- **GeneXpert (Xpert MTB/RIF)** — simultaneous detection of *M. tuberculosis* and **rifampicin resistance** (rpoB); for mycobacteria, phenotypic AST uses **liquid culture (BACTEC MGIT)** and the **agar proportion method**.
- **MALDI-TOF mass spectrometry** — rapid species identification (and adjunctive resistance detection, e.g., carbapenemase hydrolysis assays).
- **Whole-genome sequencing (WGS)** — comprehensive resistome and epidemiological typing.
- Caveat: genotype predicts phenotype only for known mechanisms; **phenotypic AST remains the standard** because a gene may be present but unexpressed, or resistance may arise by uncharacterised routes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Disk-diffusion (Kirby–Bauer) plate** — Mueller–Hinton agar with confluent bacterial lawn; several antibiotic disks; clear circular *zone of inhibition* around a sensitive disk vs growth up to the edge of a resistant disk. Labels: *Mueller–Hinton agar*, *antibiotic disk*, *zone of inhibition (mm)*, *confluent lawn (0.5 McFarland inoculum)*, *susceptible*, *resistant*.
- **Broth microdilution row + MIC/MBC schematic** — a row of wells/tubes with doubling antibiotic concentrations: turbid (growth) wells then the first clear well = **MIC**; subculture of clear wells to agar with the first plate showing ≥99.9% kill = **MBC**. Labels: *doubling dilutions (µg/mL)*, *turbid = growth*, *first clear well = MIC*, *subculture → MBC*, *MBC/MIC ≥32 = tolerance*.

Clinical / Diagnostic significance

- Obtain specimens for culture **before** starting antibiotics so AST can convert empirical therapy into narrow-spectrum **directed therapy**, reducing toxicity, resistance selection, and *C. difficile* risk.
- MIC + breakpoint individualise drug choice — e.g., pneumococcal endocarditis treated by **penicillin MIC** (penicillin if MIC ≤2 µg/mL; ceftriaxone/vancomycin if higher); **meningitis breakpoints** are stricter (penicillin MIC 0.06 µg/mL) because of limited CSF penetration.
- The **MIC anchors PK/PD targets**: aminoglycosides → **Cmax/MIC** (concentration-dependent); β-lactams → **T > MIC** (time-dependent); fluoroquinolones & vancomycin → **AUC/MIC** (e.g., AUC/MIC > 30 maximises fluoroquinolone kill of *S. pneumoniae*; > 125 for gram-negatives).

- The **cumulative antibiogram** (local S/I/R rates, usually annual) guides empirical regimens and stewardship; therapeutic drug monitoring (e.g., vancomycin) is interpreted against the MIC.
- Recognise the **MBC/MIC ratio** (tolerance) and **hVISA** as reasons for clinical failure despite a "susceptible" routine report.

High-yield exam pointers

- **MIC = lowest concentration inhibiting visible growth; MBC = lowest killing ≥99.9% (≥3 $\log_{10}$).**
- **Kirby–Bauer disk diffusion**: Mueller–Hinton agar, **0.5 McFarland** inoculum, 16–18 h/35 °C, read **zone diameter** → S/I/R; gives a category, *not* an MIC.
- **Broth microdilution = reference standard** for numeric MIC; **agar dilution** for many isolates/one drug; **E-test** gives MIC by gradient diffusion.
- **Breakpoints** are set by **CLSI / EUCAST**; categories are **S / I / R**.
- **Tolerance = MBC/MIC ≥32**; **synergy = FIC index ≤0.5** (checkerboard) or **≥2 $\log_{10}$** extra kill (time–kill).
- **Automated systems**: VITEK 2, BD Phoenix, MicroScan (turbidimetric microdilution).
- **Molecular**: PCR for *mecA*, *vanA/B*, KPC/NDM/OXA; **Xpert MTB/RIF** for rifampicin resistance; **MALDI-TOF** for rapid ID; phenotypic AST still the gold standard.
- **hVISA** is missed by routine AST — needs **population analysis profiling**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Treatment and Prophylaxis of Bacterial Infections"* (MIC definition; bacteriostatic vs bactericidal; PK/PD indices Cmax/MIC, T>MIC, AUC/MIC; postantibiotic effect; antibiogram); *"Bacterial Resistance to Antimicrobial Agents"* (MIC, breakpoints, S/I/R interpretation, resistance mechanisms); *"Infective Endocarditis"* (vancomycin/penicillin MICs, meningitis breakpoints, hVISA not detected by routine testing); diagnostic-microbiology content (*mecA*/NAAT detection).
- **CMDT 2026** — *Anti-infective Treatment* (mechanism/"tolerance", MIC-targeted dosing) and *Common Problems in Infectious Diseases & Antimicrobial Therapy*.

Coverage note: The corpus (Harrison 22e, CMDT 2026) is pharmacology- and resistance-focused and covers the **endpoints** (MIC, breakpoints, S/I/R, bacteriostatic/bactericidal, tolerance, PK/PD, antibiogram, hVISA, *mecA*/NAAT) but is **thin on the step-by-step laboratory procedures**. The procedural detail of disk diffusion (Kirby–Bauer), broth macro-/micro-dilution, agar dilution, E-test, MBC determination, serum bactericidal titre, checkerboard/time-kill synergy, β-lactamase/nitrocefin and D-tests, automated systems and MALDI-TOF/WGS is supplied here from **universally accepted standard clinical microbiology (CLSI/EUCAST methodology)** and is faithful to that standard.

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Gastrointestinal system & hepatology

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Acute pancreatitis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Acute pancreatitis is an acute, reversible inflammatory process of the pancreas caused by premature intra-acinar activation of digestive enzymes (autodigestion), ranging pathologically from self-limited **interstitial (oedematous) pancreatitis** (perfusion preserved) to life-threatening **necrotizing pancreatitis** (perfusion interrupted). It is one of the commonest gastrointestinal causes of hospitalization (incidence ~15–45/100,000/year), is self-limited in 85–90% of cases, but carries an overall mortality of ~1% that rises to ~30–50% when persistent organ failure and infected necrosis coexist. Diagnosis rests on the **Revised Atlanta (2012)** framework, which standardised definitions of severity, phases and morphology.

Etiology

- **Gallstones (including microlithiasis) — leading cause, 30–60%.** Risk is fourfold greater with stones <5 mm (these pass and transiently impact the ampulla). Suggested by **ALT >3× ULN** (CMDT: ALT >150 U/L).
- **Heavy alcohol use — second commonest, 15–30%.** Smoking and genetic predisposition are co-factors.
- **Severe hypertriglyceridemia** (1–4%) — triglycerides usually **>1000 mg/dL**; often uncontrolled diabetes or apolipoprotein C-II deficiency.
- **Post-ERCP** — pancreatitis in 5–10%; risk reduced by rectal indomethacin/NSAID and prophylactic pancreatic duct stent.
- **Drugs** (<2% of cases): azathioprine/6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproate, 5-ASA, DPP-4 inhibitors.
- **Others:** hypercalcemia, trauma (blunt abdominal), post-operative, pancreas divisum, hereditary (PRSS1), cystic fibrosis, periampullary diverticulum, autoimmune (IgG4 type 1/duct-centric type 2), infections (mumps, coxsackie, CMV), pancreatic/ampullary tumour (~2–4% of pancreatic cancers present as AP), and idiopathic.
- A useful aide-mémoire is *GET SMASHED* (Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune, Scorpion sting, Hypercalcemia/Hypertriglyceridemia, ERCP, Drugs), but the grounded big three are **gallstones + alcohol + hypertriglyceridemia**.

Pathogenesis

- Core defect is **loss of acinar autoprotection** and premature activation of trypsinogen → trypsin, which then triggers a cascade activating chymotrypsinogen, proelastase and phospholipase A2.
- Normal safeguards (any of which, when lost, leads to autodigestion): zymogen packaging as proenzymes, low cytosolic calcium, acid-base balance, and protective inhibitors **SPINK1** (serine protease inhibitor, Kazal type 1) and chymotrypsin C (CTRC), which inactivate trypsin.
- **Three evolving phases:** (1) intra-acinar trypsin activation mediated by lysosomal **cathepsin B** co-localizing with zymogens → acinar injury; (2) intrapancreatic inflammation with neutrophil/macrophage chemoattraction; (3) systemic release of activated proteases and cytokines → **SIRS, ARDS and multiorgan failure**.

- **Genetic susceptibility genes** (centred on trypsin control): *PRSS1* (cationic trypsinogen — the only variant sufficient to cause AP alone), *SPINK1*, *CFTR*, *CTRC*, *CASR* (calcium-sensing receptor) and *CLDN2* (claudin-2); the latter five are disease *modifiers*.

Clinical features

- **Abdominal pain** — the cardinal symptom: steady, boring epigastric pain radiating to the back, relieved by sitting forward, with nausea, vomiting and abdominal distension from ileus.
- Examination: low-grade fever, tachycardia, **hypotension/shock** (third-space loss, kinin release, circulating enzymes); diminished bowel sounds; epigastric tenderness often disproportionately mild relative to pain.
- **Specific signs** (rare, reflect haemorrhagic necrosis and worse prognosis): *Cullen's sign* (periumbilical bluish discolouration), *Grey Turner's sign* (flank discolouration), *pancreatic panniculitis* (subcutaneous fat-necrosis nodules), and *Purtscher's retinopathy* (sudden blindness).
- Pulmonary findings in 10–20% (basal rales, atelectasis, left pleural effusion); transient jaundice in ~10%.

Laboratory & imaging diagnosis

- **Serum lipase and/or amylase >3× ULN** is strongly supportive. **Lipase is more specific and preferred** (remains elevated 7–14 days vs amylase normalising in 3–7 days). There is **no correlation** between enzyme level and severity. Amylase is spuriously raised in DKA/acidaemia (pH ≤7.32) and spuriously low in severe hypertriglyceridemia.
- Supportive labs: leukocytosis (15,000–20,000/μL), **haemoconcentration (Hct >44%)** and rising BUN (azotaemia — strong mortality marker), hyperglycemia, **hypocalcemia (~25%)**, hyperbilirubinemia (~10%), hypoxaemia (PaO2 ≤60 mmHg) heralding ARDS.
- **Diagnosis = any 2 of 3 criteria:** (1) typical epigastric pain radiating to back; (2) lipase/amylase **>3× ULN**; (3) characteristic findings on cross-sectional imaging.
- **Imaging:** transabdominal **ultrasound is the initial test** (gallstones, CBD). **Contrast-enhanced CT** is best at **day 3–5** (not routinely in first 48–72 h) to detect necrosis/local complications; MRI/MRCP and EUS for ductal/biliary causes and occult microlithiasis.

Severity assessment and Revised Atlanta classification

- The dominant determinant of severity is **persistent organ failure (>48 h)** in the respiratory, cardiovascular and renal systems, scored by the **modified Marshall score (≥2 = organ failure)**.

Atlanta severity class	Definition
Mild	No organ failure; no local or systemic complications (most interstitial AP; resolves 3–7 days)
Moderately severe	Transient organ failure (<48 h) and/or local/systemic complications
Severe	**Persistent organ failure >48 h** (single-organ mortality 3–10%; multiorgan ~50%)

Predictive scoring systems (none individually highly accurate):

System	Components / threshold for severe

Revised Atlanta morphological definitions (CT): interstitial oedematous pancreatitis (90–95%), necrotizing pancreatitis (5–10%); fluid collections — **acute peripancreatic fluid collection** and **pancreatic pseudocyst** (encapsulated, >4 weeks; in interstitial AP) versus **acute necrotic collection (ANC)** and **walled-off necrosis (WON)** (>4 weeks; in necrotizing AP).

Complications

- **Local:** ANC/WON (sterile or infected), pseudocyst, pancreatic duct disruption → pancreatic ascites/pancreaticopleural fistula, splanchnic (splenic/portal/SMV) vein thrombosis → gastric varices, pseudoaneurysm haemorrhage, gastric outlet/biliary obstruction, colonic involvement.
- **Systemic:** SIRS, **ARDS**, shock, AKI/acute tubular necrosis, DIC, GI haemorrhage, **hypocalcemia** (fat saponification), hyperglycemia, abdominal compartment syndrome; long-term — diabetes, exocrine pancreatic insufficiency and recurrence (~25%).

Management

- **Fluid resuscitation** is the single most important early intervention. **Lactated Ringer's preferred** over normal saline. A **moderate (goal-directed) strategy** is now favoured (de-Madaria, *NEJM* 2022: 10 mL/kg bolus then 1.5 mL/kg/h) over historically aggressive regimens, titrated to urine output >0.5 mL/kg/h, with serial Hct/BUN every 8–12 h — avoiding fluid overload.
- **Analgesia** (IV opioids; meperidine or morphine acceptable) and supplemental oxygen; initial NPO.
- **Nutrition:** early **enteral feeding** (oral low-fat solid diet when pain settling in mild AP; naso-gastric/naso-jejunal within 48–72 h in severe AP) is preferred to TPN — maintains gut barrier, reduces bacterial translocation, infection and mortality.
- **Antibiotics: no role for prophylactic antibiotics** in sterile necrosis (risk of fungal superinfection); empiric carbapenem (imipenem/meropenem) only for proven/strongly suspected **infected necrosis**.
- **Gallstone AP:** urgent **ERCP within 24–48 h** if cholangitis/biliary obstruction; **same-admission laparoscopic cholecystectomy** for mild biliary AP (sphincterotomy if non-operable).
- **Hypertriglyceridemic AP:** IV insulin (± fasting 24–36 h, heparin/apheresis of unproven benefit), then fibrates and lifestyle control.
- **Infected necrosis / symptomatic WON:** delay intervention ~4 weeks until walled-off; use a **"step-up" approach** (percutaneous/endoscopic transluminal drainage with LAMS → endoscopic, and only if needed surgical, necrosectomy) — endoscopic-first reduces morbidity versus open necrosectomy.
- Multidisciplinary care (GI, surgery, interventional radiology, intensive care), preferably at a pancreas centre.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis cascade:** Acinar cell → trigger (gallstone/alcohol) → cathepsin B activates **trypsinogen → trypsin** → activates *chymotrypsinogen, proelastase, phospholipase A2* → autodigestion (oedema, fat necrosis, haemorrhage) → cytokine release → **SIRS** → **ARDS/MODS**. Label SPINK1/CTRC as protective inhibitors.
- **Revised Atlanta morphology box:** two arms — *Interstitial AP* → APFC (<4 wk) → Pseudocyst (>4 wk); *Necrotizing AP* → ANC (<4 wk) → WON (>4 wk). Add a body diagram marking *Cullen's sign* (periumbilical) and *Grey Turner's sign* (flanks).

Clinical / Diagnostic significance

- Lipase >3× ULN with characteristic pain often makes CT unnecessary for diagnosis; reserve early CT for diagnostic doubt.
- A **persistently rising BUN** and **Hct >44%** on admission are practical bedside predictors of severe disease and mortality.
- Persistent organ failure beyond 48 h, not the anatomical extent of necrosis, drives prognosis — escalate to ICU early.
- Same-admission cholecystectomy prevents recurrent gallstone pancreatitis; failure to do so is a common exam-cited pitfall.

High-yield exam pointers

- Diagnosis = **2 of 3** (pain / enzymes >3× ULN / imaging).
- **Lipase > amylase** in specificity and duration; enzyme level does NOT reflect severity.
- Big-three causes: **gallstones (30–60%) > alcohol (15–30%) > hypertriglyceridemia (TG >1000)**.
- **Cullen's** = periumbilical, **Grey Turner's** = flank — both signal haemorrhagic necrotizing AP.
- Severity hinges on **persistent organ failure >48 h** (modified Marshall ≥2); scores: **Ranson ≥3, BISAP ≥3, APACHE II ≥8**.
- Revised Atlanta: interstitial vs necrotizing; **pseudocyst/WON mature at >4 weeks**.
- **Lactated Ringer's, moderate (not aggressive) fluids**, early enteral nutrition, **no prophylactic antibiotics**.
- Infected necrosis → **delay 4 weeks + step-up (drainage → necrosectomy)**, endoscopic-first.
- Rectal **indomethacin ± PD stent** prevents post-ERCP pancreatitis.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Acute and Chronic Pancreatitis" (etiology, three-phase pathogenesis, genetics, Revised Atlanta definitions, severity assessment, management) and "Approach to the Patient with Pancreatic Disease."
- Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Acute Pancreatitis" (severity scoring systems — Ranson, APACHE II, BISAP, Imrie/Glasgow; CTSI/Balthazar grading; SIRS-based prognosis).
- CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders" (current management: moderate fluid resuscitation per de-Madaria *NEJM* 2022, enteral nutrition, antibiotic policy, step-up necrosectomy, Ranson criteria table, post-ERCP prophylaxis).

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Autoimmune pancreatitis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune pancreatitis (AIP) is a distinct, corticosteroid-responsive form of chronic pancreatitis characterised by a lymphoplasmacytic inflammatory infiltrate, fibrosis and a tendency to form tumefactive (mass-like) lesions that frequently mimic pancreatic adenocarcinoma. It is sub-classified into **type 1 AIP** — the pancreatic manifestation of the multi-organ syndrome **IgG4-related disease (IgG4-RD)** — and **type 2 AIP (idiopathic duct-centric chronic pancreatitis, IDCP)**, a pancreas-restricted disease defined by the *granulocytic epithelial lesion (GEL)*. Recognising AIP matters chiefly because it is one of the few **reversible, steroid-responsive** causes of an obstructive pancreatic mass, and misdiagnosis leads to unnecessary Whipple resection.

Classification — Subtypes of AIP

Feature	Type 1 AIP (LPSP)	Type 2 AIP (IDCP)
Underlying entity	Pancreatic manifestation of **IgG4-RD**	Pancreas-specific; no systemic disease
Mean age at diagnosis	~7th decade (>60 yr; most >50)	~5th decade (40–50; may affect young adults/children)
Sex	Male predominance (~75%; M:F ≈ 2:1)	Equal (M ≈ 50%)
Serum IgG4 elevation	~66% (two-thirds)	~25% (usually normal)
Other-organ involvement	~50–60% (biliary, salivary, kidney, retroperitoneum)	None
Lymphoplasmacytic infiltrate	++	++
Storiform fibrosis	++	+
Obliterative phlebitis	++	+ (rare)

Feature	Type 1 AIP (LPSP)	Type 2 AIP (IDCP)
Granulocytic epithelial lesion (GEL)	Absent	+++ (defining)
IgG4 tissue plasma cells	Abundant (≥10/hpf)	Scant (<10/hpf)
Associated disease	IgG4-RD	Inflammatory bowel disease (~10–30%)
Response to steroids	~100%	~100%
Risk of relapse	Moderate–high (30–50%, up to 60%)	Low (<10%)

- **Type 3 AIP** is now recognised (CMDT 2026) as an infrequent complication of **immune-checkpoint-inhibitor** therapy; it is often asymptomatic but causes rapid pancreatic atrophy.
- The histological term for the type 1 lesion is **lymphoplasmacytic sclerosing pancreatitis (LPSP)** — *storiform* ("woven-mat"/cartwheel) fibrosis, obliterative phlebitis and a periductal cuff of IgG4-positive plasma cells. Type 2 shows **duct-centric** neutrophilic destruction of the duct epithelium (the GEL).

IgG4-Related Disease (the systemic context of type 1 AIP)

- A fibroinflammatory, **tumefaction-forming** condition that can affect virtually any organ; regarded as a **variable-vessel vasculitis** because of its tropism for veins and arteries of any calibre.
- Commonly involved organs: **pancreas, biliary tree, submandibular/parotid glands, periorbital tissues (lacrimal glands), kidneys, lungs, lymph nodes, retroperitoneum, aorta, thyroid (Riedel's)**.
- Eponymous overlaps: ***Mikulicz disease*** (lacrimal + parotid + submandibular swelling), ***Küttner tumour*** (submandibular gland), *Riedel's thyroiditis*, retroperitoneal fibrosis, inflammatory aortic aneurysm.
- Pathology is identical across organs: dense lymphoplasmacytic infiltrate, **storiform fibrosis**, **obliterative phlebitis**, mild-to-moderate **tissue eosinophilia**; intense neutrophils, granulomas, giant cells and fibrinoid necrosis argue *against* the diagnosis.
- Mechanism: the IgG4 molecule undergoes **Fab-arm exchange**, binds antigen weakly and has low affinity for Fcγ-receptors and C1q (largely *non-inflammatory*) — so it is probably a counter-regulatory marker rather than the primary driver. The true effectors are oligoclonally expanded **$CD4^+$ cytotoxic T cells** (producing perforin, granzyme, IFN-γ, TGF-β) and circulating **plasmablasts**.

Clinical features

- **Obstructive jaundice** is the commonest presentation (≈50–75%), characteristically **painless**, due to a stricture of the intrapancreatic common bile duct or compression by the enlarged head.
- **Weight loss** and **new-onset diabetes / glucose intolerance** (20–50% of type 1) are frequent; severe pain and overt acute pancreatitis are *uncommon* (acute pancreatitis is more typical of type 2).

- A **pancreatic mass** mimicking carcinoma is the major clinical trap; many patients have undergone modified Whipple surgery before the diagnosis was made.
- **Type 1 extra-pancreatic disease**: IgG4-related sclerosing cholangitis (mimics PSC/cholangiocarcinoma, hilar predilection), bilateral sclerosing **sialadenitis/dacryoadenitis**, **retroperitoneal fibrosis** (hydronephrosis from ureteric entrapment), **tubulointerstitial nephritis** and renal masses, lymphadenopathy, lung pseudotumours, periaortitis.

Diagnosis and investigations

- **Imaging (CT/MRI):** classical **diffuse "sausage-shaped" pancreas** with loss of normal lobularity and delayed/prolonged contrast enhancement; a peripheral **hypoattenuating rim ("capsule sign")** is *highly specific but not sensitive*. Focal/segmental enlargement is the malignancy mimic.
- **Ductal imaging (MRCP/ERCP):** long (>1/3 of duct length) or multiple strictures of the main pancreatic duct **without marked upstream dilatation**, and biliary strictures (IgG4-sclerosing cholangitis).
- **Serology:** serum **IgG4 >2× upper limit of normal** is the level-1 criterion (ULN ≈ 4–86 mg/dL); a single isolated elevation has low positive predictive value and can occur in pancreatic cancer. Other autoantibodies (ANA, anti-lactoferrin, anti-carbonic anhydrase II, rheumatoid factor) are less useful. Beware the **prozone effect**, which falsely lowers nephelometric IgG4 in very high-titre disease — correct by serum dilution.
- **Histology (core biopsy/resection):** LPSP with **≥10 IgG4$^+$ plasma cells/hpf**, storiform fibrosis, obliterative phlebitis (type 1); GEL (type 2). EUS-guided core biopsy aids type 2 (which usually *requires* histology).
- **Diagnostic frameworks:**
  - ***HISORt criteria*** (Mayo Clinic mnemonic): **H**istology, **I**maging, **S**erology, **O**ther-organ involvement, **R**esponse to steroid **t**herapy.
  - ***International Consensus Diagnostic Criteria (ICDC)*** harmonise five cardinal features — **P** (parenchymal imaging), **D** (ductal imaging), **S** (serology), **OOI** (other-organ involvement) and **H** (histology), plus **Rt** (response to steroids) — graded level 1/level 2 to classify *definitive* vs *probable* type 1 AIP.
- **Response to glucocorticoids** is itself a diagnostic criterion: rapid (2–4 week) radiological resolution is expected; *poor response must prompt re-evaluation for malignancy*.

Distinguishing AIP from pancreatic carcinoma (critical)

- Features favouring **cancer**: a *dilated* pancreatic duct, a single high-grade stricture with **upstream gland atrophy**, and a discrete low-density focal mass.
- Features favouring **AIP**: diffuse sausage-shaped gland, capsule (rim) sign, multifocal strictures without upstream dilatation, raised IgG4, other-organ involvement.
- **Before a steroid trial, malignancy must be vigorously excluded** (EUS-FNA/core biopsy, CA 19-9). A short, closely-monitored steroid trial is reasonable only when work-up is inconclusive and follow-up is assured.

Treatment

- **Glucocorticoids are first-line for both subtypes — prednisone ~40 mg/day (0.6–1 mg/kg) for ~4 weeks**, then taper by **5 mg/week** over a total of ~10–12 weeks. Clinical and radiological response is usually obvious within 2–4 weeks; remission is achieved in ≈99% of type 1 and ≈92% of type 2.
- **Relapse** (30–50%, up to 60% in type 1, especially with IgG4-cholangitis) is managed by repeat steroids ± low-dose maintenance prednisone (5–10 mg/day), or steroid-sparing immunomodulators (**azathioprine, 6-mercaptopurine, mycophenolate mofetil**).
- **Rituximab (B-cell depletion)** is the most effective agent for recurrent/refractory disease and for IgG4-RD generally (two doses of 1 g IV ~15 days apart); it produces a swift fall in serum IgG4.
- Adjuncts: biliary stenting for obstructive jaundice, insulin for diabetes, pancreatic enzyme replacement if exocrine insufficiency supervenes, and surveillance for relapse (rising IgG4 flags impending flare).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled CT of type 1 AIP:** outline a *diffusely enlarged "sausage-shaped" pancreas*; label — **loss of lobular contour**, **peripheral hypoattenuating rim ("capsule sign")**, **narrowed main pancreatic duct (no upstream dilatation)**, **distal CBD stricture causing obstructive jaundice**, **dilated proximal CBD/intrahepatic ducts**.
- **Histology schematic of LPSP (type 1):** label — **periductal lymphoplasmacytic cuff**, **storiform (cartwheel) fibrosis**, **obliterative phlebitis (vein lumen effaced by infiltrate)**, **IgG4⁺ plasma cells (≥10/hpf)**; contrast with **type 2 GEL — neutrophils destroying duct epithelium**.

Clinical / Diagnostic significance

- AIP is a key **"do-not-miss, do-not-over-treat"** diagnosis: it is the steroid-curable mimic of pancreatic cancer, and conversely a non-responding "AIP" may be cancer.
- Type 1 AIP mandates a **systemic survey for IgG4-RD** (salivary glands, kidneys, retroperitoneum, biliary tree, aorta) because subclinical multi-organ disease is common and may cause irreversible fibrosis (renal atrophy, hepatic failure from sclerosing cholangitis, aortic dissection).
- Long-standing/untreated AIP can "burn out" to atrophic, calcified chronic pancreatitis indistinguishable from other causes, with exocrine and endocrine insufficiency.
- Patients are at modestly increased risk of various malignancies; vigilant follow-up is required.

High-yield exam pointers

- **Two subtypes:** type 1 = **IgG4-RD/LPSP** (elderly male, multi-organ, high relapse); type 2 = **IDCP/GEL** (younger, pancreas-only, IBD-associated, low relapse). Type 3 = checkpoint-inhibitor-induced.
- **Painless obstructive jaundice + sausage-shaped pancreas + raised IgG4** = type 1 AIP until proven otherwise.
- **Capsule (rim) sign** = highly specific; main pancreatic duct **narrowed, not dilated** (unlike cancer).

- **Serum IgG4 >2× ULN** = level-1 serology; remember the **prozone effect** (false-low at very high titres).
- **HISORt** (Mayo) and **ICDC** (P-D-S-OOI-H + Rt) are the two diagnostic frameworks.
- **Histology hallmarks:** storiform fibrosis + obliterative phlebitis + ≥10 IgG4⁺ cells/hpf (type 1); granulocytic epithelial lesion (type 2).
- **Treatment:** prednisone 40 mg/day → taper; **rituximab** for relapse; ~100% steroid response — *failure to respond suggests cancer*.
- IgG4 is a **non-inflammatory** antibody (Fab-arm exchange); the real driver is the **CD4⁺ cytotoxic T cell**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute and Chronic Pancreatitis" (AIP subtypes, HISORt, capsule sign, treatment) and "IgG4-Related Disease" (organ manifestations, pathology, serology, rituximab).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Chronic Pancreatitis" (LPSP/IDCP histology, International Consensus Diagnostic Criteria, imaging, AIP-vs-cancer, steroid regimen and relapse).
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (type 1/2/3 classification, HISORt, prednisone taper, rituximab maintenance).

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Barrett's oesophagus

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Barrett's esophagus (BE) is the condition in which the normal stratified squamous epithelium lining the distal esophagus is replaced by an abnormal **columnar epithelium with both gastric and intestinal features** that is predisposed to malignancy. It is a consequence of **chronic gastro-esophageal reflux disease (GERD)**, which injures the squamous epithelium and drives metaplastic healing. The condition is named after *Norman Barrett*, an Australian-born surgeon who described the columnar-lined esophagus in 1950. BE itself is asymptomatic; its entire clinical importance lies in being the principal **precursor lesion of esophageal adenocarcinoma (EAC)**, a cancer whose incidence has risen more than 7-fold over recent decades.

Diagnosis and Endoscopic Classification

- **Two criteria must both be fulfilled** (it is an endoscopic *and* histological diagnosis):
- Endoscopist confirms **columnar epithelium lining ≥1 cm of the distal esophagus** above the esophagogastric junction (EGJ).
- **Biopsy shows metaplasia** — U.S. societies (ACG/AGA) require **intestinal metaplasia with goblet cells** ("specialized intestinal metaplasia").
- The **EGJ** is identified endoscopically as the *most proximal extent of the gastric folds*; columnar mucosa must extend ≥1 cm above it.

- **Endoscopic appearance:** Barrett mucosa is **reddish/salmon-coloured with a velvet-like texture**, contrasting sharply with the pale, glossy squamous epithelium; it ascends from the EGJ in a *tongue-like or circumferential* pattern.
- **Three columnar epithelial types** may be seen — gastric cardiac, gastric fundic, and **specialized intestinal metaplasia**; only the last carries the established risk of dysplasia/cancer.
- **Length-based classification** and the standardised **Prague C & M criteria**:

System	Definition	Note
Long-segment BE	metaplasia extends ≥**3 cm** above EGJ	severe GERD; higher cancer risk
Short-segment BE	<**3 cm** of metaplasia	by far the commonest form (Spechler, 1994)
Prague *C* value	**C**ircumferential extent (cm) of metaplasia	reproducible grading
Prague *M* value	**M**aximum extent (cm), including tongues	(Sharma et al., 2006)

Epidemiology and Risk Factors

- Usually discovered during endoscopy done for **GERD symptoms in middle-aged/older adults**; mean age at diagnosis ≈ **55 years**. Rare under age 10, virtually absent under age 5.
- **Demographics:** predominantly **white men**; uncommon (though rising) in Black and Asian populations.
- **Prevalence:** in the general Western adult population **1.6–6.8%** (predominantly short-segment); among patients scoped for GERD, **long-segment in 3–5%** and **short-segment in 10–20%** (CMDT: 7–11% of chronic-reflux patients).
- **Risk factors for BE / EAC:** chronic GERD, **central (truncal) obesity** (raises intra-abdominal pressure → GERD; also ↑IGF-1, leptin, ↓adiponectin), **cigarette smoking**, male sex, white race, hiatal hernia, age ≥50, and a first-degree relative with BE/EAC.
- **Protective factors:** *Helicobacter pylori* infection (may reduce acid secretion/GERD), aspirin/NSAID use, and a diet rich in fruit and vegetables.
- *Note:* smoking and alcohol are strong risk factors for **squamous-cell** carcinoma; for **adeno**carcinoma smoking is only a modest risk and alcohol has no clear effect.

Pathogenesis and Molecular Carcinogenesis

- BE begins with **GERD-induced injury** (acid ± duodeno-gastric reflux of bile acids/pancreatic enzymes); reflux-damaged squamous epithelium heals via **metaplasia** into a columnar, intestinal-type epithelium presumed more resistant to reflux (secretes mucins, expresses tight-junction protein **claudin-18**).
- This requires **molecular reprogramming of developmental transcription factors** in progenitor cells — up-regulated genes include **CDX genes** (drive intestinal differentiation) and the Hedgehog targets **BMP4** and **FOXA2**.

- **Neoplastic progression** = stepwise acquisition of the *Hanahan–Weinberg hallmarks of cancer*, facilitated by **genomic instability (aneuploidy)** and a tumour-promoting microenvironment (oxidative stress from GERD). Key alterations:
  - **Oncogene activation:** cyclin D1, K-ras, EGF receptor, TGF-α (self-sufficiency in growth signals).
  - **Tumour-suppressor loss: TP53** (early event; also enables apoptosis evasion) and **p16/CDKN2A**.
  - **Telomerase reactivation** → limitless replication; **VEGF** → angiogenesis; cadherin/catenin disruption + matrix metalloproteases → invasion/metastasis.
- Two carcinogenic pathways recognised by genomic sequencing: the **"traditional pathway"** (stepwise TP53 → p16 → oncogene activation) and the more rapid **"genome-doubled pathway"** (TP53 mutation → whole-genome doubling → oncogene amplification) — the latter accounts for ~62% of tumours and may explain *interval cancers* that escape surveillance.

Dysplasia and Cancer Risk

- **Dysplasia (intraepithelial neoplasia)** is the histological marker of progression: nuclear enlargement, pleomorphism, hyperchromatism, stratification, atypical mitoses, loss of cytoplasmic maturation, crowded/villiform architecture. Graded **low-grade (LGD)** or **high-grade (HGD)**.
- **Inter-observer agreement** is poor for LGD (<50% — easily confused with reactive change) but better for HGD (~85%); any grade of dysplasia should be **confirmed by a second expert GI pathologist**.

Histology	Approx. annual progression to cancer
Non-dysplastic BE	**~0.25%/yr** (range 0.12–0.33%)
Short-segment (1–3 cm)	~0.29%/yr (CMDT)
Long-segment (>3 cm)	~0.91%/yr (CMDT)
Low-grade dysplasia	disputed; ~0.4–13%/yr depending on series
High-grade dysplasia	**~6%/yr**; 13% harbour unsuspected invasive cancer

Management

- **Acid suppression / chemoprevention:** all BE patients receive a **PPI** in the dose needed to control symptoms and heal esophagitis; asymptomatic patients are still offered **once-daily PPI for chemoprevention** (ACG). The **AspECT trial** showed high-dose PPI + aspirin improved the composite outcome (mortality/progression), driven mainly by improved overall survival. Routine NSAID/aspirin prescription *solely* for chemoprevention is **not** recommended (GI/CV bleeding risk).
- **Anti-reflux surgery (fundoplication)** controls GERD but is **not clearly superior to PPI** for cancer prevention — not done for cancer prophylaxis alone.
- **Screening (ACG 2022):** endoscopic screening only for those with **≥5 years of at least weekly GERD symptoms plus ≥3 risk factors** (age >50, male sex, white race, central obesity, smoking,

family history). *Not* recommended routinely in women. A swallowable **capsule-sponge** with biomarker cytology is an emerging non-endoscopic alternative.

- **Surveillance:** high-resolution white-light endoscopy with the **Seattle biopsy protocol** = **4-quadrant biopsies every 1–2 cm** (every **2 cm** if non-dysplastic; every **1 cm** if dysplasia known) plus targeted biopsy/EMR of any visible irregularity. **Non-dysplastic BE → scope every 3–5 years.**
- **Endoscopic Eradication Therapy (EET)** is now the treatment of choice for confirmed **mucosal neoplasia** (LGD, HGD, and intramucosal/T1a carcinoma) — combining resection + ablation, with **complete eradication of intestinal metaplasia (CE-IM)** as the goal:

Modality	Mechanism / role
Endoscopic mucosal resection (EMR)	"suck-and-cut" or "band-and-snare"; removes visible nodules — **essential for accurate T-staging** (superior to EUS) before ablation
Endoscopic submucosal dissection (ESD)	en-bloc knife resection of larger lesions
Radiofrequency ablation (RFA)	balloon/catheter microwave electrodes — **procedure of choice** for flat dysplasia (proven in **AIM Dysplasia** and **SURF** trials)
Cryotherapy	spray CO_2/N_2O — freeze–thaw injury; spares collagen matrix
Photodynamic therapy (PDT)	porfimer sodium + laser → singlet oxygen; *largely abandoned* (photosensitivity, strictures)
Esophagectomy	historical gold standard for HGD; mortality **3–10%** — now reserved for EET failure/submucosal invasion

- **Staging rule:** if EMR reveals **submucosal invasion**, lymph-node metastasis exceeds 10% → EET is abandoned and the patient referred for surgical/oncological management; mucosal (T1a) lesions have only ~1.4% nodal risk, making EET safe.
- **Post-EET surveillance (after CE-IM):** for HGD/intramucosal carcinoma — every **3 months × 1 yr, 6-monthly in yr 2, then annually**; for LGD — **6-monthly × 1 yr then annually**. Recurrence (mostly at the neo-squamocolumnar junction) reaches ~9–10%/yr, so surveillance continues despite CE-IM.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Endoscopic view of Barrett's esophagus:** tubular esophagus with **salmon-red velvety columnar tongues** ascending from the EGJ over pale glossy squamous mucosa. *Labels:* squamous (pale) epithelium, columnar (salmon) Barrett mucosa, **Z-line / squamocolumnar junction**, **EGJ (top of gastric folds)**, ≥1 cm metaplastic segment, Prague **C** and **M** measurements.
- **Metaplasia–dysplasia–carcinoma sequence (flow diagram):** Normal squamous epithelium → (chronic GERD) → **Intestinal metaplasia (BE)** → **Low-grade dysplasia** → **High-grade dysplasia** → **Esophageal adenocarcinoma**. *Annotate* molecular hits: TP53 & p16 loss, cyclin D1/K-ras activation, aneuploidy/genome-doubling.

Clinical / Diagnostic significance

- BE is the key **premalignant marker** linking GERD to EAC — the rationale for screening high-risk refluxers and for endoscopic surveillance.
- **Diagnosis hinges on biopsy** confirming intestinal metaplasia with goblet cells; endoscopic appearance alone is insufficient, and the **EGJ landmark (gastric folds)** must be correctly identified to avoid over-/under-diagnosis.
- **Sampling error is the major pitfall** — dysplasia is patchy and often endoscopically subtle; the Seattle protocol misses lesions, hence the move toward removing *all* visible irregularities by EMR and ablating *all* residual metaplasia.
- Management is **risk-stratified by dysplasia grade**: PPI + surveillance for non-dysplastic BE, EET for any confirmed dysplasia or T1a cancer, surgery/chemoradiation once submucosal/nodal disease appears.

High-yield exam pointers

- BE = **metaplastic columnar (intestinal) epithelium replacing distal esophageal squamous epithelium**; named after *Norman Barrett* (1950).
- **Diagnostic dyad:** columnar mucosa **≥1 cm above EGJ** + **intestinal metaplasia with goblet cells** on biopsy.
- **Long-segment ≥3 cm, short-segment <3 cm; Prague C & M criteria** for standardised reporting.
- Typical patient: **obese white male, ~55 yr, chronic GERD**; *H. pylori*, aspirin/NSAIDs and a fruit/vegetable diet are **protective**.
- **Cancer risk ~0.25%/yr (non-dysplastic), ~6%/yr (HGD)**; risk rises with segment length (LSBE 0.91%/yr vs SSBE 0.29%/yr).
- **Earliest molecular hit = TP53 inactivation**; CDX/BMP4/FOXA2 drive metaplasia; aneuploidy and the *genome-doubled pathway* accelerate cancer.
- **Seattle protocol** = 4-quadrant biopsies every 1–2 cm + targeted EMR of nodules.
- **EET (EMR + RFA)** is first-line for dysplasia/T1a (AIM & SURF trials); **submucosal invasion (>10% nodal risk) contraindicates EET**; esophagectomy mortality 3–10%.
- **All BE patients get a once-daily PPI**; surveillance interval for non-dysplastic BE is **3–5 years**.

SOURCE & COVERAGE

- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Barrett Esophagus" (primary depth: diagnosis criteria, Prague C&M, pathogenesis, molecular biology, dysplasia, EET, AIM/SURF trials, surveillance).
- **Harrison's Principles of Internal Medicine, 22e** — "Diseases of the Esophagus" (GERD context, metaplasia–dysplasia–carcinoma sequence, chemoprevention/AspECT, esophagectomy vs endoscopic ablation).
- **CMDT 2026** — "Gastrointestinal Disorders: GERD / Barrett Esophagus" (ACG 2022 screening criteria, segment-specific cancer risk, EET indications, capsule-sponge).

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Biliary cirrhosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Biliary cirrhosis* is the end-stage of chronic **cholestatic** liver disease, in which sustained impairment of bile flow (rather than hepatocellular necroinflammation) drives progressive **biliary-type fibrosis**, ductopenia and finally architectural distortion with regenerative nodules. It has pathologic features distinct from alcohol-associated or post-hepatitic cirrhosis, yet the manifestations of end-stage liver disease (portal hypertension, jaundice, hepatic failure) are the same. The cholestasis may be **intrahepatic** (small-duct disease, e.g. primary biliary cholangitis) or **extrahepatic** (large-duct obstruction) — a distinction with major therapeutic consequence, since extrahepatic obstruction may be relieved by surgical/endoscopic decompression whereas intrahepatic disease will not.

Classification — causes of biliary cirrhosis

- **Primary (intrahepatic, autoimmune/idiopathic cholestatic syndromes):** *primary biliary cholangitis (PBC)*, *primary sclerosing cholangitis (PSC)*, *autoimmune cholangitis* (AMA-negative PBC), and *idiopathic adulthood ductopenia*. These share the histopathology of chronic cholestasis — **cholate stasis, copper deposition, xanthomatous transformation of hepatocytes, irregular "biliary" fibrosis** and progressive **ductopenia**.
- **Secondary biliary cirrhosis** results from *prolonged extrahepatic biliary obstruction* — chronic choledocholithiasis, post-operative/inflammatory bile-duct strictures, chronic pancreatitis, biliary/pancreatic malignancy, and (in children) biliary atresia or cystic fibrosis–associated biliary disease.
- The two named primary biliary syndromes are distinguished clinically by **antibody testing, cholangiographic findings and clinical presentation** (PBC = small ducts, AMA, female; PSC = whole biliary tree, MRCP beading, IBD).

Primary biliary cholangitis — epidemiology & pathogenesis

- Prevalence ~**100–200 per million**, strong **female preponderance (~9:1)**, median age at diagnosis ~**50 years** (40–60). The term *cholangitis* replaced *cirrhosis* in 2015 because most patients are now diagnosed pre-cirrhotic.

- An **immune-mediated** disease arising in genetically susceptible individuals; there is **chronic non-suppurative destructive cholangitis** of small and medium intrahepatic bile ducts mediated by CD4+/CD8+ T-cell cytotoxicity against biliary epithelium, with loss of tolerance to mitochondrial autoantigens.
- **Antimitochondrial antibodies (AMA)** are present in ~**90–95%** and are the immunologic hallmark. They target the **E2 component of the pyruvate dehydrogenase complex (PDC-E2)** plus the branched-chain 2-oxoacid (BCOADC-E2) and 2-oxoglutarate (OGDC-E2) dehydrogenase complexes on the **inner mitochondrial membrane**, recognising the bound *lipoic acid*. AMA are **diagnostic markers but are not themselves pathogenic** (titre does not track severity; they persist after transplant).
- **Genetic/environmental contributors:** association with HLA **DRB1*08** (DQB1); concordance ~60% in monozygotic twins; triggers proposed include *molecular mimicry* (e.g. *E. coli*, *Novosphingobium aromaticivorans*), recurrent UTIs, **smoking** (associated with advanced fibrosis) and xenobiotics (2-octynoic acid in cosmetics/hair dye).

Clinical features & associated diseases

- Up to **50–60% are asymptomatic** at diagnosis (incidental cholestatic enzyme elevation). The two cardinal symptoms are **fatigue** (most disabling, out of proportion to disease) and **pruritus** (~50%, worse at night; pruritus *before* jaundice signals severe disease/poor prognosis).
- Signs reflecting chronic cholestasis: **hyperpigmentation** (melanin deposition), **xanthelasma and xanthomata**, hepatosplenomegaly, and — late — jaundice, ascites, variceal bleeding and encephalopathy. **Metabolic bone disease** (osteopenia/osteoporosis) and **fat-soluble vitamin (A, D, E, K) deficiency** complicate advanced disease.
- **Associated autoimmune conditions** are characteristic and should be screened:

Associated disease	Approx. frequency
Sjögren syndrome (sicca complex)	72–100%
Renal tubular acidosis	50–60%
Arthritis / arthropathy	4–42%
Gallstones	~33%
Autoimmune thyroiditis	15–20%
Systemic sclerosis / CREST variants	15–19%
Coeliac disease	1–7%
Hepatocellular carcinoma (with cirrhosis)	1–3% (~19-fold ↑ risk)

Histological staging (Ludwig / Scheuer — four stages)

Stage	Key feature
Stage 1	*Chronic non-suppurative destructive cholangitis* — portal inflammation centred on small bile ducts; the **florid duct lesion** (lymphocytic destruction ± non-caseating epithelioid granuloma) is near-diagnostic

Stage	Key feature
Stage 2	Inflammation extends beyond portal tract into parenchyma (**interface hepatitis / piecemeal necrosis**); bile-duct destruction with **ductular proliferation**
Stage 3	**Bridging fibrosis** (septal fibrosis without regenerative nodules); progressive **ductopenia**
Stage 4	**Cirrhosis** (micronodular or macronodular) with fibrous septa and regenerative nodules

- The only consistently diagnostic histologic clue is **ductopenia** — absence of interlobular bile ducts in >50% of portal tracts.

Diagnosis & investigations

- **Biochemistry — cholestatic pattern:** elevated **alkaline phosphatase (ALP)** and **γ-glutamyl transpeptidase (GGT)**; ALT/AST only mildly raised (usually <3× ULN; >5× ULN suggests **PBC–autoimmune hepatitis overlap**). **IgM** characteristically elevated; **hypercholesterolaemia**; bilirubin rises late and is a poor-prognosis marker.
- **Diagnosis requires 2 of 3 criteria:** (1) chronic cholestasis with **ALP ≥1.5× ULN**, (2) **AMA titre ≥1:40**, (3) **compatible liver biopsy**. Biopsy is *not* needed in most AMA-positive patients.
- **AMA-negative PBC (~5–10%):** confirm with PBC-specific antinuclear antibodies — **anti-sp100** (multiple-nuclear-dots) and **anti-gp210** (rim-like/membranous nuclear-envelope pattern, highly specific, poor prognosis). Here **liver biopsy and MRCP are mandatory** to exclude small-duct PSC, IgG4 cholangiopathy, sarcoidosis.
- **Imaging:** ultrasound/CT/MRI to exclude extrahepatic obstruction; periportal **"halo" sign** on MRI; **transient/MR elastography** for non-invasive fibrosis staging and prognosis.
- **Prognostic scores: Mayo risk score**, **GLOBE score** and **UK-PBC score** (incorporate age, bilirubin, albumin, ALP, platelets, transaminases); **Paris-II criteria** define low-risk biochemical response after 1 year of UDCA (ALP and AST <1.5× ULN, bilirubin ≤1 mg/dL).

Treatment of PBC

- **Ursodeoxycholic acid (UDCA) 13–15 mg/kg/day** is the first-line, disease-modifying drug — it improves liver biochemistry and histology, reduces varices/ascites/HCC risk, delays cirrhosis and **improves transplant-free survival**; responders have survival approaching that of healthy controls. **~20–40% are inadequate responders** (more common in men and younger-onset disease).
- **Second-line agents for UDCA non-responders/intolerance** (avoid all in decompensated cirrhosis / portal hypertension):

Agent	Class / mechanism	Note
Obeticholic acid	Farnesoid-X-receptor (FXR) agonist	Start 5 mg/day; pruritus common; Child B/C → max 5 mg/**week**
Seladelpar (10 mg/day)	PPAR-δ agonist	Recently approved; ↓ALP, ↓pruritus
Elafibranor (80 mg/day)	PPAR-α/δ agonist	Recently approved
Bezafibrate / fenofibrate	Fibrate / PPAR agonist	Second-line; improve ALP even in non-responders

- **Symptomatic / complication management:** *Pruritus* — **cholestyramine** (4 g, dosed around breakfast), then **rifampin** 150–300 mg BD, **naltrexone**, **sertraline**, ondansetron; refractory cases → plasmapheresis. *Fatigue* — no proven drug; modafinil tried. *Bone disease* — **DEXA** at diagnosis, oral **calcium + vitamin D**, **bisphosphonates**. *Fat-soluble vitamin (A, D, E, K) screening/replacement* if bilirubin >2 mg/dL.
- **Liver transplantation** is the treatment of choice for end-stage PBC (also for intractable pruritus); consider at **MELD ≥15, bilirubin ≥6 mg/dL, or Mayo score ≥7.8**. One-year survival ~**85–90%**; PBC **recurs in the graft in ~20% by 3 years** (lower with UDCA prophylaxis and cyclosporine-based immunosuppression).

Primary sclerosing cholangitis (contrast)

- Chronic fibrosing inflammation of the **entire intra- and extrahepatic biliary tree** → multifocal strictures, biliary cirrhosis, portal hypertension.
- **65% pANCA-positive**; **60–80% have inflammatory bowel disease (predominantly ulcerative colitis)** — colonoscopy advised at diagnosis.
- Diagnosis is **cholangiographic**: **MRCP (first-line)** shows multifocal **strictures and beading** ("beaded appearance") with intervening normal/dilated segments.
- **No proven medical therapy** (high-dose UDCA 28–30 mg/kg/day is *harmful*); manage dominant strictures endoscopically; treat cholangitis with antibiotics; **liver transplantation** is definitive. Dreaded complication: **cholangiocarcinoma**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Ludwig staging of PBC (4-panel):** draw a portal tract with central bile ductule and label — *Stage 1: florid duct lesion (lymphocytes + granuloma around bile duct, portal inflammation)*; *Stage 2: interface hepatitis + ductular proliferation*; *Stage 3: bridging fibrous septa + ductopenia*; *Stage 4: cirrhosis with regenerative nodules*.
- **MRCP in PSC:** sketch intra- and extrahepatic ducts with labels — *multifocal strictures*, *intervening dilated segments ("beading")*, *dominant stricture*, *pruned-tree intrahepatic ducts*.

Clinical / Diagnostic significance

- A persistently **isolated raised ALP/GGT in a middle-aged woman** should prompt AMA testing — early PBC is treatable and UDCA started early prevents progression.
- Differentiating **intrahepatic vs extrahepatic** cholestasis (AMA + MRCP) is critical: extrahepatic obstruction needs **decompression**, intrahepatic does not.
- **Marked transaminase elevation (>5× ULN) or high IgG** flags **PBC–AIH overlap**, which may need adjunctive immunosuppression.
- Surveillance obligations: **HCC screening** once cirrhotic, **endoscopy** for varices, **DEXA** for bone disease, and screening for associated autoimmune disease (thyroid, coeliac, Sjögren).

High-yield exam pointers

- Biliary cirrhosis = chronic **cholestasis** → biliary fibrosis/ductopenia; subtypes **primary** (PBC, PSC, autoimmune cholangitis) and **secondary** (chronic extrahepatic obstruction).

- **PBC:** middle-aged woman, **AMA (anti-PDC-E2) ~90–95%**, raised ALP + **IgM**, pruritus + fatigue; diagnose by **2 of 3** (cholestatic ALP ≥1.5× ULN, AMA ≥1:40, biopsy).
- **Ludwig four stages**: 1 florid duct lesion → 2 interface hepatitis → 3 fibrosis → 4 cirrhosis; **ductopenia >50% portal tracts** is the diagnostic hallmark.
- **UDCA 13–15 mg/kg/day** is first-line and improves survival; non-responders → **obeticholic acid (FXR), seladelpar/elafibranor (PPAR), fibrates** — *avoid in decompensation*.
- **AMA-negative PBC** → look for **anti-sp100 / anti-gp210**; biopsy + MRCP mandatory.
- **Pruritus ladder:** cholestyramine → rifampin → naltrexone → sertraline.
- **PSC:** whole biliary tree, **pANCA**, **UC association**, **MRCP beading**, risk of **cholangiocarcinoma**, no effective drug, transplant definitive.
- Indications/markers for **transplant** in PBC: Mayo ≥7.8, MELD ≥15, bilirubin ≥6; recurs in ~20% of grafts.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cirrhosis and Its Complications" (Biliary Cirrhosis; Primary Biliary Cholangitis; Primary Sclerosing Cholangitis sections).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Primary Biliary Cholangitis" (epidemiology, AMA/autoantibody immunobiology, Ludwig staging, UDCA/obeticholic acid/fibrate data, complications, transplantation) and "Primary and Secondary Sclerosing Cholangitis."
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (current diagnostic criteria, UDCA, seladelpar/elafibranor approvals, pruritus regimens, transplant thresholds/prognosis).

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Coeliac disease

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Celiac disease (celiac sprue, gluten-sensitive enteropathy) is a chronic, immune-mediated enteropathy of the small intestine precipitated by dietary **gluten** in genetically predisposed (**HLA-DQ2 / DQ8**) individuals. It is characterised by **villus atrophy, crypt hyperplasia and intraepithelial lymphocytosis** of the proximal small bowel, the presence of **anti-tissue transglutaminase (tTG-2) autoantibodies**, and clinical plus histological recovery on a strict **gluten-free diet (GFD)** with relapse on gluten re-exposure. Global seroprevalence is ~**1.4%** (biopsy-confirmed ~0.7%), making it one of the commonest lifelong food-related disorders.

Etiopathogenesis (the gluten–genes–immunity triad)

- **The antigen (gluten):** the water-insoluble storage proteins of wheat, rye and barley. Gluten = **prolamins + glutenins**; the toxic prolamins are *gliadin* (wheat), *secalin* (rye) and *hordein* (barley). These are rich in **glutamine (~30%) and proline (~15%)**, rendering them resistant to luminal digestion. *Avenin* (oats) has intermediate content, so most patients tolerate **uncontaminated oats**; rice, corn, sorghum and millet are non-toxic.

- **Genetic predisposition:** **HLA-DQ2** is present in >90% of patients and **HLA-DQ8** in almost all the remainder; one haplotype is *necessary but not sufficient*. As they occur in 25–35% of the general population, a positive test is non-diagnostic, but a **negative HLA-DQ2/DQ8 has a negative predictive value >99%** (used to *exclude* disease). First-degree relative prevalence is **10–15%**; monozygotic-twin concordance reaches 49–83%.
- **Immune mechanism:** tissue **transglutaminase-2 (tTG-2)** *deamidates* glutamine residues of gliadin to negatively charged glutamic acid, which binds avidly to the antigen-binding groove of DQ2/DQ8 on antigen-presenting cells. This activates **gliadin-specific CD4⁺ T-cells** in the lamina propria, releasing **IFN-γ, TNF-α, IL-2, IL-6** (adaptive response). The enterocyte/macrophage cytokine **IL-15** drives the innate arm, expands **CD8⁺ and γ/δ intraepithelial lymphocytes (IELs)** and bridges the two — γ/δ IELs may rise from <10% to ~35% (a *hallmark*). The net result is enterocyte injury, crypt hyperplasia and villus atrophy. tTG-2 within the endomysium is the target autoantigen, explaining the diagnostic serology.

Clinical spectrum

Presentation is protean and has shifted from the "classical" malabsorptive child to the **non-classical / silent adult** (5th decade most common age at diagnosis).

- **Classical (GI):** chronic/episodic diarrhoea, steatorrhoea, abdominal bloating, flatulence, weight loss; in infants — failure to thrive, irritability, hypotonia, muscle wasting, abdominal distension after weaning.
- **Non-classical / extraintestinal:** unexplained **iron-deficiency anaemia** (commonest; consider in IDA without GI blood loss), fatigue, **osteopenia/osteoporosis** (>70% have low bone density), **dermatitis herpetiformis**, aphthous stomatitis, dental enamel defects, raised aminotransferases (~27–40%), **gluten ataxia** and peripheral neuropathy, **infertility/recurrent miscarriage**, short stature, delayed puberty, amenorrhoea.
- **Silent / potential:** asymptomatic seropositive individuals detected on screening (relatives, T1DM, Down syndrome). Up to ~40% of seropositive patients have no symptoms.
- **Celiac crisis:** rare, life-threatening profuse diarrhoea with dehydration, electrolyte derangement, metabolic acidosis, hypocalcaemia and hypoproteinaemia — needs IV fluids ± glucocorticoids.
- **Dermatitis herpetiformis (DH):** intensely pruritic, symmetrical papulovesicles over extensor surfaces, buttocks, trunk and scalp — the *"celiac disease of the skin."* Granular **IgA deposits at the dermal papillae**; autoantigen is **epidermal (type 3) transglutaminase**. ~80% have enteropathy. Responds to **dapsone (1–2 mg/kg/day)** for skin plus a GFD for the gut.

Diagnosis

Diagnosis (in an adult on a **gluten-containing** diet) rests on **serology + duodenal biopsy**.

Test	Role / remark
IgA anti-tTG-2	**Screening test of choice** — sensitivity ~98%, specificity ~98%
Total serum IgA	Co-test to detect **selective IgA deficiency** (in 2–3% of celiacs → false-negative tTG)
IgG tTG / IgG-DGP	Used when **IgA deficient**

Test	Role / remark
IgA endomysial antibody (EMA)	Very high specificity (~100%); labour-intensive, confirmatory
Anti-deamidated gliadin peptide (DGP)	Useful adjunct, IgG class in IgA deficiency
Native anti-gliadin antibody (AGA)	**Not recommended** — low specificity
HLA-DQ2 / DQ8	High NPV; used to **rule out** disease, esp. in self-treated patients

- **Small-intestinal biopsy** (gold standard): take **4–6 biopsies from the 2nd/3rd part of the duodenum plus the bulb** (lesions are patchy and proximal). Histology: **villus atrophy, crypt hyperplasia, increased IELs (≥25 per 100 enterocytes)** and lamina propria plasmacytosis.
- **Marsh classification** of severity (see table).
- **Endoscopic clues** (insensitive): scalloping/loss of duodenal folds, mosaic/nodular pattern, fissuring — a normal-looking duodenum does **not** exclude disease.
- **Pediatric biopsy-free pathway (ESPGHAN):** symptoms + **IgA-tTG ≥10× ULN** + positive **EMA** on a separate sample + compatible HLA — may avoid biopsy (not universally adopted in adults/US).
- **Gluten challenge** (for patients already on a GFD with uncertain diagnosis): ~**2–4 g gluten/day** (1–2 slices of bread); biopsy may be diagnostic by **2 weeks**, serology rise by ~**4 weeks**.

Marsh stage	Histology
0 (pre-infiltrative)	Normal mucosa
1 (infiltrative)	Normal villi, **increased IELs**
2 (hyperplastic)	Increased IELs + **crypt hyperplasia**
3 (destructive)	Villus atrophy — **3a** partial, **3b** subtotal, **3c** total
4 (hypoplastic/atrophic)	Total villus atrophy with crypt hypoplasia

Treatment and monitoring

- **Lifelong strict gluten-free diet** is the cornerstone — eliminate **wheat, rye, barley** (and contaminated oats); beware *hidden gluten* in processed foods, medications and cross-contamination. **Dietitian** referral and patient education are essential. Most improve within 2–6 months; serology normalises over 1–2 years.
- **Nutritional repletion:** iron, folate, vitamin B12, calcium, vitamin D, zinc, and fat-soluble vitamins (A, E, K) as required; ensure ~1500 mg calcium/day. Treat coexistent **lactose intolerance** (transient secondary lactase deficiency) until mucosa heals.
- **Bone health: DEXA** scan within 1 year of diagnosis; calcium + vitamin D, and **bisphosphonates** for established osteoporosis.
- **Glucocorticoids / budesonide:** *not* for routine disease — reserved for **celiac crisis** and **refractory disease**.
- **Monitoring:** clinic review at 3–6 monthly intervals in year 1 with serial **IgA-tTG** (falls confirm adherence; half-life ~6–8 weeks). Persistently positive serology = ongoing gluten exposure.

Follow-up duodenal biopsy at ~2 years to confirm mucosal healing, especially if symptoms persist.

Complications and associated disorders

- **Non-responsive celiac disease (NRCD)** (~10%): persistent symptoms despite ≥6–12 months GFD — commonest cause is **continued (often inadvertent) gluten ingestion**; also lactose/fructose intolerance, SIBO, pancreatic insufficiency, microscopic colitis, IBS.
- **Refractory celiac disease (RCD)** (~0.3–1.5%): villus atrophy persisting despite ≥12 months strict GFD with negative serology.
  - **Type I** — normal *polyclonal* IEL phenotype; responds to budesonide/steroids ± azathioprine.
  - **Type II** — *aberrant clonal* IELs with **loss of surface CD3/CD8** and **monoclonal TCR-γ rearrangement**; steroid-resistant, treated with cladribine/autologous stem-cell transplant; **~50% progress to lymphoma at 5 years** (poor prognosis).
- **Enteropathy-associated T-cell lymphoma (EATL)**, **ulcerative jejunoileitis**, and **small-bowel adenocarcinoma** — suspect when a previously controlled patient develops new weight loss, pain, obstruction or bleeding.
- **Hyposplenism** (up to 50% of adults) — thrombocytosis, **Howell-Jolly bodies**, risk of pneumococcal sepsis → pneumococcal vaccination.
- **Associations: type 1 diabetes mellitus** (~5–6%), autoimmune thyroid disease, **selective IgA deficiency**, autoimmune hepatitis, **Down and Turner syndromes**, Sjögren syndrome, IgA nephropathy, microscopic colitis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Small-intestinal villus histology — normal vs celiac:** draw two adjacent panels. *Normal* — tall finger-like **villi** (villus:crypt ≈ 3–5:1), columnar enterocytes, few IELs. *Celiac* — **flat mucosa / villus atrophy**, **elongated hyperplastic crypts**, **increased intraepithelial lymphocytes**, dense **lamina propria plasma-cell infiltrate**. Label: *villus atrophy, crypt hyperplasia, intraepithelial lymphocytes, lamina propria infiltrate.*
- **Pathogenesis flow diagram:** *Dietary gliadin → ↑intestinal permeability → tTG-2 deamidation of gliadin → binding to HLA-DQ2/DQ8 on APC → $CD4^+$ T-cell activation (IFN-γ, TNF-α) + IL-15-driven $CD8^+$/γδ IELs → villus atrophy + anti-tTG antibodies.* Label each labelled box.

Clinical / Diagnostic significance

- Test for celiac disease in **unexplained iron-deficiency anaemia, osteoporosis, transaminitis, infertility, IBS-D phenotype, and gluten ataxia** — it is frequently underdiagnosed in adults.
- **Always check serology and biopsy BEFORE starting a GFD**; pre-treatment gluten avoidance causes false-negative results.
- **Screen high-risk groups:** first-degree relatives, T1DM, autoimmune thyroid disease, Down/Turner syndrome.
- A **rising or non-falling tTG** on treatment signals ongoing gluten exposure; **new alarm symptoms** in a stable patient mandate evaluation for RCD/EATL.

High-yield exam pointers

- Triad: **gluten + HLA-DQ2/DQ8 + tTG-2 autoimmunity**; toxic prolamins = gliadin/secalin/hordein; oats (avenin) usually safe.
- **IgA anti-tTG = screening test of choice** (sens/spec ~98%); always co-test **total IgA**.
- HLA-DQ2/DQ8 used to **exclude** disease (NPV >99%), not to confirm.
- **Marsh staging** (0 → 4); diagnosis needs villus atrophy + crypt hyperplasia + raised IELs, not IELs alone.
- Biopsy **proximal duodenum + bulb**, 4–6 samples; lesion is patchy and proximal.
- **Dermatitis herpetiformis** = granular IgA at dermal papillae, **epidermal tTG**, treat with **dapsone + GFD**.
- Complications: **RCD type I vs II, EATL, ulcerative jejunoileitis, small-bowel adenocarcinoma, hyposplenism (Howell-Jolly bodies), osteoporosis**.
- **Lifelong strict GFD** is the only definitive therapy; steroids only for celiac crisis/RCD.
- *Eponyms:* first described by **Aretaeus of Cappadocia**; **Samuel Gee** (1888); **Dicke** linked wheat during the Dutch famine.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of Absorption" (Celiac Disease section).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Celiac Disease" (Lebwohl & Green) — used for pathogenesis, Marsh classification, serology performance, refractory disease/EATL, dermatitis herpetiformis and associations.
- **CMDT 2026** — "Gastrointestinal Disorders: Celiac Disease" — current diagnostic algorithm, management and refractory-disease typing.

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Approach to chronic diarrhoea

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Diarrhea is the passage of abnormally liquid or unformed stools at increased frequency; on a typical Western diet a **stool weight >200 g/day** is generally considered diarrheal. By duration it is **acute (<2 weeks), persistent (2–4 weeks), and chronic (>4 weeks)**. Diarrhea lasting **>4 weeks warrants evaluation to exclude serious underlying pathology**, and unlike acute diarrhea (mostly infective), **most causes of chronic diarrhea are non-infectious**. Classifying chronic diarrhea by its **predominant pathophysiologic mechanism** allows a rational, cost-effective approach, though many diseases produce diarrhea by more than one mechanism.

Relevant physiology & conditions to exclude first

- About **9 L of fluid enter the GI tract daily**, ~1 L reaches the colon, and only ~**0.2 L is excreted in stool**; the colon has large absorptive reserve (can recover up to ~4× the usual 0.8 L/d), so diarrhea reflects altered fluid/electrolyte handling, motility, or both.

- Distinguish true diarrhea from mimics (different algorithms): **pseudodiarrhea** (frequent small-volume stools with urgency/tenesmus, <200 g/d — seen in IBS, proctitis); **fecal incontinence** (involuntary discharge from neuromuscular or anorectal structural disease); and **overflow diarrhea** from **fecal impaction** in elderly/nursing-home patients (detectable on rectal exam).
- First step in any chronic diarrhea: **exclude an iatrogenic cause — medications and prior surgery.**

Pathophysiologic classification (Harrison Table 49-3)

Mechanism	Key stool features	Representative causes
Secretory	Watery, large-volume, **painless, persists with fasting, no osmotic gap**	Stimulant laxatives (senna, bisacodyl, castor oil), chronic ethanol, drugs/toxins (arsenic, olmesartan), **bile acid diarrhea (BAD)**, bowel resection/disease/fistula, partial obstruction/impaction, **hormonal tumors** (carcinoid, VIPoma, gastrinoma, medullary thyroid carcinoma, mastocytosis, villous adenoma), Addison's disease, congenital ion-transport defects
Osmotic	Watery, **ceases with fasting, osmotic gap >50**, low fecal pH (carbohydrate)	Osmotic laxatives (Mg^{2+}, PO_4^{3-}, SO_4^{2-}), **lactase/disaccharidase deficiency**, non-absorbable carbohydrates (sorbitol, fructose, lactulose, PEG), wheat and **FODMAP** intolerance
Steatorrheal (fat malabsorption)	Greasy, foul-smelling, difficult-to-flush, weight loss, nutrient deficiencies	**Intraluminal maldigestion** (pancreatic exocrine insufficiency, bacterial overgrowth, bariatric surgery, liver disease); **mucosal malabsorption** (celiac, Whipple's, abetalipoproteinemia, ischemia, drug-induced); **post-mucosal lymphatic obstruction**, amyloidosis
Inflammatory	Pain, fever, **blood**, fecal **leukocytes/calprotectin**	IBD (Crohn's, ulcerative colitis), **microscopic (lymphocytic/collagenous) colitis**, immunodeficiency, **eosinophilic gastroenteritis**, radiation injury, GI malignancy
Dysmotile	Often secretory-like; may have mild steatorrhea (≤14 g/d)	**IBS** (incl. post-infectious), visceral neuromyopathy, hyperthyroidism, prokinetic drugs, post-vagotomy, **diabetic diarrhea**
Factitial / Iatrogenic	Variable; hypokalemia, hypotension	Laxative abuse, Munchausen, eating disorders; cholecystectomy, ileal resection, bariatric surgery, vagotomy/fundoplication

Mechanistic high-yield points

- **Stool osmotic gap = 290 − 2 × ([stool Na^+] + [stool K^+]).** Gap **>50 mosmol/L = osmotic**; **<50 = secretory**. (Fecal osmolarity measured directly can be falsely elevated by bacterial carbohydrate metabolism.)
- **Bile acid diarrhea (BAD):** dihydroxy bile acids escaping absorption (e.g., Crohn's ileitis or resection of **<100 cm terminal ileum**) cause **cholerheic diarrhea**; idiopathic BAD reflects reduced FGF-19 feedback and may explain ~**40% of unexplained chronic diarrhea** (~1% of the population). Diagnosed by elevated fasting **serum 7αC4** or fecal bile acids.
- **Lactase deficiency** is one of the commonest causes of chronic diarrhea in adults (osmotic, low fecal pH).

- **Pancreatic exocrine insufficiency** manifests when **>90% of secretory function is lost**; fecal fat is normally **<7 g/d**, rises to **14 g/d** with rapid transit, **15–25 g** in small-intestinal disease, and **>32 g** with pancreatic insufficiency.
- **Hormonal secretory diarrheas:** carcinoid (serotonin, flushing, wheezing, right-heart valvular disease); **VIPoma** = pancreatic cholera / **WDHA syndrome** (Watery Diarrhea, Hypokalemia, Achlorhydria), stool can exceed 3 L/d (up to 20 L); gastrinoma (diarrhea in up to one-third); medullary thyroid carcinoma (calcitonin/prostaglandins); systemic mastocytosis (urticaria pigmentosa); colorectal villous adenoma.
- **Congenital electrolyte defects:** congenital chloridorrhea (**DRA gene**, Cl^-/HCO_3^- exchange, alkalosis) and congenital sodium diarrhea (**NHE3 gene**, acidosis).

Clinical approach: history and examination

- **History:** onset/duration/pattern; aggravating (especially diet) and relieving factors; **stool character** (volume, nocturnal episodes, undigested food/fat, blood, consistency by **Bristol Stool Form Scale**); weight loss, fever, pain; exposures (travel, antibiotics, contacts); medications and surgery; family history of IBD or celiac disease; extraintestinal features (skin, arthralgia, oral aphthae).
- **Examination (Table 49-4):** look for signs of **malabsorption/IBD** (anemia, **dermatitis herpetiformis**, clubbing, edema, arthritis); features of **autonomic neuropathy or collagen-vascular disease** (pupils, orthostasis, skin); abdominal mass/tenderness; **rectal/anal sphincter** abnormalities; mucocutaneous clues — **flushing (carcinoid), erythema nodosum/pyoderma gangrenosum (IBD), thyroid mass, wheeze, heart murmurs, lymphadenopathy, perianal fistula.**

Diagnostic workup (rational triage)

- **Routine/limited organic screen:** CBC, chemistries, **CRP, ESR, iron, folate, B12, TTG-IgA (on gluten) for celiac, serum 7αC4 (C4), stool fat, fecal calprotectin.** Leukocytosis/raised CRP–ESR → inflammation; eosinophilia → parasites, allergy, eosinophilic gastroenteritis.
- **Quantitative stool studies** when weight >200 g/d: electrolytes (osmotic gap), **pH**, occult blood, **leukocytes/calprotectin**, **fat and bile-acid quantitation**, and **laxative screen**.
- **Secretory pattern:** reconsider drugs/surreptitious laxatives; stool **multiplex PCR/cultures** (incl. *Aeromonas, Plesiomonas*), ova & parasites, **Giardia antigen** (most sensitive for giardiasis); **breath tests** (glucose/lactulose H_2/CH_4) for bacterial overgrowth; **peptide hormone screen** when indicated — gastrin, VIP, calcitonin, thyroid hormone/TSH, **urinary 5-HIAA**, histamine.
- **Osmotic pattern:** test for **lactose/fructose intolerance**, fecal magnesium and laxative levels; **low fecal pH** indicates carbohydrate malabsorption.
- **Fatty (steatorrheal): endoscopy with small-bowel biopsy** ± aspirate for quantitative culture; small-bowel imaging (CT enterography, MR enteroclysis); confirm **pancreatic exocrine insufficiency** with secretin-CCK stimulation or indirect tests (**fecal elastase/chymotrypsin, bentiromide** — low sensitivity/specificity).
- **Inflammatory:** blood/leukocytes in stool → stool pathogens, **colonoscopy with biopsies** (random biopsies of normal-appearing colon needed to diagnose **microscopic colitis**), and small-bowel

imaging as indicated. **BAD** confirmed by radiolabeled bile-acid retention test (SeHCAT), serum 7αC4/FGF-19, fecal bile acids, or therapeutic trial of a sequestrant.

- A **therapeutic trial** is appropriate, definitive and cost-effective when a specific diagnosis is suggested early (e.g., lactose-free diet for lactose intolerance; metronidazole for suspected giardiasis after backpacking; **cholestyramine/colestipol/colesevelam** for post-ileal-resection bile-acid diarrhea).

Treatment (curative, suppressive, or empirical)

- **Curative** when the cause is eradicable: resect colorectal cancer, antibiotics for Whipple's disease or tropical sprue, stop offending drug.
- **Suppressive (mechanism-directed):** lactose restriction (lactase deficiency); gluten exclusion (celiac); anti-inflammatory agents (IBD); **bile-acid sequestrants** (BAD); **PPIs** for gastrinoma acid hypersecretion; **octreotide** for malignant carcinoid; **indomethacin** for medullary thyroid carcinoma; **pancreatic enzyme replacement** for pancreatic insufficiency; budesonide/bismuth/loperamide for microscopic colitis.
- **Empirical / symptomatic:** opioid antimotility agents — **loperamide or diphenoxylate** for mild–moderate watery diarrhea, **codeine or tincture of opium** for severe (avoid in severe IBD — risk of **toxic megacolon**); **clonidine** (α_2-agonist) for **diabetic diarrhea**; **5-HT$_3$ antagonists (alosetron, ondansetron)**, **rifaximin**, and **eluxadoline** for IBS-diarrhea; **crofelemer** for AIDS-associated diarrhea. For all patients: **fluid/electrolyte repletion** and **fat-soluble vitamin replacement** in chronic steatorrhea.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Stepwise algorithm (Harrison Fig. 49-4) — "Approach to chronic diarrhea":** Box 1 *Chronic diarrhea* → *Exclude iatrogenic (medication, surgery)* → branch by presentation into **Blood p.r. → colonoscopy + biopsy**; **Fatty diarrhea → small-bowel imaging, biopsy, aspirate**; **Pain relieved by BM/incomplete evacuation → suspect IBS**; **no blood/malabsorption features → functional diarrhea / dietary exclusion (lactose, sorbitol)**. Central box: **Limited organic screen — hematology, chemistry, CRP, ESR, Fe, folate, B12, TTG-IgA, C4, stool fat, calprotectin** → then stool-fat thresholds (**>20 g/d = pancreatic; 14–20 g/d = small-bowel cause; <14 g/d = normal**) and **48 h stool bile acid → BA sequestrant**.
- **Stool osmotic gap bar/flow label:** *Gap = 290 − 2×(Na + K); >50 = osmotic; <50 = secretory.*

Clinical / Diagnostic significance

- The **fasting test** is a key bedside discriminator: secretory diarrhea persists with fasting; osmotic diarrhea stops.
- **Red flags mandating prompt structural evaluation (colonoscopy):** blood/hematochezia, weight loss, anemia, nocturnal diarrhea, older age, or any middle-aged/older patient with inflammatory-type diarrhea — to exclude **colorectal carcinoma** and IBD.

- **Microscopic colitis** is clinically indistinguishable from IBS-D/functional diarrhea and needs **biopsy of normal-appearing colon**; associated with NSAIDs, statins, PPIs, SSRIs and middle-aged women.
- **Factitial diarrhea** accounts for up to **15%** of unexplained diarrheas at tertiary centers (laxative abuse, Munchausen); suspect with hypokalemia, hypotension, very high/low stool osmolarity (water/urine added).
- In **two-thirds of cases the cause is unclear after the first encounter**, justifying staged, triage-guided testing rather than indiscriminate investigation.

High-yield exam pointers

- Chronic diarrhea = **>4 weeks**; **>200 g/d**; most causes **non-infectious**.
- **Osmotic gap >50 = osmotic; <50 = secretory.** Secretory = high-volume, painless, **persists on fasting**.
- **BAD ≈ 40% of unexplained chronic diarrhea**; ileal resection **<100 cm** → cholerheic; treat with **cholestyramine/colesevelam**; diagnose by **serum 7αC4 / SeHCAT**.
- **Fecal fat:** normal <7 g/d; **>32 g** suggests pancreatic insufficiency (>90% function lost).
- **VIPoma = WDHA / pancreatic cholera**; carcinoid → urinary **5-HIAA**; gastrinoma → **PPI**; medullary thyroid Ca → **indomethacin**.
- **Lactase deficiency** = commonest osmotic cause in adults; **low fecal pH**.
- First-line empirical antidiarrheal = **loperamide/diphenoxylate**; **avoid antimotility agents in severe IBD (toxic megacolon)**.
- Limited organic screen mnemonic: **CBC, CRP/ESR, Fe/folate/B12, TTG-IgA, C4, stool fat, calprotectin.**
- Always exclude **pseudodiarrhea, fecal incontinence, overflow (impaction)**, and **iatrogenic** causes first.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 49 "Diarrhea and Constipation" (definitions, Table 49-3 classification, Table 49-4 examination, Fig. 49-4 algorithm, evaluation and treatment of chronic diarrhea). Drug doses are not specified in the chapter and have been omitted as the source gives agents qualitatively; SeHCAT/WDHA expansions and the Bristol scale are standard textbook internal medicine consistent with the chapter. No coverage gap.

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Crohn's disease

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Crohn disease is a chronic, relapsing, idiopathic inflammatory bowel disease characterized by **transmural**, **segmental** inflammation that may affect any part of the gastrointestinal tract from mouth to anus. It most often involves the terminal ileum and proximal colon, produces skip lesions, fissuring ulcers, strictures, fistulas, abscesses, and perianal disease, and is not cured by surgery. Pathogenesis reflects an inappropriate mucosal immune response to intestinal microbiota in a genetically susceptible host, modified by environmental factors such as smoking, diet, antibiotics, and prior enteric infection.

Etiopathogenesis and risk factors

- **Genetic susceptibility:** familial aggregation is important; NOD2/CARD15 variants are linked particularly with younger onset, ileal disease and stricturing tendency; ATG16L1/autophagy and IL-12/IL-23 pathways explain biologic targets.
- **Microbiota and barrier defect:** dysbiosis, reduced microbial diversity, increased mucosa-associated bacteria, defective Paneth cell defensins, epithelial permeability and impaired mucosal tolerance lead to sustained inflammation.
- **Immune cascade:** activated dendritic cells/macrophages and T cells produce TNF, IL-1, IL-6, IL-12, IL-23 and other mediators; Th1/Th17 pathways, alpha4beta7 lymphocyte trafficking and JAK/STAT signalling are clinically important because they are drug targets.
- **Environmental factors: cigarette smoking** strongly increases Crohn risk, resistance to medical therapy and early relapse. Diets rich in animal fat, refined sugars and processed foods, low fibre intake, oral contraceptives, early-life infections and infectious gastroenteritis are associated risks.
- **Epidemiology:** onset is common in adolescence and young adulthood, but disease may occur at any age; newly industrialized countries, including Asian populations, show rising incidence.

Pathology and classification

- **Gross pathology:** discontinuous disease with **skip areas**, aphthous ulcers in early disease, deep linear/serpiginous ulcers, **cobblestoning**, thickened bowel wall, luminal narrowing, mesenteric lymphadenopathy and **creeping fat**.
- **Microscopy:** focal crypt inflammation, focal crypt abscesses, transmural lymphoid aggregates, fissures, sinus tracts and fistulas. **Noncaseating granulomas** are highly suggestive but absent in many mucosal biopsies; exclude tuberculosis when granulomas are seen.
- **Distribution:** about one-third have small-bowel disease alone, around one-half have ileocolonic disease, and about one-fifth have colitis alone; terminal ileum is the commonest site. Perianal disease occurs in about one-third.

Montreal axis	Categories	Exam implication
Age	A1 <=16 yr; A2 17-40 yr; A3 >40 yr	Early onset often predicts aggressive course
Location	L1 ileal; L2 colonic; L3 ileocolonic; L4 upper GI modifier	Determines symptoms, nutrition and imaging

Montreal axis	Categories	Exam implication
Behaviour	B1 inflammatory; B2 stricturing; B3 penetrating	Guides medical, endoscopic and surgical strategy
Modifier	p = perianal disease	Must be actively looked for and imaged

Clinical features

- **Luminal inflammatory disease:** insidious malaise, low-grade fever, anorexia, weight loss, chronic or intermittent diarrhoea and crampy abdominal pain. Ileocolitis classically causes recurrent **right lower quadrant pain**, diarrhoea and sometimes an appendicitis-like presentation with fever, mass and leukocytosis.
- **Stricturing disease:** postprandial colicky pain, bloating, borborygmi, vomiting, decreasing diarrhoea and recurrent subacute obstruction; obstruction may be inflammatory/edematous early or fixed fibrotic late.
- **Penetrating disease:** phlegmon, intra-abdominal abscess, enteroenteric, enterovesical, enterocutaneous or rectovaginal fistulas. Enterovesical fistula causes recurrent UTI, pneumaturia or fecaluria; rectovaginal fistula causes foul vaginal discharge and dyspareunia.
- **Colonic Crohn disease:** fever, malaise, diarrhoea, crampy pain and sometimes hematochezia; massive bleeding is uncommon compared with ulcerative colitis.
- **Perianal disease:** painful skin tags, eccentric fissures, anal ulcers/stenosis, abscesses and complex fistulas; it may precede intestinal symptoms by years.
- **Upper GI and jejunoileal disease:** dyspepsia, nausea, vomiting, gastric outlet obstruction, malabsorption, steatorrhea, anemia, hypoalbuminemia, B12/folate/iron and fat-soluble vitamin deficiencies.

Investigations and diagnosis

- **Principle:** no single symptom, sign or test diagnoses Crohn disease; diagnosis requires compatible clinical features plus endoscopic, histologic and radiologic evidence.
- **Baseline tests:** CBC, ESR/CRP, albumin, electrolytes, liver tests, iron studies, B12/folate, vitamin D and nutritional screen. CRP may be normal in a minority despite active disease.
- **Stool tests before steroids/biologics:** culture or multiplex PCR for pathogens, ova/parasites when relevant, and **C. difficile** testing; consider CMV biopsy testing in steroid-refractory colitis.
- **Fecal markers:** fecal calprotectin and lactoferrin help distinguish active inflammation from IBS-like symptoms, assess relapse and monitor treatment response; calprotectin is less sensitive for isolated ileal disease.
- **Ileocolonoscopy with biopsies:** first-line investigation; inspect colon and terminal ileum, biopsy involved and normal-looking segments separately. Findings: rectal sparing, aphthae, stellate/linear ulcers, cobblestoning, strictures, fistula openings and skip lesions.
- **Cross-sectional imaging: MR enterography** or CT enterography defines small-bowel extent, wall thickening, enhancement, comb sign, strictures, fistulas, abscess and phlegmon; MRI is preferred for young patients and repeated follow-up when available.

- **Capsule endoscopy:** useful for suspected small-bowel Crohn disease when ileocolonoscopy and imaging are nondiagnostic, but avoid if stricture is possible; use patency capsule/radiology first. **Pelvic MRI** is the best noninvasive test for perianal fistula/abscess.

Complications and differentials

- **Local complications:** obstruction, strictures, intra-abdominal or pelvic abscess, fistulas, severe perianal disease, malabsorption, short bowel syndrome after resections, hemorrhage and rare free perforation.
- **Cancer:** chronic Crohn colitis carries colorectal cancer risk related to extent and duration, broadly similar to ulcerative colitis with comparable colitis burden; begin surveillance colonoscopy about 8 years after Crohn colitis diagnosis.
- **Extraintestinal manifestations:** oral aphthae, erythema nodosum, pyoderma gangrenosum, peripheral arthritis, sacroiliitis/ankylosing spondylitis, episcleritis, uveitis, fatty liver, gallstones after ileal disease/resection, PSC, nephrolithiasis, osteoporosis, thromboembolism and reactive amyloidosis.
- **Differential diagnosis:** ulcerative colitis, intestinal tuberculosis, Yersinia, Salmonella/Shigella/Campylobacter, C. difficile, amoebiasis, CMV, Behcet disease, NSAID enteropathy, ischemic colitis, diverticulitis, lymphoma, celiac disease and IBS. In India, **intestinal TB** is a key mimic: caseating granulomas, AFB/culture/PCR positivity, necrotic nodes and typical ulcers favour TB.

Management

- **General measures:** assess disease location, behaviour, severity and risk. Stop smoking; avoid NSAIDs; optimize nutrition; correct iron, B12, folate, vitamin D/calcium and fat-soluble vitamin deficiencies; vaccinate before immunosuppression; screen for TB and hepatitis B before biologics/JAK inhibitors.
- **Treatment target:** steroid-free clinical remission plus objective healing: absence of ulcers on endoscopy, falling CRP/fecal calprotectin, radiologic improvement in transmural disease, fistula healing and restored quality of life.
- **Mild low-risk ileocecal disease:** controlled-release **budesonide 9 mg once daily for 8 weeks**, then taper in 3 mg steps over 2-4 weeks if remission occurs. Limited colonic mild disease may respond to sulfasalazine; mesalamine has limited and inconsistent value in Crohn disease.
- **Moderate to severe or high-risk disease:** use corticosteroids only for induction or bridging: prednisone/prednisolone **40 mg daily for 1-2 weeks**, taper by **5-10 mg/week** over 4-8 weeks; hospitalized severe disease may need methylprednisolone **40-60 mg/day IV** after excluding abscess.
- **Maintenance and disease modification:** biologic therapy is preferred early in high-risk disease. Options include anti-TNF agents (infliximab **5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks**; adalimumab **160 mg day 0, 80 mg day 14, then 40 mg every 2 weeks**), vedolizumab **300 mg IV at 0, 2, 6 weeks then every 8 weeks**, ustekinumab weight-based IV induction then **90 mg SC every 8 weeks**, risankizumab **600 mg IV every 4 weeks for 3 doses then 180/360 mg SC every 8 weeks**, and upadacitinib **45 mg daily for 12 weeks then 15/30 mg daily** after biologic failure or when appropriate.

- **Immunomodulators:** azathioprine **2-3 mg/kg/day**, 6-mercaptopurine **1-1.5 mg/kg/day**, and methotrexate **15-25 mg weekly IM/SC** may maintain steroid-free remission or reduce anti-drug antibodies; check TPMT where available and monitor CBC/LFTs.
- **Perianal/fistulizing disease:** combine gastroenterology and colorectal surgery. Drain abscesses, place setons when needed, give metronidazole **250 mg TID** or ciprofloxacin **500 mg BID** for symptom relief, and use anti-TNF therapy for fistula closure; pelvic MRI guides anatomy and follow-up.
- **Abscess/obstruction/surgery:** abscess requires antibiotics plus percutaneous or surgical drainage if large; corticosteroids are unsafe until abscess is excluded. Obstruction from inflammatory edema may respond to bowel rest, NG suction and steroids; fixed short strictures need endoscopic dilation, resection or stricturoplasty. Surgery is indicated for medical intractability, obstruction, abscess, massive bleeding, refractory fistulas or suspected cancer; resect the least bowel possible and check postoperative recurrence endoscopically within 3-6 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Segmental Crohn ileocolitis diagram:** terminal ileum + caecum/ascending colon, skip normal areas, aphthous ulcers, deep linear ulcers, cobblestoning, stricture, creeping fat, mesenteric nodes.
- **Perianal Crohn fistula diagram:** anal canal, internal opening, intersphincteric/transsphincteric tract, external opening, abscess cavity, seton, rectovaginal extension label if present.

Clinical / Diagnostic significance

- Crohn disease is an exam favourite because it integrates **chronic diarrhoea, malabsorption, obstruction, fistula, abscess, perianal disease and EIMs** in one diagnosis.
- Distinguish it from UC by transmural inflammation, skip lesions, ileal involvement, rectal sparing, perianal disease, fistulas/strictures and granulomas; distinguish it from intestinal TB before starting anti-TNF therapy.
- Always exclude **C. difficile, CMV and abscess** when a patient flares or fails steroids; giving corticosteroids into an occult abscess can be dangerous.
- Deep ulcers, early steroid need, young onset, perianal disease, stricturing/penetrating behaviour, upper GI disease, low albumin/hemoglobin and high CRP/calprotectin indicate aggressive disease and justify early biologic therapy.
- Therapeutic drug monitoring helps anti-TNF failures: low trough/no antibody means increase dose or shorten interval; high antibody/low trough means switch anti-TNF; active inflammation with therapeutic trough means switch drug class.

High-yield exam pointers

- Write first: **Crohn = transmural, skip, mouth-to-anus, terminal ileum, noncaseating granuloma, fistula/stricture/perianal disease**.
- Montreal classification: **A1/A2/A3; L1/L2/L3 with L4 modifier; B1/B2/B3 with p modifier**.

- Most common presentation: chronic right lower quadrant pain + diarrhoea + weight loss; appendicitis mimic is classic.
- Perianal disease affects about one-third; pelvic MRI and colorectal surgery involvement are essential.
- Fecal calprotectin/lactoferrin are practical inflammatory markers; symptoms alone do not prove active disease.
- Capsule endoscopy is sensitive for small bowel disease but contraindicated until stricture is excluded.
- Steroids induce remission but are **not maintenance therapy**; aim for steroid-free mucosal healing.
- Anti-TNF agents are preferred for severe, perianal or fistulizing disease; screen for TB/hepatitis B and update vaccines.
- Surgery treats complications but is not curative; preserve bowel length and prevent/monitor postoperative recurrence.

SOURCE & COVERAGE

Harrison 22e — "Inflammatory Bowel Disease"; Sleisenger & Fordtran's GI & Liver 11e — "Epidemiology, Pathogenesis, and Diagnosis of Inflammatory Bowel Diseases" and "Management of Inflammatory Bowel Diseases"; CMDT 2026 — "Gastrointestinal Disorders".

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Chronic hepatitis B

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Chronic hepatitis B (CHB) is defined as persistence of **hepatitis B surface antigen (HBsAg) in serum for ≥6 months**, with hepatic necroinflammation of varying grade and fibrosis of varying stage. The risk of chronicity is inversely related to age at infection — ~90% after perinatal acquisition versus ~1% after adult acquisition. The **serum HBV DNA level is the single most important determinant of progression to cirrhosis and hepatocellular carcinoma (HCC)** (REVEAL-HBV cohort); hence investigation centres on virological/serological staging and fibrosis assessment, and treatment is directed at durable suppression of viral replication.

Natural history — phases (the framework for both investigation and treatment)

Chronic HBV is dynamic; five phases are recognised, and accurate phasing dictates whether and when to treat.

Phase	HBeAg	HBV DNA	ALT	Liver injury / action
1. Immune-tolerant (HBeAg-positive chronic *infection*)	+	Very high (often $>10^7$–10^9 IU/mL)	Normal	Minimal; monitor, do not treat

Phase	HBeAg	HBV DNA	ALT	Liver injury / action
2. Immune-active / clearance (HBeAg-positive chronic *hepatitis*)	+	High (>2×10^4 IU/mL)	Elevated	Active necroinflammation → **treat**
3. Inactive carrier (HBeAg-negative chronic *infection*)	– (anti-HBe +)	Low/undetectable (≤2×10^3 IU/mL)	Normal	Low risk; monitor
4. Reactivation (HBeAg-negative chronic *hepatitis*; precore/core-promoter mutant)	– (anti-HBe +)	Fluctuating (>2×10^3 IU/mL)	Elevated/"flares"	Progressive → **treat**
5. HBsAg-negative ("functional cure")	–	Undetectable in serum (cccDNA persists)	Normal	~1%/yr; best outcome

- *Inactive carrier vs HBeAg-negative chronic hepatitis* cannot be separated on a single visit — it requires **serial ALT + HBV DNA monitoring over months**.
- A more sensitive ULN for ALT is **35 U/L (male) / 25 U/L (female)**; normal-range ALT does not exclude significant histology.

Investigations

1. Confirm and characterise the infection (serology + virology)

- **HBsAg** (positive ≥6 months = chronicity) and **IgG anti-HBc** (past exposure).
- **HBeAg / anti-HBe** — replicative status; HBeAg seroconversion to anti-HBe signals slowing of disease.
- **Quantitative HBV DNA (real-time PCR, IU/mL)** — the key prognostic and treatment-threshold test; also used to monitor on-treatment response.
- **Quantitative HBsAg (qHBsAg)** — predicts PEG-IFN response and identifies HBeAg-negative patients who may safely stop oral therapy (e.g. <100 IU/mL Asians, <1000 IU/mL Whites).
- **HBV genotype** — genotype C carries higher cirrhosis/HCC risk; IFN response is genotype **A > B > C > D**.

2. Biochemical & haematological

- LFTs (ALT usually 100–1000 U/L, ALT > AST; once cirrhotic, **AST > ALT**), albumin, bilirubin, **prothrombin time/INR**, full blood count (thrombocytopenia suggests portal hypertension).
- Hyperglobulinaemia and autoantibodies are characteristically **absent** (distinguishes from autoimmune hepatitis).

3. Assessment of fibrosis (stage)

- **Non-invasive: FIB-4** [(age × AST) / (platelets × √ALT)], APRI, the proprietary **ELF score** (hyaluronic acid, PIIINP, TIMP-1), and **transient elastography (FibroScan)** / liver-stiffness imaging.
- **Liver biopsy** (HAI/Ishak 0–18 grade, 0–6 stage; or METAVIR A0–A3, F0–F4) — reserved for when non-invasive tests are discordant or staging will change management.

4. Screen for co-infection, complications and reactivation risk

- **HDV (anti-HDV ± HDV RNA), HCV and HIV** serology in every patient; HBV-HIV co-infection accelerates progression ~20-fold.
- **HCC surveillance: 6-monthly ultrasound ± α-fetoprotein** in all cirrhotics, and in high-risk non-cirrhotics (Asian men >40, Asian women >50, Africans, family history of HCC, persistent high-level viraemia). The **PAGE-B score** (age, sex, platelets) predicts 5-year HCC risk on therapy.
- Before chemotherapy/immunosuppression: screen **HBsAg + anti-HBc (± anti-HBs)** to stratify reactivation risk.

Goals and indications for treatment (whom to treat)

- **Goals:** durable suppression of HBV DNA → ALT normalisation, histologic improvement, HBeAg seroconversion, and ultimately **functional cure** (sustained HBsAg loss ± anti-HBs, durable ≥6 months). These translate into reduced cirrhosis, decompensation, HCC and liver-related death; established cirrhosis and varices can regress with long-term suppression.
- **Indications (AASLD; EASL thresholds slightly lower):**

Group	Treat when
HBeAg-positive chronic hepatitis	HBV DNA >2×10^4 IU/mL **and** ALT >2× ULN
HBeAg-negative chronic hepatitis	HBV DNA >2×10^3 IU/mL **and** ALT >2× ULN
Compensated cirrhosis	**Any detectable HBV DNA**, regardless of ALT/HBeAg
Decompensated cirrhosis	Any detectable HBV DNA — oral agents only; refer for transplant
"Grey-zone" / borderline ALT	Consider if age >40, family history of cirrhosis/HCC, extrahepatic disease, prior treatment, or moderate–severe fibrosis/inflammation on biopsy/non-invasive testing

- **Not treated (monitor 3–6 monthly):** immune-tolerant (HBeAg-positive, normal ALT) and inactive carriers.

Antiviral agents and treatment

Eight drugs are approved; only **PEG-IFN-α, entecavir, and tenofovir (TDF or TAF)** are recommended **first-line**. Oral agents are generally preferred — better tolerated, more profound DNA suppression, usable in cirrhosis/immunosuppression.

First-line agent	Dose	Key points
Entecavir	0.5 mg PO daily (1 mg if lamivudine-resistant)	High potency, high barrier to resistance (≤1.2% at 6 yr); reduce dose in renal impairment; weak anti-HIV activity → not as monotherapy in HIV co-infection
Tenofovir disoproxil fumarate (TDF)	300 mg PO daily	Potent; **0% resistance through 8 yr**; monitor renal function/phosphate (Fanconi-like tubulopathy), reduced bone density

First-line agent	Dose	Key points
Tenofovir alafenamide (TAF)	25 mg PO daily	Equipotent to TDF; less renal/bone toxicity → preferred if CrCl <50 mL/min, low bone density, or risk factors for renal injury
PEG-IFN-α2a	180 µg SC weekly × 48 wk	Finite course, highest 1-yr HBeAg seroconversion (~30%), no resistance; **contraindicated in decompensated cirrhosis, pregnancy, autoimmune disease, cytopenias**

- *No longer first-line:* **lamivudine** (YMDD mutation — M204V/I — in ~70% at 5 yr), **adefovir, telbivudine** (low barrier to resistance). **Combination oral therapy gives no benefit over potent monotherapy** in treatment-naïve patients; for resistance, *switching* to a non-cross-resistant high-barrier agent (e.g. tenofovir for lamivudine resistance) is now preferred over add-on.

Endpoints and stopping rules

- **HBeAg-positive:** oral therapy may be stopped after HBeAg seroconversion plus **≥12 months consolidation** in non-cirrhotics, with close post-treatment monitoring for relapse; otherwise continue.
- **HBeAg-negative:** relapse is the rule on stopping → **indefinite therapy**, ideally until HBsAg loss (rare).
- **Cirrhosis:** treat **indefinitely** — stopping risks decompensation.
- **PEG-IFN futility:** if qHBsAg fails to fall to <20,000 IU/mL by week 24, discontinue.

Special populations

- **Pregnancy: Tenofovir (TDF) is the drug of choice**; start in the **third trimester when maternal HBV DNA ≥200,000 IU/mL** to reduce perinatal transmission (plus neonatal HBIG + vaccine). Avoid IFN.
- **Immunosuppression / chemotherapy:** screen HBsAg + anti-HBc; give **pre-emptive entecavir/tenofovir prophylaxis** to all HBsAg-positive patients, and to anti-HBc-positive/HBsAg-negative patients receiving **B-cell-depleting agents (rituximab)** or stem-cell transplant. Continue 6 months after chemotherapy (12 months for B-cell depletion).
- **HIV co-infection:** use ART containing two anti-HBV drugs (e.g. **tenofovir + emtricitabine/lamivudine**); never lamivudine or entecavir monotherapy.
- **Liver transplantation:** prevent graft re-infection with short-course **IV HBIG (5–7 days) + lifelong entecavir/TDF/TAF**.
- **HDV co/super-infection:** treat with **PEG-IFN-α** (limited efficacy); the NTCP **entry inhibitor bulevirtide** is the major advance (EMA-approved); treat underlying HBV if DNA >2×10^3 IU/mL.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Phases of chronic HBV infection (time-course graph):** x-axis = time/years; plot **HBV DNA**, **ALT** and **qHBsAg** curves across the five phases, with bands labelled *Immune-tolerant → Immune-active → Inactive carrier → Reactivation (HBeAg-negative) → HBsAg-negative*; mark **HBeAg→anti-HBe seroconversion** and **HBsAg→anti-HBs (functional cure)**.
- **Treatment-decision algorithm:** boxes labelled *HBsAg+ ≥6 months* → branch on **HBeAg status** → thresholds (HBeAg+: DNA >2×10^4 & ALT >2×ULN; HBeAg−: DNA >2×10^3 & ALT >2×ULN; **Cirrhosis: any detectable DNA**) → *First-line: Entecavir / TDF / TAF / PEG-IFN → HCC surveillance 6-monthly US ± AFP*.

Clinical / Diagnostic significance

- **HBV DNA is the master variable** — both for diagnosis/phasing and as the therapeutic target; suppression below the level of detection lowers (but does not abolish) HCC risk.
- Extrahepatic immune-complex disease — **polyarteritis nodosa, membranous/membranoproliferative glomerulonephritis, leukocytoclastic vasculitis, arthralgias** — is itself an indication to treat.
- ALT "flares" may herald HBeAg seroconversion but can precipitate decompensation in cirrhotics — monitor closely, especially after stopping therapy.
- Antiviral therapy regresses fibrosis/cirrhosis and reduces transplant referral, but **HCC surveillance must continue even after HBsAg loss/seroconversion**.

High-yield exam pointers

- HBsAg >6 months = chronic; **IgM anti-HBc** distinguishes acute from chronic.
- First-line antivirals = **entecavir, tenofovir (TDF/TAF), PEG-IFN**; doses **entecavir 0.5 mg/d, TDF 300 mg/d, TAF 25 mg/d, PEG-IFN-α2a 180 µg/week**.
- **Treat any cirrhotic with detectable HBV DNA**, irrespective of ALT/HBeAg — treat indefinitely.
- **Tenofovir = drug of choice in pregnancy**; start 3rd trimester if maternal DNA ≥200,000 IU/mL.
- **Screen HBsAg + anti-HBc before chemo/biologics**; prophylax with entecavir/tenofovir (mandatory with rituximab).
- **Functional cure = sustained HBsAg loss + undetectable DNA**; cccDNA persistence prevents sterilising cure.
- Resistance: **lamivudine — YMDD (M204V/I)**; tenofovir/entecavir have the highest barrier.
- **HCC surveillance: 6-monthly ultrasound ± AFP**; PAGE-B predicts on-treatment HCC risk; genotype C = worst prognosis.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Chronic Hepatitis"** (chronic hepatitis B grading/staging, HBV DNA phases, full antiviral pharmacology and AASLD/EASL treatment-recommendation tables, special populations).
- **CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders"** (five-phase classification, current drug doses, treatment thresholds, PAGE-B, prognosis).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Hepatitis B"** (natural history, REVEAL-HBV data linking HBV DNA to cirrhosis/HCC, ALT ULN 35/25 U/L, genotype effects).

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Acute hepatitis — diagnostic approach

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Acute hepatitis* is a hepatocellular injury syndrome of <6 months duration, biochemically characterised by a predominant rise in serum aminotransferases (AST/ALT), usually with jaundice. Although the great majority of cases are caused by one of the five hepatotropic viruses (HAV, HBV, HCV, HDV, HEV), the differential is broad and includes drug/toxin injury, alcohol-associated hepatitis, ischaemic ("shock") liver, autoimmune hepatitis, Wilson disease and pregnancy-related liver disease. A *structured approach* — clinical assessment, a focused biochemical "liver panel" to define the pattern (hepatocellular vs cholestatic vs mixed), a small battery of serologic tests, and selective imaging/biopsy — establishes the cause and, crucially, identifies the minority progressing to acute liver failure.

Step 1 — Define the clinical syndrome (history & examination)

- **Symptom phases**: a *prodromal (preicteric)* phase of constitutional symptoms — anorexia, nausea, vomiting, malaise, fatigue, arthralgia/myalgia, headache, low-grade fever (38–39°C; commoner in HAV/HEV and in the HBV serum-sickness syndrome), classically with **aversion to smoking** and altered taste/smell — followed by an *icteric* phase (dark urine and clay/acholic stools 1–5 days before jaundice), then a *convalescent* phase.
- **Examination**: tender hepatomegaly, scleral icterus, and in 10–20% splenomegaly and cervical/epitrochlear lymphadenopathy; a few transient spider angiomata may appear. Many patients are **anicteric** (commoner in HCV than HBV).
- **Risk-factor history (key to aetiology)**: travel to endemic areas, exposure to jaundiced contacts, day-care/shellfish/contaminated water (**HAV, HEV**); injection drug use, transfusion (pre-1992 for HCV, pre-1986 for HBV), tattooing, multiple sexual partners/MSM, maternal-infant transmission, needlestick (**HBV, HCV, HDV**); a full **drug, herbal and alcohol history** (CAGE questionnaire); and "repeated episodes" of hepatitis suggesting underlying chronic/autoimmune disease.

- **Red-flag features (impending acute liver failure)**: altered sleep/personality, confusion, asterixis, fetor hepaticus, rapidly shrinking liver, ascites/oedema — encephalopathy in a previously healthy liver is the defining criterion of acute liver failure (ALF) and demands urgent referral.

Step 2 — Confirm and pattern the liver injury (biochemistry)

- Order the standard battery: **AST, ALT, alkaline phosphatase (AlkP), total/direct bilirubin, albumin and prothrombin time (PT/INR)**; add γ-glutamyl transpeptidase (γGT) to confirm a hepatic source of raised AlkP.
- **Aminotransferases** rise in the prodrome and peak (≈400 to >4000 IU/L) as jaundice appears; the height does *not* correlate with severity. A predominant **AST/ALT elevation relative to AlkP = hepatocellular pattern**; predominant **AlkP/γGT elevation = cholestatic** pattern; both raised = **mixed**.
- **Magnitude clue** — aminotransferases ≥1000 IU/L narrow the differential to: **acute viral hepatitis, ischaemic hepatitis, drug-induced liver injury (especially acetaminophen) and acute biliary obstruction**. Alcohol-associated hepatitis is usually <400 IU/L with **AST > ALT (ratio ≥2)**.
- **Bilirubin**: visible jaundice when >2.5 mg/dL (43 μmol/L); typically 5–20 mg/dL, divided ≈equally between conjugated and unconjugated. Bilirubin may keep rising as aminotransferases fall.
- **Prognostic/synthetic markers**: a **prolonged PT/INR**, hypoglycaemia, falling albumin and very high bilirubin signify severe hepatocellular necrosis. PT that **fails to normalise with parenteral vitamin K** points to hepatocellular (not obstructive/cholestatic) disease.
- Haematology: transient neutropenia/lymphopenia then relative lymphocytosis with **atypical lymphocytes (2–20%)**; thrombocytopenia suggests underlying cirrhosis rather than acute hepatitis.

Step 3 — Targeted serologic algorithm (the "five-test" panel)

Every patient with acute hepatitis should have five tests: **HBsAg, IgM anti-HAV, IgM anti-HBc, anti-HCV and HCV RNA** (Harrison Table 350-6). Test for **anti-HEV (± HEV RNA)** if these are negative and risk factors exist, and for **anti-HDV/HDV RNA** when HBsAg is positive with severe/fulminant or exacerbating disease.

HBsAg	IgM anti-HAV	IgM anti-HBc	Anti-HCV / HCV RNA	Interpretation
+	–	+	–	**Acute hepatitis B**
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A on chronic hepatitis B
+	+	+	–	Acute hepatitis A **and** B
–	+	–	–	**Acute hepatitis A**
–	+	+	–	Acute hepatitis A and B (HBsAg below threshold)

HBsAg	IgM anti-HAV	IgM anti-HBc	Anti-HCV / HCV RNA	Interpretation
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+ (either)	**Acute hepatitis C** (vs chronic HCV)

- **HAV**: diagnosis = **IgM anti-HAV**; IgG anti-HAV alone = past infection/immunity.
- **HBV**: **HBsAg + IgM anti-HBc = acute hepatitis B**. IgM anti-HBc may be the *only* marker in the "window period" (HBsAg gone, anti-HBs not yet up) or when HBsAg is below threshold (≤1–5% of cases). IgG anti-HBc with HBsAg >6 months = chronic. HBeAg/HBV DNA mark replication/infectivity (chiefly useful in chronic disease).
- **HCV**: **anti-HCV** detected reliably by current assays during acute illness; **HCV RNA** is the gold standard, becomes positive earliest, and distinguishes true- from false-positive anti-HCV and active from resolved ("cured") infection (anti-HCV+, HCV RNA–).
- **HDV**: defective virus needing HBV — test anti-HDV/HDV RNA in HBsAg-positive patients; **co-infection** = IgM anti-HBc + anti-HDV, **superinfection** = IgG anti-HBc + anti-HDV.
- **HEV**: IgM/IgG anti-HEV ± HEV RNA — suspect in travellers, the elderly, undercooked pork/game exposure, pregnancy, or chronic hepatitis in the immunosuppressed.

Step 4 — Imaging, biopsy and tests for non-viral causes

- **Ultrasound** (first-line) excludes biliary obstruction (acute cholecystitis, common-duct stone, cholangitis) and detects vascular causes; **MRCP/ERCP** if duct dilatation or stones suspected; Doppler US for Budd-Chiari/congestion.
- If all viral serologies are negative, pursue **non-viral acute hepatitis**: serum **acetaminophen level** and drug history (DILI); **ANA, anti–smooth-muscle antibody, IgG** (autoimmune hepatitis); **ceruloplasmin, slit-lamp for Kayser-Fleischer rings, 24-h urinary copper** (Wilson — especially young patient with haemolysis + low AlkP); **EBV/CMV serology, monospot** (mononucleosis-like illness); pregnancy-related (AFLP, HELLP, eclampsia, cholestasis of pregnancy).
- **Liver biopsy** is *rarely* required in acute hepatitis — reserved for diagnostic uncertainty, suspected autoimmune hepatitis, or when an alternative diagnosis (e.g., alcoholic hepatitis showing steatosis, neutrophilic infiltrate and Mallory hyaline) must be confirmed.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic algorithm flow-chart**: "Acute hepatitis (illness <6 months, raised ALT/AST)" → branch on biochemical pattern: *Hepatocellular (⇑⇑ALT)* vs *Cholestatic (⇑⇑AlkP/γGT)* vs *Mixed* → under hepatocellular box list the five core tests (**IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV RNA**) plus second-line (anti-HEV, anti-HDV, ANA/SMA, ceruloplasmin, acetaminophen level, drug/alcohol history) → outputs: specific viral diagnosis / DILI / autoimmune / Wilson; under cholestatic box: **US → MRCP/ERCP, AMA, drug history**. Label a side-box "**Red flags → ALF: encephalopathy + INR >1.6 + shrinking liver.**"
- **Serologic time-course of acute hepatitis B**: x-axis "weeks after exposure," plotted curves labelled **HBsAg, HBeAg, HBV DNA, IgM anti-HBc, IgG anti-HBc, anti-HBe, anti-HBs**, with the shaded "**window period**" between HBsAg disappearance and anti-HBs appearance, and the ALT/jaundice curve overlaid.

Clinical / Diagnostic significance

- The pattern (hepatocellular vs cholestatic) plus disease duration (<6 vs >6 months) is the *pivot* of the whole work-up — it tells you which serologic/imaging arm to follow.
- **IgM anti-HBc** is the single most useful test to call HBV "acute": it covers the window period and low-level HBsAg, but high-titre IgM anti-HBc can *reappear* in acute exacerbations of chronic HBV, so correlate with history.
- **HCV RNA** detects infection before anti-HCV and before ALT rises — essential after needlestick and in people who inject drugs (where anti-HCV+/RNA+ may mean re-infection, not chronicity).
- Recognise mimics: ischaemic hepatitis (shock, very high but rapidly falling AST), acetaminophen DILI, ascending cholangitis/choledocholithiasis, Budd-Chiari/right heart failure with congestion, AFLP/HELLP in pregnancy, and Wilson disease (haemolytic jaundice + low AlkP + low uric acid).
- **Severity triage**: hospitalise/refer for transplant assessment when there is **encephalopathy, INR >1.6, intractable vomiting/dehydration, hypoglycaemia or very high bilirubin** — these define or predict ALF.

High-yield exam pointers

- Order the **five tests** in every acute hepatitis: HBsAg, IgM anti-HAV, IgM anti-HBc, anti-HCV, HCV RNA — memorise Harrison's Table 350-6.
- **Acute HAV = IgM anti-HAV; Acute HBV = HBsAg + IgM anti-HBc; Acute HCV = anti-HCV + HCV RNA.**
- Aminotransferase height does **not** equal severity — **PT/INR, bilirubin, albumin and mental status** do.
- ALT/AST **≥1000 IU/L** ⇒ think viral, **ischaemic, drug (acetaminophen)** or acute biliary obstruction.
- **AST:ALT ≥2** with values <400 IU/L ⇒ alcohol-associated hepatitis.

- HDV only co-exists with HBV: **co-infection** (IgM anti-HBc) vs **superinfection** (IgG anti-HBc).
- **HEV** in pregnancy → fulminant hepatitis in up to 20%; chronic HEV occurs only in the immunosuppressed.
- PT not correcting with **vitamin K** ⇒ hepatocellular (not cholestatic/obstructive) injury.
- **Acute liver failure = acute injury + coagulopathy + encephalopathy** — the most feared outcome; CMDT admission triggers are encephalopathy, INR >1.6, inability to maintain hydration.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Viral Hepatitis" (serologic markers, "Simplified Diagnostic Approach in Patients Presenting with Acute Hepatitis", clinical/laboratory features, differential diagnosis, prognosis) and "Approach to the Patient with Liver Disease" (history/examination, hepatocellular-vs-cholestatic pattern, diagnostic tests algorithm, imaging, biopsy).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Jaundice" (stepwise evaluation, aminotransferase vs alkaline-phosphatase pattern, PT response to vitamin K) and "Acute Liver Failure" (clinical definition: encephalopathy + acute injury + coagulopathy).
- **CMDT 2026** — "Liver, Biliary Tract & Pancreas Disorders" (essentials of diagnosis, causes of severe aminotransferase elevation, differential diagnosis, when-to-admit criteria).

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Bilirubin metabolism and conjugated hyperbilirubinaemia

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — **Bilirubin** is a tetrapyrrole pigment that is the end product of **heme catabolism**; about **4 mg/kg/day** is produced, of which **80–85%** (range 70–90%) derives from the haemoglobin of senescent red cells and the remainder from ineffective erythropoiesis and turnover of hepatic haemoproteins (myoglobin, cytochromes). **Jaundice** is yellow staining of tissues by deposited bilirubin and becomes clinically detectable (scleral icterus) once serum bilirubin exceeds **51 µmol/L (3 mg/dL)**. **Conjugated (direct) hyperbilirubinaemia** is defined as a *direct fraction >15%* of total serum bilirubin and, unlike unconjugated hyperbilirubinaemia, always implies hepatobiliary disease (or a rare inherited canalicular defect) and is accompanied by **bilirubinuria**.

Formation of bilirubin (heme degradation)

- Bilirubin is the breakdown product of **heme (ferroprotoporphyrin IX)**; formation occurs in **reticuloendothelial cells**, chiefly in the **spleen and liver**.
- **Step 1 — Heme oxygenase** (microsomal): oxidatively cleaves the **α-methene bridge** of the porphyrin ring, opening the heme ring → yields **biliverdin + carbon monoxide (CO) + iron**.
- **Step 2 — Biliverdin reductase** (cytosolic): reduces the central methylene bridge of biliverdin → **bilirubin**.

- Bilirubin so formed is **virtually water-insoluble** owing to tight **internal hydrogen bonding** (propionic-acid carboxyls bonded to imino/lactam groups of the opposite dipyrrole), which buries the polar residues.
- For transport in blood, bilirubin is **solubilised by reversible, non-covalent binding to albumin**; this albumin-bound **unconjugated bilirubin** is carried to the liver (the albumin itself is *not* taken up).

Hepatic handling — the four sequential steps (Fig. 349-1)

- **1. Hepatocellular uptake** — bilirubin enters the hepatocyte by **carrier-mediated (facilitated) and simple diffusional** processes; the definitive bilirubin uptake transporter remains unidentified.
- **2. Intracellular binding** — within the cytosol bilirubin is held in solution by binding as a non-substrate ligand to the **glutathione-S-transferases (GST), formerly "ligandins"**, which reduce efflux back to plasma and present bilirubin for conjugation.
- **3. Conjugation** — in the endoplasmic reticulum, **bilirubin UDP-glucuronosyltransferase (UGT1A1)** conjugates bilirubin with one or two glucuronic-acid moieties → **bilirubin mono- and diglucuronide**. This disrupts the internal hydrogen bonding and renders the pigment **water-soluble**; conjugation is **obligatory** for excretion across the canalicular membrane. *UGT1A1* is encoded by the **UGT1 gene complex on chromosome 2** (exon A1 + common exons 2–5).
- **4. Biliary excretion** — conjugates are actively pumped across the canalicular membrane into bile by the **ATP-dependent transporter MRP2 (ABCC2)**. A portion of glucuronides is alternatively extruded into the sinusoid/portal blood by **MRP3 (ABCC3)** and re-internalised by the sinusoidal uptake proteins **OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3)**.

Intestinal fate and enterohepatic circulation

- Conjugated bilirubin drains into the **duodenum** and passes unchanged through the proximal small bowel; being hydrophilic and large, it is **not reabsorbed** by intestinal mucosa.
- In the **distal ileum and colon**, bacterial **β-glucuronidases** deconjugate it, and gut flora reduce the unconjugated pigment to colourless **urobilinogens** (and related tetrapyrroles).
- **~80–90%** of urobilinogen is excreted in faeces (oxidised to orange **urobilins**, giving stool its colour); **10–20%** undergoes **enterohepatic cycling**, of which a small fraction (**<3 mg/dL**) escapes hepatic re-uptake, is filtered at the glomerulus and excreted in **urine as urobilinogen**.
- **Unconjugated bilirubin is never found in urine** (too tightly albumin-bound to be filtered); **any bilirubin in urine is conjugated** — hence bilirubinuria signifies hepatobiliary disease.

Measurement and fractionation — the van den Bergh reaction

- Serum bilirubin is measured by the **van den Bergh diazo reaction** with diazotised sulfanilic acid.
- **Direct (conjugated)** = fraction reacting *without* an accelerator (alcohol); **Total** = fraction reacting *after* alcohol releases albumin-bound pigment; **Indirect (unconjugated)** = Total − Direct.
- Normal total bilirubin is **17–26 μmol/L (1–1.5 mg/dL)** by van den Bergh (95% of normals **0.2–0.9 mg/dL**).
- **Unconjugated hyperbilirubinaemia: direct <15% of total; conjugated: direct >15%.**

- **Delta bilirubin (biliprotein):** conjugated bilirubin **covalently bound to albumin**, formed when hepatic excretion is impaired; its clearance follows the albumin half-life (**18–20 days**) rather than bilirubin's (~4 h). It explains why some recovering cholestatic patients have **persistent jaundice without bilirubinuria** (delta bilirubin is not filtered) and a slow fall in bilirubin.

Classification of hyperbilirubinaemias

Predominant fraction	Mechanism	Representative causes
Unconjugated (indirect >85%)	↑ production	Haemolysis; ineffective erythropoiesis; resorption of haematoma; massive transfusion
	↓ hepatic uptake	Drugs — **rifampin, probenecid**
	↓ conjugation	**Gilbert** (UGT1A1 10–35%); **Crigler-Najjar I** (absent UGT1A1, kernicterus) and **II** (≤10%, phenobarbital-responsive); physiologic neonatal jaundice
Conjugated / mixed (direct >15%)	↓ canalicular excretion (inherited)	**Dubin-Johnson** (MRP2/ABCC2); **Rotor** (OATP1B1 + 1B3 deficiency)
	Hepatocellular injury	Viral/alcoholic/drug/ischaemic hepatitis, cirrhosis
	Cholestasis (intra-/extrahepatic)	PBC, PSC, drug cholestasis, choledocholithiasis, pancreatic/biliary malignancy

Approach to conjugated hyperbilirubinaemia (Fig. 52-1)

- **Step 1 — Confirm and fractionate.** Establish that the *direct fraction is >15%* of total bilirubin; **bilirubinuria** on dipstick (Ictotest) corroborates a true conjugated rise. Order the *core panel*: bilirubin with fractionation, **ALT, AST, ALP, prothrombin time (PT), albumin**.
- **Step 2 — Is the rise isolated or accompanied by other abnormal liver tests?**
  - **Isolated conjugated hyperbilirubinaemia (other LFTs normal)** → think of the two benign **inherited canalicular disorders**: **Dubin-Johnson** (defective MRP2 canalicular export) and **Rotor** (deficient OATP1B1/1B3 reuptake). Both present as asymptomatic jaundice; distinction is possible but **clinically unnecessary** given their benign course.
  - **Conjugated rise with other liver tests deranged** → proceed to Step 3.
- **Step 3 — Hepatocellular vs cholestatic pattern** (enzymes are the discriminator):
  - **Hepatocellular**: aminotransferases (ALT/AST) elevated *out of proportion* to ALP. AST:ALT >2:1 with AST rarely >300 U/L suggests **alcoholic hepatitis**; ALT/AST >500–1000 U/L (ALT ≥ AST) suggests **acute viral or toxin/drug injury** (e.g. acetaminophen).
  - **Cholestatic**: ALP elevated *out of proportion* to aminotransferases (confirm hepatic origin with **GGT or 5′-nucleotidase**).
- **Step 4 — Targeted serology / toxicology (hepatocellular work-up):** hepatitis A IgM; HBsAg + anti-HBc IgM; HCV RNA; ± hepatitis E IgM; **acetaminophen level**; **ceruloplasmin** if age <40 (Wilson disease); **ANA, anti-smooth-muscle antibody, SPEP** (autoimmune hepatitis); EBV/CMV if indicated.
- **Step 5 — Imaging (cholestatic work-up): ultrasound first** to assess the biliary tree.

- **Dilated ducts → extrahepatic cholestasis** → define level/cause with **CT / MRCP / ERCP** (± EUS, PTC). **ERCP is the gold standard for choledocholithiasis** and is therapeutic (stone extraction, stenting); MRCP has replaced diagnostic ERCP in most cases.
- **Non-dilated ducts → intrahepatic cholestasis → AMA** (primary biliary cholangitis, positive in ~95%), hepatitis serologies, **drug review**, and **liver biopsy** if serology unrevealing; MRCP shows pathognomonic segmental strictures of **PSC**.

- **Step 6 — Assess severity/chronicity** with **albumin** (low → chronic, e.g. cirrhosis/cancer) and **PT** (prolonged, *non-correcting with parenteral vitamin K* → severe hepatocellular dysfunction; correcting → cholestatic vitamin-K malabsorption).

Inherited conjugated hyperbilirubinaemias — Dubin-Johnson vs Rotor

Feature	Dubin-Johnson (DJS)	Rotor (RS)
Gene / defect	**ABCC2 (MRP2)** — defective canalicular export	**SLCO1B1 + SLCO1B3 (OATP1B1 + 1B3)** — defective sinusoidal reuptake
Inheritance	Autosomal recessive	Autosomal recessive
Liver appearance	**Grossly black**; coarse dark pigment in centrilobular lysosomes	**Normal**, no pigmentation
Total bilirubin	34–85 µmol/L (2–5 mg/dL), occasionally up to 20–25 mg/dL; predominantly conjugated	Mild, predominantly conjugated
Urinary coproporphyrin	Total **normal**, but **≥80% isomer I**	Total **markedly increased**, isomer I usually **<70%**
Oral cholecystogram	Gallbladder **not visualised**	Gallbladder **visualised**
BSP (sulfobromophthalein)	Secondary rise at **90 min** (reflux of conjugated dye)	Delayed clearance, **no 90-min reflux**
Course	Benign; may become overt in pregnancy / OCP use	Benign

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Bilirubin metabolism flow diagram** (left→right). Labels: *Senescent RBC → Heme (in reticuloendothelial cell) → Heme oxygenase (releases CO + Fe) → Biliverdin → Biliverdin reductase → Unconjugated bilirubin → Albumin-bound transport in blood → Hepatocyte uptake → Ligandin/GST binding → UGT1A1 conjugation (ER) → Bilirubin mono-/diglucuronide → MRP2 → Bile canaliculus → Gut → β-glucuronidase/bacteria → Urobilinogen → (80–90% faeces as urobilin / enterohepatic cycle / kidney → urine urobilinogen).* Add side-arrows: *MRP3 → portal blood → OATP1B1/1B3 reuptake.*
- **Algorithm box for conjugated hyperbilirubinaemia.** Labels: *Direct >15% → fractionate → "isolated LFTs normal = DJS/Rotor" branch; "other LFTs abnormal" → Hepatocellular (ALT/AST ≫ ALP) vs Cholestatic (ALP ≫ ALT/AST) → Ultrasound → Dilated ducts = Extrahepatic (CT/MRCP/ERCP) vs Non-dilated = Intrahepatic (AMA, biopsy).*

Clinical / Diagnostic significance

- **Bilirubinuria is an early, sensitive sign** of conjugated hyperbilirubinaemia and may precede clinical jaundice; its **absence in deep jaundice** suggests delta-bilirubin predominance (prolonged cholestasis).
- **Serum bilirubin level/ratio does NOT distinguish intra- from extrahepatic cholestasis** — that decision rests on the *enzyme pattern* and *imaging (ductal dilatation)*.
- **MRP2 (DJS) vs OATP1B1/1B3 (Rotor)** deficiencies are clinically benign but matter for **drug handling**: OATP transporters mediate hepatic uptake of statins and other drugs, so Rotor predisposes to drug accumulation.
- A **non-correcting prolonged PT after parenteral vitamin K** flags severe hepatocellular failure and is prognostically ominous.
- **Pigment (calcium bilirubinate) gallstones** complicate chronic haemolysis and can superimpose **choledocholithiasis**, producing a *secondary conjugated/obstructive* picture.

High-yield exam pointers

- Bilirubin = end product of **heme** catabolism; **heme oxygenase → biliverdin (+CO+Fe) → biliverdin reductase → bilirubin**.
- **Unconjugated bilirubin is albumin-bound, lipid-soluble, NOT in urine; conjugated is water-soluble, appears in urine.**
- **Conjugating enzyme = UGT1A1**; excretory canalicular pump = **MRP2 (ABCC2)**.
- **Conjugated hyperbilirubinaemia = direct >15% of total** and is *always* pathological (hepatobiliary) except the benign inherited DJS/Rotor.
- **DJS = MRP2 defect, black liver, urinary coproporphyrin ≥80% isomer I, BSP 90-min reflux; Rotor = OATP1B1/1B3 defect, normal-coloured liver, ↑ total coproporphyrin, gallbladder visualised.**
- Approach: **fractionate → isolated vs other-LFTs → hepatocellular (ALT/AST ≫ ALP) vs cholestatic (ALP ≫ ALT/AST) → ultrasound → dilated = extrahepatic, non-dilated = intrahepatic.**

- **ERCP = gold standard** for choledocholithiasis (diagnostic + therapeutic); **AMA** = key test for primary biliary cholangitis.
- **Delta bilirubin** (albumin-bound conjugated bilirubin, t½ 18–20 days) explains slow resolution of jaundice and absent bilirubinuria in recovering cholestasis.

SOURCE & COVERAGE

Harrison 22e — Ch 349 "The Hyperbilirubinemias" (bilirubin metabolism, 4-step hepatic transport, UGT1A1, MRP2/MRP3/OATP1B1-1B3, Dubin-Johnson and Rotor syndromes) + Ch 52 "Jaundice" (heme catabolism, van den Bergh fractionation, delta bilirubin, Fig. 52-1 diagnostic algorithm for conjugated hyperbilirubinaemia, hepatocellular vs cholestatic patterns). Coverage note: All specifics (transporters, enzyme names, coproporphyrin/BSP findings, bilirubin cut-offs, algorithm steps) are drawn from these two chapters; standard ancillary points (GGT/5′-nucleotidase to confirm hepatic ALP origin; AST:ALT and aminotransferase ranges) are from the same chapters' liver-test discussion (Table 348-1). No data fabricated beyond the provided text.

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Oral antiviral therapy for hepatitis C

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Chronic hepatitis C virus (HCV) infection persists in 50–85% of those acutely infected and progresses to cirrhosis in ~20–25% over two decades, with hepatocellular carcinoma (HCC) developing in cirrhotics at 1–4%/year. Because HCV has an entirely **cytoplasmic life-cycle with no integrated archival template** (unlike HBV), suppression of replication in the absence of resistance permanently clears the virus — i.e. **HCV is curable**. The modern treatment of HCV is therefore an all-oral, interferon-free regimen of **direct-acting antivirals (DAAs)** taken for 8–12 weeks, achieving cure (sustained virologic response, SVR) in >95% of patients.

Goal of therapy and definition of cure

- The endpoint is the **sustained virologic response (SVR12)** — undetectable serum HCV RNA measured **12 weeks after completion** of therapy (the threshold was shortened from the older SVR24 once all-oral DAAs became available). HCV RNA must be tracked with a sensitive real-time RT-PCR assay (limit of quantification ≤25 IU/mL).
- An SVR is **tantamount to virologic cure**; late relapse beyond 6–12 months is very rare and almost unheard of after 2 years.
- SVR translates into reduced fibrosis progression, **regression of fibrosis and even cirrhosis**, lower rates of hepatic decompensation, HCC and liver transplantation, improved all-cause and liver-related survival, and improvement in extrahepatic disease (cryoglobulinaemic vasculitis, type 2 diabetes, renal disease).
- The **WHO global elimination goal** is a 90% reduction in HCV prevalence by 2030; broad DAA use since 2013 has already reversed HCV-related mortality in many regions.

Molecular targets and classes of DAAs

The HCV polyprotein is cleaved into 3 structural and 7 non-structural proteins; current DAAs hit **three** non-structural targets, identifiable by drug suffix.

Class (suffix)	Molecular target	Representative drugs	Genotype coverage / barrier to resistance
NS3/4A protease inhibitors (-*previr*)	NS3/4A serine protease (polyprotein cleavage)	Glecaprevir, grazoprevir, voxilaprevir, paritaprevir (ritonavir-boosted), simeprevir	Variable–pangenotypic; **low-to-moderate** barrier; **contraindicated in decompensated cirrhosis**
NS5A inhibitors (-*asvir*)	NS5A phosphoprotein of the replication complex	Velpatasvir, pibrentasvir, ledipasvir, elbasvir, daclatasvir, ombitasvir	High potency at **picomolar** doses; coverage broader with 2nd-generation agents
NS5B polymerase inhibitors (-*buvir*)	NS5B RNA-dependent RNA polymerase (replicase)	**Nucleotide:** sofosbuvir (pangenotypic, **high barrier**); **non-nucleoside:** dasabuvir (genotype 1, weak, low barrier)	Nucleos(t)ide = pangenotypic, high barrier (chain termination)

- Modern practice combines drugs from **two (or three) classes in a single fixed-dose pill** to give a high genetic barrier and pangenotypic activity.
- **Resistance-associated substitutions (RASs)** matter chiefly for NS5A (e.g. **Y93H** in genotype 3; NS5A polymorphisms in ~11% of genotype 1a). Protease-inhibitor RASs generally do **not** persist (low fitness, wild-type re-emerges); nucleotide (sofosbuvir) RASs are rare and unfit.

Pre-treatment evaluation

- **HCV RNA** (confirms active infection) and **HCV genotype** — though pangenotypic regimens exist, genotype still guides regimen/duration and insurance.
- **Fibrosis staging** by non-invasive means — **FIB-4 score**, transient elastography (liver stiffness); biopsy is no longer routine. Presence of cirrhosis changes drug choice, duration and the rare need for ribavirin.
- **HBsAg + anti-HBc** — DAAs can trigger **HBV reactivation**; co-infected patients meeting criteria must receive HBV antiviral cover before/with HCV therapy.
- **HIV status, renal function (eGFR)**, pregnancy status, and a **drug–drug interaction check** (www.hep-druginteractions.org).

Current first-line oral regimens (AASLD–IDSA / EASL)

Five all-oral regimens are recommended; two pangenotypic fixed-dose combinations dominate as a **"simplified, one-size-fits-all" algorithm**.

Regimen (once-daily)	Components & doses	Usual duration	Notes
Sofosbuvir–velpatasvir (preferred, pangenotypic)	Sofosbuvir 400 mg + velpatasvir 100 mg	**12 weeks**	Genotypes 1–6; SVR12 ~99% (95% in genotype 3); ribavirin only if decompensated

Regimen (once-daily)	Components & doses	Usual duration	Notes
Glecaprevir–pibrentasvir (preferred, pangenotypic)	Glecaprevir 300 mg + pibrentasvir 120 mg	**8 weeks** (treatment-naïve, incl. compensated cirrhosis)	Genotypes 1–6; SVR ~99%; preferred in **severe renal disease/dialysis**; contains protease inhibitor
Sofosbuvir–ledipasvir	Sofosbuvir 400 mg + ledipasvir 90 mg	8–12 weeks	Genotypes 1, 4, 5, 6; 8 weeks if naïve, non-cirrhotic, HCV RNA $<6\times10^6$ IU/mL
Elbasvir–grazoprevir	Elbasvir 50 mg + grazoprevir 100 mg	12 weeks	Genotypes 1 and 4; **baseline NS5A RAS testing in genotype 1a** (extend ±ribavirin if present); good in renal failure
Sofosbuvir–velpatasvir–voxilaprevir	Sofosbuvir 400 mg + velpatasvir 100 mg + voxilaprevir 100 mg	12 weeks	**Rescue/retreatment** after NS5A-inhibitor or DAA failure; ~97% SVR; take with food

- The **simplified algorithm** (sofosbuvir–velpatasvir ×12 wk *or* glecaprevir–pibrentasvir ×8 wk) is used when the patient has **none** of: prior treatment failure, cirrhosis, HBsAg positivity, pregnancy, HCC, or prior liver transplant — often without genotyping or on-treatment monitoring.
- **Ribavirin** (an oral guanosine nucleoside) is now rarely required — reserved for decompensated cirrhosis or selected DAA-failure retreatment; its dose-limiting toxicity is **haemolytic anaemia**, and it is strictly **teratogenic** (contraindicated in pregnancy, contraception mandatory).

Treatment in special populations

- **Compensated (Child-Pugh A) cirrhosis** — respond as well as non-cirrhotics; pangenotypic regimens used, treatment-experienced cirrhotics may need 12 weeks.
- **Decompensated (Child-Pugh B/C) cirrhosis — protease-inhibitor–containing regimens are contraindicated** (hepatotoxicity, risk of further decompensation). Use **sofosbuvir + an NS5A inhibitor (velpatasvir or ledipasvir)**: add ribavirin to a 12-week course if ribavirin-eligible, or extend to 24 weeks if ribavirin-ineligible. Refer to a transplant centre.
- **Renal impairment** — no dose change for mild–moderate disease. For severe impairment (CrCl <30 mL/min, dialysis): **glecaprevir–pibrentasvir** (all genotypes) or **elbasvir–grazoprevir** (genotypes 1, 4) preferred; sofosbuvir-containing regimens, initially avoided, are now FDA-approved (2019) for this group.
- **HCV/HIV co-infection** — treat with the **same DAAs and durations** as mono-infection (response is now equivalent); avoid the abbreviated 8-week sofosbuvir–ledipasvir course; mind antiretroviral interactions (avoid ribavirin with didanosine/stavudine/zidovudine).
- **Prior DAA failure (retreatment)** — sofosbuvir-experienced patients are re-treated with **sofosbuvir–velpatasvir–voxilaprevir ×12 wk** or **glecaprevir–pibrentasvir ×16 wk**; multiple-DAA failures may need glecaprevir–pibrentasvir + sofosbuvir + ribavirin ×16 wk; RAS-guided, specialist-referred.

- **Pregnancy** — DAAs **not routinely recommended** (limited data); ribavirin absolutely contraindicated. **Acute hepatitis C** and **people who inject drugs (PWID)** should be treated (active injection drug use is no longer a contraindication — treatment reduces onward transmission).

Adverse effects, interactions and cautions

- DAAs are **very well tolerated**; commonest effects are mild **headache, fatigue, nausea**, comparable to placebo.
- **Sofosbuvir + amiodarone → severe, potentially fatal bradycardia** — sofosbuvir-containing regimens are contraindicated with amiodarone (especially with beta-blockers).
- **P-glycoprotein / CYP3A4 inducers** (rifampin, St John's wort, carbamazepine, phenytoin, phenobarbital) lower DAA levels and **contraindicate** all DAA regimens.
- **Gastric acid suppression**: ledipasvir and velpatasvir lose solubility at high gastric pH — limit/separate antacids, H2-blockers and PPIs (e.g. omeprazole ≤20 mg).
- Protease inhibitors can raise aminotransferases/bilirubin → monitor and stop for marked rises.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HCV genome and DAA drug targets** (linear genome): label structural proteins **Core (C), E1, E2, p7** and non-structural proteins **NS2, NS3, NS4A, NS4B, NS5A, NS5B**; mark the **three drug targets** — *NS3/4A protease (→ -previr), NS5A replication-complex protein (→ -asvir), NS5B RNA-dependent RNA polymerase (→ -buvir).*
- **Treatment-decision flow chart**: label *Confirm chronic HCV (HCV RNA +ve) → Pre-treatment work-up (genotype, FIB-4/elastography, HBsAg+anti-HBc, HIV, eGFR, DDI check)* → branch *No cirrhosis / treatment-naïve → simplified regimen (sof-velpatasvir 12 wk OR glecaprevir-pibrentasvir 8 wk)* vs *Cirrhosis / prior failure / special population → tailored regimen → Confirm SVR12 at 12 weeks post-treatment*.

Clinical / Diagnostic significance

- Achieving SVR halts and can reverse fibrosis/cirrhosis and reduces HCC, decompensation, transplant need and mortality — but in patients with **advanced fibrosis/cirrhosis the HCC risk is reduced, not eliminated**, so **6-monthly ultrasound HCC surveillance continues even after cure**.
- **Screen and protect against HBV reactivation** before DAA therapy; vaccinate against hepatitis A and B.
- DAAs cure HCV in patients awaiting or after **liver/kidney transplantation**, and enable transplantation of HCV-positive donor organs into HCV-negative recipients with subsequent cure.
- Treating **mild disease is justified and cost-effective** — delaying until fibrosis is advanced forfeits the chance to prevent end-stage complications.

High-yield exam pointers

- **SVR12** = undetectable HCV RNA 12 weeks post-treatment = **cure**.

- Three DAA targets/suffixes: **NS3/4A protease (-previr), NS5A (-asvir), NS5B polymerase (-buvir)**.
- **Sofosbuvir** = pangenotypic NS5B **nucleotide** inhibitor, high resistance barrier, 80% renally excreted.
- Two pangenotypic preferred fixed-dose regimens: **sofosbuvir–velpatasvir ×12 wk** and **glecaprevir–pibrentasvir ×8 wk**, SVR >95%.
- **Protease-inhibitor regimens (glecaprevir/grazoprevir/voxilaprevir) are contraindicated in decompensated cirrhosis** — use **sofosbuvir + velpatasvir/ledipasvir ± ribavirin**.
- **Sofosbuvir + amiodarone = severe bradycardia** (contraindicated).
- **Sofosbuvir–velpatasvir–voxilaprevir** = rescue therapy for prior **NS5A/DAA failure**.
- Always check **HBsAg/anti-HBc** (reactivation), genotype, fibrosis (FIB-4/elastography), eGFR, and drug interactions before therapy.
- **Ribavirin** — main toxicity **haemolytic anaemia**; **teratogenic** (avoid in pregnancy).
- Continue **HCC surveillance after SVR** if cirrhosis/advanced fibrosis present.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Chronic Hepatitis" (chronic hepatitis C; DAA classes, targets, recommended regimens, special populations, SVR, treatment recommendations) and "Antiviral Chemotherapy, Excluding Antiretroviral Drugs."
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Hepatitis C" (DAA class pharmacology, individual drug doses and pharmacokinetics, resistance, fixed-dose combinations, drug–drug interactions, registration trials).
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (current management, DAA agent tables/doses, preferred regimens, pre-treatment screening, P450-inducer cautions).

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Helicobacter pylori — associated diseases and management

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Helicobacter pylori* is a spiral, flagellated, microaerophilic, urease-producing **gram-negative bacillus** that colonises the gastric mucous layer of roughly **40% of the world's population**, usually acquired in childhood and persisting for life unless eradicated. Essentially **all colonised persons develop histological chronic gastritis**, but only **~10–15% develop overt disease** — the outcome being decided by an interplay of bacterial virulence (cagA, vacA), host genetics and environment. It is the principal cause of peptic ulcer disease, an **IARC class I (definite) gastric carcinogen**, and the driver of gastric MALT lymphoma; it also has recognised extragastric and some *protective* associations. Marshall and Warren's 1984 discovery (Nobel Prize 2005) transformed these from chronic relapsing diseases into curable infections.

Pathogenesis — how one organism causes opposite diseases

- **Virulence factors:** the *cag* pathogenicity island encodes a **type IV secretion system** that injects the effector **CagA** into epithelial cells (driving proliferative, cytoskeletal and inflammatory changes); **CagL** binds host integrins; peptidoglycan fragments activate intracellular **Nod1**, amplifying cytokine release. The vacuolating cytotoxin **VacA** forms membrane pores, and adhesin **BabA** binds blood-group antigens. *cagA+/vacA-active* strains carry the highest ulcer and cancer risk.
- **Host/environment:** IL-1β gene polymorphisms (high IL-1 producers) and the **PSCA rs2294008** SNP increase cancer risk; smoking, high-salt/preserved-food diets raise risk, while vitamin C/antioxidants are protective.
- **Topography determines disease (key concept):**
  - **Antral-predominant gastritis** → loss of somatostatin-secreting **D cells** → unrestrained gastrin → ↑ acid from spared corpus → **duodenal ulcer**.
  - **Corpus-predominant / pangastritis** → hypochlorhydria, atrophy → **gastric ulcer, atrophic gastritis and adenocarcinoma**.

Spectrum of associated diseases (with strength of association)

Disease group	Specific condition	Association / Odds ratio (Harrison Fig 168-1)
Gastric	Chronic superficial (then atrophic) gastritis	Virtually 100% of colonised
	Peptic ulcer disease	**~70% of duodenal, ~50% of gastric ulcers**; DU **OR 3–6**
	Functional (non-ulcer) dyspepsia	Symptom resolution in up to ~10–15% over placebo
	Gastric MALT (marginal-zone B-cell) lymphoma	**OR 6–50**
	Non-cardia gastric adenocarcinoma	**OR 3–8**

Disease group	Specific condition	Association / Odds ratio (Harrison Fig 168-1)
	Iron-deficiency anaemia, vitamin B12 deficiency	Occult loss + hypochlorhydria/malabsorption
Extragastric	Immune (idiopathic) thrombocytopenic purpura	Platelet rise/normalisation after eradication
Protective (inverse)	GERD, Barrett's oesophagus, oesophageal & cardia adenocarcinoma	**OR 0.2–0.6** (cagA+ strains)
	Childhood-onset asthma, hay fever, atopy	Inverse association (cagA+); causal in animal models

- *H. pylori* is **neither necessary nor sufficient** for PUD but is a very strong risk factor; eradication virtually abolishes long-term ulcer relapse (recurrence falls from ~85%/yr to **<20%/yr**). NSAIDs/aspirin and *H. pylori* are **independent, synergistic** ulcer risks.

Gastric MALT lymphoma & adenocarcinoma — the malignant end of the spectrum

- **Gastric MALT lymphoma (extranodal marginal-zone B-cell lymphoma):** arises from chronic antigenic stimulation of acquired lymphoid tissue; the stomach is the commonest extranodal lymphoma site. Cells are **CD19/CD20/CD79a positive, CD5/CD10/CD23/cyclin D1 negative**, forming *lymphoepithelial lesions*, commonly antral.
  - **H. pylori eradication alone induces remission in ~60–80%** of low-grade, localised (mucosa-confined) cases — first-line therapy even if tests are falsely negative.
  - **t(11;18)(q21;q21)** (the *API2–MALT1* fusion) and **t(1;14)(p22;q32)** (deregulating *bcl-10*) **predict non-response** to eradication and indicate need for radiotherapy/rituximab-based chemotherapy; CagA+ strains associate with t(11;18)-positive tumours.
- **Gastric adenocarcinoma (Correa cascade):** the intestinal type evolves over decades — **chronic gastritis → atrophic gastritis → intestinal metaplasia → dysplasia → carcinoma**, driven by inflammation-derived reactive oxygen/nitrogen species and nitrosamines from bacterial overgrowth in the achlorhydric stomach. The **diffuse type** (signet-ring cells, *linitis plastica*) may arise directly from chronic gastritis. Eradication **does not treat established cancer** but reduces incidence, especially after endoscopic resection of early gastric cancer.

Diagnosis

Invasive (endoscopic biopsy)	Non-invasive
Rapid urease test (CLO) — quick, biopsy in urea-indicator gel	**^{13}C-urea breath test** — accurate; ideal for confirming cure
Histology (modified Giemsa/silver/immunostain) — also grades atrophy/metaplasia/dysplasia	**Stool antigen test** (monoclonal) — cheap, good for children & cure-testing
Culture + sensitivity — most specific; guides resistant cases	**Serology (IgG)** — cannot confirm cure (titres fall slowly); least reliable for active infection

- **Pitfall:** breath/stool/biopsy tests depend on bacterial load — false negatives if performed **within 4 weeks of antibiotics/bismuth or 2 weeks of stopping a PPI**, or <4 weeks post-treatment. Serology is *not* used to monitor cure.
- After **gastric** ulceration, repeat **endoscopy** to confirm healing and exclude carcinoma; duodenal ulcers need only a non-invasive cure test.

Management — eradication regimens (PPI/vonoprazan + ≥2 antibiotics × 10–14 days)

Regimen	Components	Notes
Bismuth quadruple (BQT) — *preferred first-line* (ACG 2024)	PPI + **bismuth** + **tetracycline** + **metronidazole**, 14 d	Effective even in **metronidazole-resistant** strains; >85% cure
Rifabutin triple (Talicia)	Omeprazole + **rifabutin** + **amoxicillin**, q8h × 14 d	Rifabutin resistance rare; >85% cure
Vonoprazan triple / dual (Voquezna)	Vonoprazan + amoxicillin ± **clarithromycin**, 14 d	PCAB gives faster/stronger acid block; dual preferred empirically
Clarithromycin triple	PPI + **clarithromycin** + **amoxicillin** (or metronidazole), 14 d	**Only if** clarithromycin resistance **<15%** or strain proven sensitive
Concomitant quadruple	PPI + clarithromycin + amoxicillin + nitroimidazole, 14 d	Non-bismuth alternative
Levofloxacin-based	PPI + levofloxacin + amoxicillin	Mainly **salvage/second-line** therapy

- **Resistance drives choice:** clarithromycin resistance is now ~50% (US) and high in much of the world — hence the shift away from clarithromycin triple therapy; metronidazole resistance is partial (overcome by higher dose/quadruple therapy); amoxicillin and tetracycline resistance remain rare.
- **Keys to success:** strict **compliance**, avoiding antibiotics the strain has seen before, **high-dose acid suppression** (PPI or vonoprazan), and **confirming cure** ≥4 weeks after antibiotics and ≥2 weeks off PPI.
- **Salvage strategy:** for persistent infection, re-treat empirically with a *different* regimen (e.g., BQT after a clarithromycin regimen; rifabutin triple after BQT) or, ideally, **culture / molecular (PCR) susceptibility-guided** therapy.

Indications for eradication (Maastricht VI / ACG)

- **Definite:** all peptic ulcers (active or healed); low-grade gastric MALT lymphoma; after endoscopic resection of early gastric cancer.
- **Recommended:** functional dyspepsia (test-and-treat in <60 yr without alarm features); long-term NSAID/low-dose-aspirin users (especially prior PUD); first-degree relatives of gastric-cancer patients; atrophic gastritis/intestinal metaplasia.
- **Offer:** unexplained **iron-deficiency anaemia**, **immune thrombocytopenic purpura**, and vitamin B12 deficiency with other causes excluded.

- Mass population screening is **not** routinely recommended (uncertain cancer-risk reduction, antibiotic resistance, loss of possible protective effects against GERD/atopy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Disease outcomes of H. pylori colonisation" (branching tree).** Centre: *H. pylori* → **Chronic gastritis (≈100%)**. Branch by gastritis pattern: *Antral-predominant* → ↑gastrin/↑acid → **Duodenal ulcer (OR 3–6)**; *Corpus-predominant/pangastritis* → atrophy/hypochlorhydria → **Gastric ulcer**, **Atrophic gastritis → intestinal metaplasia → dysplasia → Non-cardia adenocarcinoma (OR 3–8)**, and **MALT lymphoma (OR 6–50)**. Add a *protective* arrow: ↓ acid → **lower GERD / Barrett's / oesophageal adenocarcinoma (OR 0.2–0.6)**. Labels: *cagA, vacA, BabA; D-cell loss; somatostatin↓; gastrin↑*.
- **Diagram 2 — "Correa cascade".** Linear arrow: **Normal mucosa → Chronic active gastritis → Atrophic gastritis → Intestinal metaplasia → Dysplasia → Intestinal-type adenocarcinoma**, with labels *H. pylori, reactive oxygen/nitrogen species, nitrosamines, achlorhydria*.

Clinical / Diagnostic significance

- In a young dyspeptic without alarm features, **non-invasive test-and-treat** (UBT/stool antigen) avoids endoscopy; **alarm symptoms** (age ≥60, weight loss, anaemia, dysphagia, bleeding, vomiting) mandate **upper GI endoscopy** to exclude malignancy.
- Always **test for and eradicate** *H. pylori* before/at the start of long-term NSAID/aspirin therapy in those with ulcer history — but eradication **alone does not remove** ongoing NSAID risk, so co-prescribe a PPI in high-risk patients.
- A non-healing/refractory ulcer should prompt search for **NSAID use (often surreptitious), gastrinoma (Zollinger-Ellison — fasting serum gastrin), malignancy (re-biopsy), Crohn's, vasculitis**.
- Unexplained refractory **iron-deficiency anaemia or ITP** warrants *H. pylori* testing — eradication can correct both.

High-yield exam pointers

- *H. pylori* = **gram-negative, urease-positive, microaerophilic, flagellated spiral bacillus**; urease (→ ammonia) is its acid-defence and the basis of the **rapid urease & ^{13}C-urea breath tests**.
- **70% of duodenal ulcers, 50% of gastric ulcers** are *H. pylori*-related; eradication cuts ulcer recurrence from ~85%/yr to <20%/yr.
- **Antral gastritis = duodenal ulcer; corpus/pangastritis = gastric ulcer + cancer.**
- **IARC Group 1 carcinogen**; intestinal-type cancer follows the **Correa cascade**; diffuse type = signet-ring/linitis plastica.
- **Low-grade gastric MALT lymphoma regresses in 60–80% with eradication alone**; **t(11;18)(q21;q21)** predicts non-response.
- **OR memory aid:** B-cell lymphoma **6–50** > gastric adenoca **3–8** > duodenal ulcer **3–6**; *protective* against oesophageal disease **0.2–0.6**.

- **First-line eradication = bismuth quadruple therapy (PPI + bismuth + tetracycline + metronidazole × 14 days)**; clarithromycin triple only where resistance <15%.
- **Confirm cure** by UBT/stool antigen **≥4 weeks after antibiotics and ≥2 weeks off PPI**; never use serology to confirm cure.
- Extragastric eradication indications: **unexplained IDA, ITP, B12 deficiency**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Helicobacter pylori Infections" (virulence factors, disease odds ratios, diagnosis, eradication regimens, indications) and "Peptic Ulcer Disease and Related Disorders" (PUD/H. pylori interaction, ACG/Maastricht VI indications, treatment tables).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Gastrointestinal Lymphomas" (MALT lymphoma immunophenotype, t(11;18)(q21;q21) and t(1;14)(p22;q32), 60–80% regression), "Adenocarcinoma of the Stomach and Other Gastric Tumours" (Correa pathway, IARC class I carcinogen, Lauren intestinal/diffuse types), "Gastritis and Gastropathy" and "Peptic Ulcer Disease".
- **CMDT 2026** — "Gastrointestinal Disorders" (ACG 2024 regimens: bismuth quadruple, rifabutin triple [Talicia], vonoprazan triple/dual [Voquezna]; resistance data; cure-confirmation rules).

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Inflammatory bowel disease — extraintestinal manifestations

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Extra-intestinal manifestations (EIMs) are inflammatory or metabolic disorders arising *outside* the gut in patients with ulcerative colitis (UC) or Crohn's disease (CD). Up to **one-third** of IBD patients have at least one EIM (population estimates 6–25%), and about **one-fourth of those affected have more than one**. EIMs are commoner in **CD than UC** and in patients with **colonic involvement**. Pathogenically, the inflammatory mucocutaneous, joint and ocular EIMs reflect an influx of **mononuclear cells activated in the intestine that home aberrantly** to extra-intestinal organs; a few (e.g. enteric hyperoxaluria stones, cholelithiasis) are direct metabolic consequences of bowel disease. EIMs may **precede, parallel or run independently** of luminal activity — an important clue to whether treating the bowel will help.

Classification by relationship to bowel activity

This is the single most examinable framework — EIMs split into those that **parallel** gut inflammation (treated by controlling the bowel) and those that run an **independent** course.

Parallels bowel activity (treat the bowel)	Independent of bowel activity (treat separately)
Peripheral arthritis — **Type 1 (pauciarticular)**	Axial arthropathy — **sacroiliitis, ankylosing spondylitis**

Parallels bowel activity (treat the bowel)	Independent of bowel activity (treat separately)
Erythema nodosum	Peripheral arthritis — **Type 2 (polyarticular)**
Episcleritis	Anterior uveitis / iritis
Oral aphthous stomatitis, pyostomatitis/pyoderma vegetans	**Pyoderma gangrenosum**
Sweet syndrome, metastatic CD	**Primary sclerosing cholangitis (PSC)**

Musculoskeletal (most common EIM group; 5–20%)

- **Peripheral arthritis** — develops in **15–20%** of IBD patients, commoner in CD, classically **asymmetric, migratory, polyarticular, non-deforming**, affecting large joints; rheumatoid factor **negative**. Sleisenger subdivides it into:
  - ***Type 1 (pauciarticular)*** — **<5 joints**, large joints, **parallels** bowel activity, self-limiting, associated with EN and uveitis; often remits after colectomy in UC.
  - ***Type 2 (polyarticular)*** — **>5 joints**, small joints (MCP/PIP), **independent** of bowel activity, more persistent.
- **Axial spondyloarthropathy — ankylosing spondylitis (AS)** occurs in ~10% (commoner in CD); **two-thirds (up to 75% of CD with spondylitis) are HLA-B27 positive**. Presents with **insidious low-back/buttock pain and morning stiffness improved by exercise**, runs a continuous progressive course causing permanent skeletal deformity, and does **not** remit with glucocorticoids or colectomy. **Sacroiliitis** is symmetric, occurs equally in UC and CD, is often asymptomatic, does not correlate with bowel activity, and does not always progress to AS. Anti-TNF agents reduce spinal inflammation.
- **Metabolic bone disease** — low bone mass in **14–42%**; risk increased by **glucocorticoids, ciclosporin, methotrexate, TPN**, malabsorption of calcium/vitamin D, and cytokines (IL-1, IL-6, TNF). Absolute fracture risk ≈ **1% per person-year** (highest age >60; OR ≈1.7 vertebral, 1.6 hip). Screen with **DEXA**, check vitamin D, treat osteopenia/osteoporosis especially on long-term steroids.
- **Osteonecrosis (avascular necrosis)** — death of osteocytes/adipocytes with bone collapse; **hips > knees/shoulders**; major risk factor is **steroid use**. Diagnosed by **MRI/bone scan**; treat with analgesia, decompression, joint replacement.
- Other: clubbing, hypertrophic osteoarthropathy, septic joint (e.g. from psoas abscess), osteomyelitis.

Mucocutaneous (10–20%)

- **Erythema nodosum (EN)** — up to **15% of CD, 10% of UC**; **hot, red, tender 1–5 cm nodules** on the anterior shins/extremities; **parallels bowel activity**, commoner in women, strongly associated with peripheral arthritis. *Avoid biopsy* (scars); treat the underlying bowel disease.
- **Pyoderma gangrenosum (PG) — 1–12% of UC**, less in Crohn's colitis; **independent** of bowel activity, usually severe disease. Begins as a pustule/nodule that ulcerates with **violaceous, undermined borders** and necrotic base, classically on the legs/dorsa of feet or peristomal; shows

pathergy (ulcers at trauma sites) and heals with a **cribriform scar**. Difficult to treat — topical/IV/intralesional glucocorticoids, ciclosporin, infliximab/adalimumab, dapsone, azathioprine; **debridement and colectomy are NOT effective**.

- **Oral** — aphthous stomatitis and "cobblestone" buccal lesions (CD > UC), pyostomatitis vegetans, granulomatous labial/facial swelling, angular cheilitis.
- **Others** — **psoriasis** (5–10%, shared IL23R/IL12B genetics, unrelated to bowel activity), pyoderma vegetans (intertriginous), **Sweet syndrome** (neutrophilic dermatosis), **metastatic CD** (cutaneous non-caseating granulomas remote from gut), perianal skin tags (75–80% of CD), leukocytoclastic vasculitis.

Ocular (1–11%)

- **Episcleritis** — commonest; mild ocular burning/injection, **does not impair vision**, **parallels bowel activity** (3–4%); topical glucocorticoids.
- **Anterior uveitis / iritis** — **ocular pain, photophobia, blurred vision, headache, ciliary flush, miosis**; in IBD often **insidious, bilateral, with posterior extension**; **independent** of bowel activity and may appear in remission. **The one ocular EIM demanding emergent ophthalmology referral** — prompt systemic steroids prevent scarring and visual loss.
- Rare: scleritis (sight-threatening), keratopathy, **night blindness** from vitamin A malabsorption.

Hepatobiliary (10–35%)

- **Primary sclerosing cholangitis (PSC)** — intra- and extra-hepatic bile-duct **inflammation and fibrosis → biliary cirrhosis/failure**. **~5% of UC patients have PSC, but 50–75% of PSC patients have IBD**; both are commonly **pANCA positive**. Often asymptomatic; runs a course **independent** of bowel activity. Diagnose with **MRCP** (initial test of choice; safer than ERCP) showing **multifocal strictures alternating with dilatations ("beaded" ducts)**. Carries a **10–15% lifetime risk of cholangiocarcinoma**, gallbladder-polyp malignancy (cholecystectomy even if <1 cm; annual USG surveillance) and **increased colon-cancer risk → yearly surveillance colonoscopy**. **Small-duct PSC / "pericholangitis"** has a normal cholangiogram and a better prognosis.
- **Cholelithiasis** — **10–35%**, in CD with **ileitis or ileal resection**; bile-acid malabsorption depletes the bile-salt pool → **lithogenic (cholesterol/pigment) stones**.
- **Hepatic steatosis (fatty liver)** — from chronic illness, malnutrition and steroids; **autoimmune hepatitis**, granulomatous hepatitis and **hepatic amyloidosis** are rarer.

Renal/urologic, vascular and other systemic

- **Nephrolithiasis (10–20%)** — highest in CD after **small-bowel resection**; **calcium-oxalate stones** from **enteric hyperoxaluria** — unabsorbed fatty acids bind luminal calcium, leaving oxalate free for colonic absorption. Manage with a **low-oxalate diet**, hydration and control of inflammation. Uric-acid stones (volume depletion), ureteric obstruction, ileovesical fistulas, and mesalamine-associated interstitial nephritis also occur.
- **Thromboembolism** — increased **venous and arterial** thrombosis **even when disease is inactive** (hypercoagulable state: thrombocytosis, raised fibrinogen/factors V & VIII,

hyperhomocysteinaemia, impaired fibrinolysis, tissue-factor microvesicles). Treat with anticoagulation plus control of inflammation; thromboprophylaxis in hospitalised flares.

- **Systemic (secondary/reactive AA) amyloidosis** — long-standing IBD, especially **CD**; causes diarrhoea, constipation and **renal failure**; renal disease responds to **colchicine**.
- **Cardiopulmonary** — endocarditis, myocarditis, pleuropericarditis, interstitial lung disease (rarely 5-ASA-induced — stop the drug).
- **Pancreatitis** — duodenal fistula, ampullary CD, gallstones, PSC, drugs (**azathioprine/mercaptopurine, rarely 5-ASA**), autoimmune, or primary CD of the pancreas.
- **Haematologic** — anaemia of chronic disease, iron and **B12 deficiency** (ileal disease).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Head-to-toe "EIM map" of IBD** — draw a body outline and label by region: **Eyes** — episcleritis, anterior uveitis/iritis; **Mouth** — aphthous stomatitis, pyostomatitis vegetans; **Skin** — erythema nodosum (shins), pyoderma gangrenosum (legs/peristomal), psoriasis, metastatic CD; **Liver/biliary** — PSC (beaded ducts), gallstones, fatty liver; **Joints/spine** — peripheral arthritis (Type 1/Type 2), sacroiliitis, ankylosing spondylitis (bamboo spine); **Bone** — osteoporosis, avascular necrosis of hip; **Kidney** — calcium-oxalate stones; **Vessels** — venous thromboembolism.
- **Two-column flow diagram** "EIMs that PARALLEL vs are INDEPENDENT of bowel activity" with the labels: *Parallel* = peripheral arthritis Type 1, EN, episcleritis, aphthous ulcers; *Independent* = sacroiliitis, AS, uveitis, pyoderma gangrenosum, PSC.

Clinical / Diagnostic significance

- **Activity-linked EIMs** (Type 1 arthritis, EN, episcleritis, oral aphthae) signal a bowel flare and respond to **inducing remission** (5-ASA, steroids, biologics); **activity-independent EIMs** (AS, uveitis, PG, PSC) need their own therapy and do **not** improve with colectomy.
- An EIM such as **PG or PSC can precede the bowel diagnosis by years**, so IBD should be sought in unexplained PG, recurrent uveitis, or cholestatic LFTs with pANCA.
- **HLA-B27** typing supports axial spondyloarthropathy; **MRCP** for cholestatic LFTs; **DEXA + vitamin D** for bone disease; **MRI** for AVN and sacroiliitis.
- **Biologics** (anti-TNF — infliximab/adalimumab; anti-IL-12/23 — ustekinumab/risankizumab; JAK inhibitors; IL-17 inhibitors for spondyloarthritis) treat both gut and several EIMs simultaneously; **vedolizumab** (gut-selective) is less effective for EIMs.
- PSC patients need **annual surveillance colonoscopy** (colon-cancer risk) and **gallbladder USG** (cholangiocarcinoma/polyp risk).

High-yield exam pointers

- **Up to one-third** of IBD patients have ≥1 EIM; commoner in **CD** and in **colonic disease**.
- **Peripheral arthritis**: Type 1 = **pauciarticular (<5 joints), parallels bowel**; Type 2 = **polyarticular (>5 joints), independent**. RF negative, non-deforming.
- **AS/sacroiliitis** are **independent** of bowel activity; **~two-thirds HLA-B27 positive**; do not remit with colectomy.

- **EN** parallels activity (treat the bowel); **PG** is independent, shows **pathergy**, heals with a **cribriform scar**, and **colectomy/debridement do not help**.
- **Uveitis** = the ocular emergency (urgent ophthalmology + systemic steroids); **episcleritis** is benign and parallels activity.
- **PSC**: ~5% of UC have it, 50–75% of PSC have IBD; pANCA+; MRCP shows **beaded strictures**; **10–15% lifetime cholangiocarcinoma** risk; surveillance colonoscopy yearly.
- **Calcium-oxalate stones** via **enteric hyperoxaluria** after ileal disease/resection.
- IBD is a **hypercoagulable state** — VTE risk persists even in remission.
- **Secondary (AA) amyloidosis** in long-standing CD; renal involvement treated with **colchicine**.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Inflammatory Bowel Disease" (extraintestinal manifestations; Table 337-7).
- Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Epidemiology, Pathogenesis, and Diagnosis of Inflammatory Bowel Diseases" (Type 1/Type 2 peripheral arthritis, axial spondyloarthropathy and HLA-B27, ocular, hepatobiliary, renal and vascular EIMs; Table 115.2) and "Management of Inflammatory Bowel Diseases".
- CMDT 2026 — "Gastrointestinal Disorders: Inflammatory Bowel Disease" (current EIM list and biologic management).

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Faecal microbiota transplant

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — The **human microbiota** is the collective community of bacteria, viruses, fungi and Archaea inhabiting body surfaces; the **microbiome** is the aggregate of their genes. A human is best viewed as a *holobiont* — host cells plus microbes — whose >2,000,000 microbial genes dwarf the ~20,000 human genes. **Fecal microbiota transplantation (FMT)** — also termed *intestinal microbiota transplantation (IMT)* or *fecal microbiota replacement therapy (FMRT)* — is the transfer of processed stool from a screened healthy donor into a diseased recipient to correct **dysbiosis** and restore *colonization resistance*. It is the single most successful microbiome-based therapy and the "poster child" for recurrent *Clostridioides difficile* infection (rCDI).

The Human Microbiota — Normal Composition and Function

- **Numbers**: >10,000 bacterial species exist in the human microbiota; the gut alone harbours >1000 species, with 100–200 present in any individual at a given time. Bacteria outnumber human cells by ~1.3:1 (a person is ~56% "bacterial"; with viruses/fungi/Archaea, microbes likely exceed 90% of cells).
- **Five dominant phyla**: *Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria*.
- **Key ecological principles** (Human Microbiome Project, *Nature* 2012):

- Composition is determined more by **body site** than by inter-individual variation (oral, gut, skin, urogenital, nasal each cluster distinctly); stool is the richest, most-studied site.
- Marked **inter-individual variability** in taxa, yet the **functional/metabolic gene capacity is conserved** — *functional redundancy*.
- Modulators of the gut microbiota: **diet, drugs (esp. antibiotics), age, host genetics (small effect), delivery mode, lifestyle, circadian rhythm**.

- **Functions**: colonization resistance against pathogens; education of innate and adaptive immunity (germ-free animals have an immature immune system); short-chain fatty acid (SCFA) production (butyrate/acetate/propionate → regulatory T cells, colonocyte energy, barrier integrity); bile-acid and drug metabolism; vitamin synthesis.

Dysbiosis and the Rationale for FMT

- **Dysbiosis** = a disease-associated shift to a new microbial equilibrium, typically with **reduced alpha- and beta-diversity** and an increase in *Enterobacteriaceae* with loss of *Lachnospiraceae*/butyrate producers.
- In **rCDI**, antibiotics deplete protective anaerobes → loss of colonization resistance → reduced phylogenetic richness with depletion of *Firmicutes* and *Bacteroidetes*.
- **Mechanisms by which FMT cures CDI**: restoration of microbial diversity and **colonization resistance**; conversion of primary to **secondary bile acids** (e.g., by *Clostridium scindens*, which inhibits *C. difficile* germination/outgrowth); restoration of **butyrate producers**; and refilling of open nutritional niches.

FMT — Donor, Preparation, Routes and Safety

Step	Detail
Donor selection	Rigorous screening; exclude donors with communicable disease or microbiome-associated conditions (metabolic disease, neuropsychiatric illness, IBD, immunocompromise). Full medical history + blood, stool and urine testing; informed consent that FMT for CDI is investigational
Stool banking	Pre-screened donor material biobanked frozen (e.g., *OpenBiome*); fresh and freeze-thawed stool have similar efficacy
Routes of delivery	Nasogastric / nasoduodenal tube, **colonoscopy** (most commonly used today), retention **enema**, or **oral capsules**. Lower-GI (colonic/rectal) cure ≈ **92%** vs upper-GI ≈ **81%**
Efficacy in rCDI	Clinical cure **~85–95%**; meta-analysis primary cure **91.2%**, recurrence **5.5%**. Donor FMT > autologous (90% vs 62.5%). Landmark *van Nood* RCT (*NEJM* 2013): nasoduodenal donor feces **81%** vs vancomycin **31%** vs vancomycin + lavage **23%**
Adverse effects	Usually transient (<48 h): altered GI motility (diarrhea/constipation), cramps, bloating. **Serious risk**: transmission of **multidrug-resistant organisms** (reported deaths from ESBL-producing *E. coli*) — drove tighter FDA donor-screening rules
Severe/refractory CDI	Sequential ("multiple") FMT during continued vancomycin improves outcome (100% cure with repeated vs 75% single infusion); poor surgical candidates with fulminant disease may receive FMT by colonoscopy every 3–5 days

Current Trends — FDA-Approved Live Biotherapeutics and Next-Generation Products

The FDA has moved FMT for rCDI from "enforcement discretion" toward **standardized, regulated live biotherapeutic products (LBPs)**. Both 2023-approved products are **adjuncts given only after completion of antibiotic therapy** for rCDI.

Product	Composition / Route	Trial outcome (recurrence)	Notes
Rebyota (fecal microbiota, *live-jslm*; RBX2660)	Donor-derived microbiota **suspension by rectal enema** (150 mL), single dose	**29% vs 42%** placebo at 8 wk (PUNCH CD3)	First FDA-approved FMT product (2023)
VOWST (fecal microbiota spores, *live-brpk*; SER-109)	**Oral capsules** of ethanol-purified bacterial **spores**, 4 capsules once daily × 3 days	**12.4% vs 38.8%** placebo at 8 wk	First FDA-approved **oral** microbiome therapy
Bezlotoxumab	Human monoclonal antibody vs **toxin B**, 10 mg/kg IV (adjunct, not an FMT)	rCDI reduced ~10% absolute (16.5% vs 26.6%)	For high-risk patients during standard antibiotics

- **Adjunctive antibiotic context** (CMDT/IDSA-SHEA): **fidaxomicin** lowers recurrence vs vancomycin (15% vs 25%); FMT/FMRT is reserved for **≥2 recurrences (multiply-recurrent CDI)** after appropriate antibiotic therapy.
- **Pipeline / future generations**: defined **bacterial consortia** (e.g., *Blautia producta* + *Clostridium bolteae* against VRE; *C. scindens* against CDI), **rationally chosen probiotics**, single strains, engineered commensals, and bacteria-derived small molecules / **pharmabiotics** (bacteriocins, phages) — aiming to replace crude stool with standardized "stool substitutes."
- **Expanding (investigational) indications**: as of mid-2024, **>500 registered trials** of FMT — IBD (ulcerative colitis is the best-studied non-CDI indication, mixed results), IBS-D, obesity and **type 2 diabetes** (lean-donor FMT transiently improved insulin sensitivity and butyrate producers), **MDRO/VRE decolonization**, cirrhosis/hepatic encephalopathy, GVHD after HSCT, and augmenting **anti-PD-1 immunotherapy** in melanoma (responder→non-responder stool restored responses).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of the FMT pathway** — boxes left→right: *Screened healthy donor → Stool collection & blood/stool/urine screening → Processing & homogenization (fresh or frozen, stool bank) → Delivery routes (NG/nasoduodenal tube, colonoscopy, enema, oral capsule) → Recipient with rCDI → Restored diversity, colonization resistance, secondary bile acids → Clinical cure ~85–95%*. Label the donor-screening exclusions (IBD, immunocompromise, metabolic/neuropsychiatric disease, communicable disease).
- **Dysbiosis vs healthy gut bar graph** — two stacked bars: *Healthy* (high diversity, abundant Firmicutes/Bacteroidetes, butyrate producers) vs *rCDI dysbiosis* (low diversity, depleted Firmicutes/Bacteroidetes, ↑Enterobacteriaceae, *C. difficile* bloom). Labels: alpha diversity, Firmicutes, Bacteroidetes, Proteobacteria, secondary bile acids.

Clinical / Diagnostic significance

- **Primary established indication**: **multiply-recurrent CDI** — FMT after the second recurrence, given following a course of vancomycin/fidaxomicin; cure rates far exceed antibiotics alone.
- **Investigations before FMT**: confirm toxigenic *C. difficile* by stool toxin/NAAT testing; assess severity (WBC ≥15,000/μL, creatinine ≥1.5 mg/dL = severe). Donors undergo communicable-disease screening to prevent pathogen transmission.
- **Safety governance**: standardized FDA-approved LBPs (Rebyota, VOWST) now offer regulated alternatives to "home-brew" stool, improving reproducibility and reducing transmission risk.
- **Microbiome as a biomarker/therapeutic target**: gut microbiota composition predicts response to checkpoint-inhibitor immunotherapy, modulates drug metabolism (digoxin inactivation by *Eggerthella lenta*; irinotecan toxicity via bacterial β-glucuronidase), and influences vaccine responses.

High-yield exam pointers

- FMT = transfer of screened-donor stool to restore a healthy microbiota; mechanism is restoration of **colonization resistance** and **secondary bile acids**.
- Historical line: 4th-century Chinese *"yellow soup"* → first English description **1958** (pseudomembranous colitis) → landmark **van Nood RCT, NEJM 2013** (81% cure).
- **Best indication = multiply-recurrent CDI**; cure ~**85–95%**; **colonic/lower-GI route > upper-GI**.
- **Two FDA-approved (2023) products**: **Rebyota** (enema, *live-jslm*) and **VOWST** (oral spore capsules, *live-brpk*) — both **adjuncts after antibiotics**.
- **Bezlotoxumab** (anti-toxin-B mAb, 10 mg/kg IV) is an adjunct, *not* an FMT.
- Five dominant gut phyla: **Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria**.
- Main FMT adverse events are transient (cramps, bloating, altered motility); the feared serious event is **MDRO transmission**.
- Non-CDI uses (IBD/UC, IBS, obesity, T2D, MDRO decolonization, immunotherapy augmentation) remain **investigational** (>500 trials).

- Future = defined consortia, engineered commensals, pharmabiotics — replacing crude stool with standardized products.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "The Human Microbiome in Health and Disease"; "Clostridioides difficile Infection, Including Pseudomembranous Colitis."
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "The Enteric Microbiota"; "Antibiotic-Associated Diarrhea and *Clostridioides difficile* Infection" (IMT efficacy data, van Nood RCT, OpenBiome, SER-109/RBX-2660, donor screening).
- **CMDT 2026** — "Gastrointestinal Disorders" (current CDI management; Rebyota and VOWST regimens and trial outcomes; AGA 2024 fecal microbiota-based therapy guidance).

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Gastroduodenal mucosal defence

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — The gastroduodenal epithelium is under constant assault by *endogenous* noxious factors (hydrochloric acid, pepsinogen/pepsin, bile salts) and *exogenous* agents (drugs, alcohol, ingested bacteria). **Gastroduodenal mucosal defense** is the highly integrated biologic system that protects the mucosa from this injury and repairs damage when it occurs. It is best conceptualised as a **three-level barrier — pre-epithelial, epithelial and subepithelial** — coordinated by prostaglandins, nitric oxide and growth factors. Peptic ulcer disease (PUD) ultimately reflects a breakdown in the equilibrium between these defensive forces and the aggressive acid–peptic milieu.

Aggressors versus defenses — the central balance

- **Aggressive (injurious) factors:** gastric acid (HCl) and pepsin are the two principal secretory products capable of inducing mucosal injury; bile salts, NSAIDs, alcohol and *H. pylori* add to the insult.
- **Defensive factors:** mucus, bicarbonate, surface phospholipids, epithelial integrity/restitution, mucosal blood flow, prostaglandins and nitric oxide.
- Acid and pepsin are not purely harmful — they serve physiological roles (protein digestion; absorption of iron, calcium, magnesium and vitamin B12; killing of ingested bacteria), so defense, not acid elimination, is the body's strategy.
- **Ulcer = aggression outweighing defense.** *H. pylori* and NSAIDs (the two commonest causes of PUD) both injure largely by undermining mucosal defense.

The three-tier mucosal defense barrier (overview)

Tier	Anatomical level	Key components	Principal protective action
First line	Pre-epithelial	Mucus–bicarbonate–phospholipid layer	Physicochemical barrier; unstirred layer holding a pH gradient
Second line	Epithelial	Surface epithelial cells, ionic transporters, tight junctions, heat-shock proteins, trefoil peptides, restitution	Maintain intracellular pH, repair small defects
Third line	Subepithelial	Submucosal microvascular bed	Delivers $HCO3^-$, O_2 and nutrients; removes toxic metabolites

Pre-epithelial defense — the mucus–bicarbonate–phospholipid layer

- The **first line of defense** is a **mucus–bicarbonate–phospholipid layer** that acts as a *physicochemical barrier* to multiple molecules, including hydrogen ions.
- **Mucus** is secreted in a regulated fashion by gastroduodenal **surface epithelial cells**; it is **~95% water** plus a mixture of **phospholipids and glycoproteins (mucin)**.
- The mucous gel functions as a **non-stirred water layer**, impeding the diffusion of ions and large molecules such as **pepsin**.
- **Bicarbonate**, secreted by surface epithelial cells into the mucous gel, establishes a **pH gradient from 1–2 at the luminal surface to 6–7 along the epithelial cell surface** — neutralising acid at the very point of contact with the cell.
- Surface **phospholipids** render the luminal surface hydrophobic, repelling the aqueous acid.

Epithelial defense — surface cells, tight junctions and restitution

- The **next line of defense** is provided by **surface epithelial cells** through:
  - **Mucus production** and **epithelial ionic transporters** that maintain intracellular pH and generate bicarbonate.
  - **Intracellular (intercellular) tight junctions** that limit back-diffusion of H^+.
  - **Heat-shock proteins** that prevent protein denaturation and protect against raised temperature, cytotoxic agents and oxidative stress.
  - **Trefoil factor family (TFF) peptides** and **cathelicidins**, which aid surface-cell protection and regeneration.
- **Restitution:** if the pre-epithelial barrier is breached, epithelial cells bordering the injury **migrate to reseal the defect**. This occurs **independent of cell division** and requires **uninterrupted blood flow and an alkaline pH** in the surrounding environment.
- **Larger defects** that restitution cannot repair require **cell proliferation**, regulated by **prostaglandins** and growth factors (**EGF, TGF-α**).
- In tandem, **angiogenesis** restores the injured microvascular bed; **basic FGF** and **VEGF** are key regulators. The peptide **gastrin** further stimulates cell proliferation, migration, invasion,

angiogenesis and autophagy; parietal cells express **sonic hedgehog (Shh)**, implicated in regulating gastric stem cells and restitution.

Subepithelial defense — the gastric microcirculation

- An **elaborate microvascular system in the gastric submucosal layer** is the key subepithelial defense/repair component.
- It supplies **$HCO3^-$** that neutralises the acid generated by parietal cells, delivers **micronutrients and oxygen**, and **removes toxic metabolic by-products**.
- Locally produced vasodilators — **nitric oxide (NO), hydrogen sulfide (H_2S) and prostacyclin (PGI_2)** — protect the mucosa by **vasodilating the microcirculation** and sustaining blood flow.
- Adequate blood flow is the *common denominator* on which restitution and bicarbonate delivery depend; ischaemia is therefore a potent ulcerogenic stress.

Chemical mediators — prostaglandins, the COX system and nitric oxide

- **Prostaglandins (chiefly PGE_2 and PGI_2)** play a *central* role in epithelial defense and repair. They:
  - regulate the release of mucosal **bicarbonate and mucus**,
  - **inhibit parietal-cell acid secretion**,
  - maintain **mucosal blood flow**, and
  - promote **epithelial cell restitution**.
- **Synthesis pathway:** membrane **phospholipids → phospholipase A_2 → arachidonic acid → (cyclooxygenase, COX) → prostaglandins.** COX is the **rate-limiting** enzyme and exists as two isoforms:

Feature	COX-1	COX-2
Expression	**Constitutive ("housekeeping")**	**Inducible** by inflammatory stimuli
Tissue distribution	Stomach, platelets, kidneys, endothelium	Macrophages, leukocytes, fibroblasts, synovial cells
Main products	TXA_2, PGI_2, PGE_2	PGI_2, PGE_2
Role	**GI mucosal integrity**, platelet aggregation, renal function	Inflammation, mitogenesis, bone formation

- The **anti-inflammatory benefit of NSAIDs is via COX-2 inhibition**, whereas their **GI mucosal toxicity (and renal dysfunction) is via COX-1 inhibition** — the basis for COX-2–selective agents (whose cardiovascular hazard led the FDA to withdraw rofecoxib and valdecoxib).
- **Nitric oxide (NO):** NO synthase is **constitutively expressed** in the mucosa and contributes to cytoprotection by **stimulating gastric mucus, increasing mucosal blood flow and maintaining epithelial barrier function**.
- **CNS and hormonal inputs** (e.g., CRF/TRF, CCK, EGF, IGF, TGF-α) modulate defense through multiple pathways.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Three-tier gastroduodenal mucosal defense" (based on Fig. 335-3).** Draw the gastric wall in layers and label: *Lumen (HCl, pepsin, bile salts)*; **Pre-epithelial layer** — *Mucus*, *Bicarbonate (HCO_3^-)*, *Phospholipids*, with a *pH gradient 1–2 (lumen) → 6–7 (cell surface)*; **Epithelial layer** — *Surface epithelial cells*, *Tight junctions*, *Restitution (cell migration)*, *Heat-shock proteins / Trefoil peptides*; **Subepithelial layer** — *Submucosal microcirculation*, *NO / H_2S / Prostacyclin*. Add an overarching label *Prostaglandins, EGF, TGF-α, gastrin*.
- **Diagram 2 — "Prostaglandin synthesis & COX isoforms" (based on Fig. 335-4).** Label the cascade: *Membrane phospholipids → (Phospholipase A_2) → Arachidonic acid → COX-1 / COX-2*; under **COX-1**: *Stomach, kidney, platelets, endothelium → TXA_2, PGI_2, PGE_2 → GI mucosal integrity, platelet aggregation, renal function*; under **COX-2**: *Macrophages, leukocytes, fibroblasts → PGI_2, PGE_2 → inflammation, mitogenesis*.

Clinical / Diagnostic significance

- **NSAID ulcers:** NSAIDs interrupt prostaglandin synthesis, **impairing mucosal defense and repair**, causing injury via a *systemic* mechanism; **neutrophil adherence to the gastric microcirculation** is essential in initiating NSAID-induced injury. Hence prophylaxis targets defense restoration.
- **Misoprostol** — a stable **prostaglandin (PGE_1) analogue**, **200 µg qid**, works by **enhancing mucosal defense and repair**; used to prevent NSAID-induced ulcers. Toxicity: **diarrhoea (10–30%)**, uterine bleeding/contractions; **contraindicated in pregnancy**.
- **Sucralfate** acts locally as a **physicochemical barrier**, binds growth factors (EGF), **enhances prostaglandin synthesis** and stimulates **mucus and bicarbonate secretion**, augmenting defense; dose **1 g qid** (constipation 2–3%; avoid in renal failure — aluminium neurotoxicity).
- **Gastric ulcers** developing despite normal/low acid output imply **impaired mucosal defense** rather than acid hypersecretion — the rationale for biopsy (to exclude malignancy) and for cytoprotective therapy.
- **Smoking** impairs defense (decreased duodenal bicarbonate, mucosal free-radical generation), reduces healing and increases complications such as perforation.
- **Duodenal defense:** duodenal mucosal **bicarbonate secretion is decreased** in active DU; *H. pylori* contributes to this, linking the organism to defective duodenal defense.

High-yield exam pointers

- Defense = **three tiers: pre-epithelial → epithelial → subepithelial.**
- **First line = mucus–bicarbonate–phospholipid layer**; mucus is **95% water + mucin**, acts as a **non-stirred layer**.
- **pH gradient: 1–2 at lumen → 6–7 at epithelial surface** (classic must-write number).
- **Restitution** = epithelial migration to reseal small defects, *no cell division*, needs **blood flow + alkaline pH**.

- **Subepithelial microcirculation** delivers HCO_3^-/O_2 and removes toxins; **NO, H_2S, prostacyclin** maintain flow.
- **Prostaglandins (PGE_2, PGI_2)** are the master cytoprotectants; **COX-1 = GI mucosal integrity**, COX-2 = inflammation.
- **NSAID toxicity = COX-1 inhibition**; benefit = COX-2 inhibition.
- **Misoprostol 200 µg qid** restores defense; contraindicated in pregnancy.
- Growth factors of repair: **EGF, TGF-α, FGF, VEGF**; gastrin and sonic hedgehog aid regeneration.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 335 "Peptic Ulcer Disease and Related Disorders" (Gastroduodenal Mucosal Defense; Prostaglandins/COX; NSAID pathophysiology; treatment of acid-peptic disorders). All physiology, the three-tier model, the pH gradient, COX isoform table, and drug doses (misoprostol 200 µg qid, sucralfate 1 g qid) are faithful to this chapter. *Coverage note:* surface phospholipid hydrophobicity is standard textbook physiology stated only briefly here; no fabrication added beyond the cited chapter.

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GERD

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Gastro-oesophageal reflux (GER) is the *physiological* retrograde movement of gastric contents into the oesophagus that occurs many times daily (chiefly post-prandially) without symptoms or mucosal damage. **GERD** is the *pathological* state — per the Montreal consensus, "a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications." It is best regarded as a **family of conditions** sharing the commonality of excessive reflux, spanning non-erosive reflux disease (NERD), erosive (reflux) oesophagitis, and the complications of stricture, Barrett's metaplasia and adenocarcinoma, plus a set of extra-oesophageal syndromes. It is one of the commonest disorders of mankind, affecting an estimated **10–15% of US adults** (≈20–30% reporting at least weekly symptoms); pooled worldwide weekly prevalence is ~13%, highest in **South Asia and South-East Europe (>25%)**.

Pathophysiology — the antireflux barrier and mechanisms of reflux

- **The antireflux barrier (oesophago-gastric junction, OGJ)** is a composite valve dependent on: (1) the intrinsic **lower oesophageal sphincter (LES)** tone; (2) the **crural diaphragm** providing extrinsic "pinch-cock" squeeze (imposing rhythmic 5–10 mmHg rises, up to 50–150 mmHg on straining); (3) the **intra-abdominal segment** of oesophagus; (4) the **acute angle of His** with its flap-valve; and (5) the **phreno-oesophageal ligament**.
- **Mechanisms of pathological reflux** (Sleisenger): (1) **Transient LES relaxations (tLESRs)** — the dominant mechanism, accounting for nearly all reflux in normals and **50–80% in GERD**; these are vagally-mediated, swallow-independent, last >10 s, are not followed by peristalsis, are accompanied by crural inhibition, and are triggered by **proximal gastric distension** (the belch

reflex); (2) **low basal LES pressure** (hypotensive sphincter, present in up to 50% of severe erosive GERD); (3) **swallow-associated LES relaxation**; and (4) **straining during periods of low LES pressure**.

- **Anatomical disruption** progressively unhinges the barrier: widening of the diaphragmatic hiatus with weak crural function; loss of the intra-abdominal segment and flap valve; **axial (sliding) hiatal hernia** (which traps acid in the hernia sac that refluxes during swallow-induced relaxation); and increased OGJ compliance.
- **Defective acid clearance** prolongs mucosal contact — refluxate is normally returned by peristalsis and the residual acid neutralised by **swallowed salivary bicarbonate**; impaired peristalsis (e.g., scleroderma) and reduced salivation worsen exposure.
- **Aggravating factors:** abdominal/truncal obesity, pregnancy, gastric hypersecretory states, delayed gastric emptying, and disrupted peristalsis.
- **Mucosal injury** results from acid + pepsin (and weakly-acidic bile, which persists despite PPIs); current evidence favours a **cytokine-mediated inflammatory pathway** rather than direct caustic burn.

Hiatal hernia (companion lesion)

Type	Description	Note
Type I (sliding)	OGJ + cardia translocate cephalad through hiatus	**~95%** of all; main GERD association
Type II (para-oesophageal)	Fundus herniates; OGJ fixed at hiatus	risk of volvulus/strangulation
Type III	Combined sliding + para-oesophageal	large hernias → "upside-down stomach"
Type IV	Non-gastric viscus herniates (commonly colon)	surgical repair often advocated

Clinical features

- **Typical (oesophageal) symptoms: Heartburn (pyrosis)** — retrosternal burning rising from the epigastrium, 30–60 min after meals, on bending or recumbency, relieved by antacids; and **regurgitation** — effortless return of sour/bitter fluid without nausea or retching. Heartburn severity correlates **poorly** with the presence/grade of oesophagitis.
- **Less common:** dysphagia (>30% — usually peptic stricture, Schatzki ring or dysmotility), chest pain (closely mimics angina — *cardiac disease must be excluded first*), water brash (reflex hypersalivation) and globus.
- **Important caveat:** *odynophagia is uncommon in reflux disease* and should prompt a search for pill, infectious or eosinophilic oesophagitis.
- **Extra-oesophageal syndromes** (associations, not always causal) — established: **chronic cough, laryngitis, asthma, dental erosions**; proposed: pharyngitis, chronic bronchitis, pulmonary fibrosis, sinusitis, arrhythmias, sleep apnoea, recurrent aspiration. Mechanisms: direct microaspiration/contact vs a **vago-vagal reflex** (oesophageal afferent activation → reflex bronchospasm, cough).

- **Differential diagnosis:** coronary artery disease (priority), infectious/pill oesophagitis, eosinophilic oesophagitis (EoE), peptic ulcer disease, functional dyspepsia, biliary colic, and oesophageal motility disorders (achalasia).

Diagnostic approach

- **Empirical PPI trial** is the dominant first strategy for typical symptoms **without alarm features** — once-daily PPI for 4–8 weeks.
- **Upper GI endoscopy (EGD)** — indicated for **alarm features** (dysphagia, odynophagia, weight loss, iron-deficiency anaemia, GI bleed), failure of empirical therapy, and **Barrett screening** (weekly symptoms ≥5 yr plus ≥3 risk factors: age >50, truncal obesity, male sex, White race, current/prior smoking, family history). Erosive oesophagitis at the OGJ is the endoscopic hallmark but is present in only **~one-third** of GERD patients.
- **Los Angeles (LA) classification** grades erosive oesophagitis (see table) — the universally used severity score.
- **Ambulatory reflux (pH / pH-impedance) testing** — demonstrates the physiological abnormality when endoscopy is normal (NERD); 24–96 h recording, with **acid exposure time (% day pH <4) >6%** indicative of GERD (Sleisenger upper limit of normal ~4–5.5%). **Impedance-pH** additionally detects **non-acid/weakly-acidic reflux** — valuable for persistent symptoms on PPI. Wireless capsule (Bravo) extends recording to 48–96 h.
- **High-resolution manometry** — not diagnostic of GERD but mandatory **before antireflux surgery** to exclude achalasia and assess peristaltic reserve.
- **Barium oesophagogram** — limited diagnostic role; used to size a hiatal hernia or define a stricture pre-operatively.

LA grade	Endoscopic appearance
A	≥1 mucosal break(s) **≤5 mm**, confined to a fold
B	≥1 mucosal break(s) **>5 mm**, confined to folds, not continuous between fold tops
C	Mucosal break(s) **continuous between tops of ≥2 folds**, but **<75%** circumference
D	**Circumferential** mucosal break (**≥75%** of circumference)

Complications

- **Erosive oesophagitis** and **peptic stricture** (up to ~5%; gradual solid-food dysphagia, treated by dilation to 15–18 mm + long-term PPI) — both now rare in the potent-antisecretory era.
- **Barrett's oesophagus** — replacement of distal squamous epithelium by **salmon/orange columnar epithelium extending >1 cm above the OGJ**, with **specialised intestinal metaplasia (goblet cells)** on biopsy. It is the precursor of **oesophageal adenocarcinoma**, progressing through low- and high-grade dysplasia; cancer risk **~0.1–0.5% per year** (an ~11-fold relative increase). Highest risk: obese White males in the sixth decade.
- **Surveillance/therapy of Barrett's:** non-dysplastic — endoscopic surveillance every 3–5 years; **low-grade dysplasia** — endoscopic eradication or 6–12-monthly surveillance; **high-grade dysplasia / intramucosal cancer (Tis–T1a)** — endoscopic eradication therapy (**EMR of nodules**

+ **radiofrequency ablation**), which has supplanted oesophagectomy (the latter carries 3–10% mortality).

- Other: haemorrhage (rare), and the rising incidence of adenocarcinoma paralleling GERD.

Treatment

- **Lifestyle modification: weight reduction** is the most evidence-based measure; elevate head end of bed and avoid recumbency for 3 h after meals (nocturnal symptoms); avoid refluxogenic foods (fatty foods, chocolate, peppermint, alcohol, coffee) and irritant acidic foods (citrus, tomato); stop smoking; left-lateral sleeping position.
- **Pharmacotherapy — antisecretory hierarchy: PCAB > PPI > H2RA** for healing oesophagitis.
- **PPIs are first-line** — taken **30–60 min before breakfast**; achieve heartburn control in 70–80% and heal erosive oesophagitis in 75–85%; **regurgitation responds less well**. Inadequate response → twice-daily dosing or switch agent.
- **Maintenance:** >80% relapse within ~3 months of stopping; severe oesophagitis, Barrett's or stricture warrant long-term PPI at the **lowest effective dose** (continuous, intermittent or "on-demand").
- **Potassium-competitive acid blocker (PCAB) — vonoprazan 20 mg OD**, FDA-approved, may be taken with meals, fast and sustained acid suppression; superior to lansoprazole in **severe LA C/D oesophagitis (92% vs 72% healing)**; reserved for PPI-refractory disease (cost, fewer long-term safety data).
- **Anti-reflux surgery — laparoscopic (Nissen) fundoplication** — efficacy similar to PPI for oesophagitis; for refractory/regurgitation-predominant disease or patients declining lifelong medication. Adverse effects: dysphagia, gas-bloat, inability to belch, flatulence. **Magnetic sphincter augmentation (LINX)** is an option for hiatal hernia <3 cm; **gastric bypass** preferred in obesity with GERD.

Drug class	Examples & typical dose	Role
PPI	Omeprazole 20 mg, rabeprazole 20 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, esomeprazole 20–40 mg, pantoprazole 40 mg	First-line; before breakfast
PCAB	Vonoprazan 20 mg OD	Refractory / severe LA C–D
H2RA	Famotidine, nizatidine, cimetidine	Mild/intermittent, on-demand, nocturnal breakthrough
Antacids / alginate	Magnesium/aluminium salts, alginate	Rapid, short (<2 h) relief
tLESR inhibitor	Baclofen 5–20 mg TID (GABA-B agonist)	Adjunct; limited by drowsiness/nausea

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Anti-reflux barrier at the oesophago-gastric junction** — label: tubular oesophagus, **lower oesophageal sphincter (LES)**, **crural diaphragm**, **intra-abdominal oesophageal segment**, **angle of His / flap valve**, phreno-oesophageal ligament, gastric cardia, squamo-columnar (Z) junction.
- **Los Angeles grading panel (A–D)** — four distal-oesophageal sketches showing: small break ≤5 mm on a fold (A); break >5 mm on a fold (B); breaks bridging ≥2 fold-tops, <75% circumference (C); circumferential ≥75% break (D).

Clinical / Diagnostic significance

- A simple **empirical PPI trial** both treats and supports the diagnosis in uncomplicated typical GERD — avoiding unnecessary endoscopy.
- **Alarm symptoms mandate prompt endoscopy** to exclude stricture, Barrett's and malignancy.
- **pH-impedance off/on PPI** distinguishes true acid reflux, non-acid reflux, **reflux hypersensitivity** and **functional heartburn** (≈30% of "PPI-refractory" patients) — the latter respond to neuromodulators (low-dose imipramine/nortriptyline) and CBT, not escalation of acid suppression.
- **PPI long-term safety:** reassuringly safe; small possible increases in enteric infection (incl. *C. difficile*), SIBO and micronutrient malabsorption (iron, B12, magnesium); reported links to fracture, CKD/interstitial nephritis, dementia and CVD are **association, not proven causation** — use the lowest effective dose.
- Exclude **Zollinger-Ellison syndrome** in refractory severe erosive oesophagitis.

High-yield exam pointers

- GER is physiological; **GERD = troublesome symptoms or complications (Montreal)** — a spectrum: NERD → erosive oesophagitis → stricture → Barrett's → adenocarcinoma.
- **tLESR is the commonest mechanism** of reflux (not low LES pressure); triggered by gastric distension (belch reflex).
- **Heartburn + regurgitation = typical; odynophagia is atypical** → think pill/infectious/eosinophilic oesophagitis.
- **Erosive oesophagitis is seen in only ~1/3** of GERD; remember the **LA classification A–D** (D = circumferential ≥75%).
- **Acid exposure time >6% (pH <4)** = pathological reflux; impedance detects non-acid reflux.
- **Barrett's** = salmon mucosa >1 cm above OGJ with **intestinal metaplasia (goblet cells)**; adenocarcinoma risk ~0.1–0.5%/yr.
- **Antisecretory potency: PCAB > PPI > H2RA**; PPI taken 30–60 min pre-breakfast; **vonoprazan** superior in LA C/D.
- **Weight loss** is the best-evidenced lifestyle measure; **laparoscopic fundoplication** / LINX for refractory or regurgitation-predominant disease.
- Always **exclude cardiac chest pain** before attributing chest pain to GERD.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diseases of the Esophagus" (GERD pathophysiology, symptoms, complications, Barrett's, treatment).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Gastroesophageal Reflux Disease" (antireflux barrier, mechanisms of reflux/tLESR, Los Angeles classification, reflux testing, PPI/H2RA/baclofen regimens) and "Barrett Esophagus".
- **CMDT 2026** — "Gastrointestinal Disorders: Gastroesophageal Reflux Disease" (diagnostic algorithm, Barrett surveillance, PPI dosing, vonoprazan/PCAB, fundoplication and magnetic sphincter augmentation, ACG 2022 screening criteria).

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Hepatitis D

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Hepatitis D virus (HDV), the *delta agent*, is a defective (satellite) single-stranded RNA virus and the only member of the genus *Deltavirus* (family *Deltaviridae*). It is the smallest known infectious agent of humans and is **replication-defective**: it absolutely requires the helper function of hepatitis B virus (HBV) — specifically **HBsAg** — for assembly, secretion and onward infection, so HDV can only infect people who are simultaneously or already infected with HBV. Although uncommon, HDV produces the **most severe form of chronic viral hepatitis**, with accelerated progression to cirrhosis, decompensation and hepatocellular carcinoma (HCC).

Virology and structure

- **Defective satellite virus**: requires HBsAg (helper from HBV/hepadnaviruses) for its life cycle; intracellular **RNA replication can occur without HBV**, but HBsAg is needed for **assembly and entry**, not replication.
- **Virion**: small, ~35–37 nm, formalin-sensitive, **hybrid particle** — an outer envelope of HBsAg (small, middle, large forms) surrounding an inner ribonucleoprotein of **hepatitis D antigen (HDAg)** complexed to the genome. Only virions bearing **large HBsAg** are infectious.
- **Genome**: ~1700-nucleotide, **circular, single-stranded, negative-sense RNA**, non-homologous with HBV DNA. High guanosine–cytosine content (~74% internal base-pairing) folds it into a stable **rod-like structure** containing a self-cleaving, self-ligating **ribozyme** — features shared with **plant viroids/satellite viruses**.
- **Replication**: in the hepatocyte **nucleus** using host **RNA polymerase II** (a host enzyme, hence not targetable by conventional antivirals), by a **double rolling-circle** mechanism with ribozyme-mediated cleavage of multimers.
- **HDAg** is the *only* HDV-encoded protein (single open reading frame) and exists in two forms generated by **RNA editing** (adenosine deaminase converts the UAG stop codon to UGG/tryptophan):
  - **Small HDAg** (195 aa / 24 kDa) — *promotes/facilitates* HDV RNA replication.

- **Large HDAg** (214 aa / 27 kDa) — *suppresses* replication but is **required for virion assembly**; differs by 19 C-terminal amino acids carrying a **prenylation (farnesylation) signal** essential for interaction with HBsAg.

- **Entry receptor**: both HBV and HDV enter hepatocytes via the **sodium taurocholate co-transporting polypeptide (NTCP)** after initial binding to heparan-sulfate proteoglycans through the pre-S1 domain of large HBsAg — the molecular basis for the entry-inhibitor *bulevirtide*.
- **Genotypes**: **eight genotypes (1–8)**. Genotype 1 is worldwide and predominant; genotype 2 in the Far East/Russia; **genotype 3 in the Amazon basin** (most divergent, severe acute disease/ALF); genotype 4 in the Far East; genotypes 5–8 in Africa.

Epidemiology and transmission

- HDV infects an estimated **~5% of the world's HBsAg carriers — roughly 12–15 million people** (Harrison cites ~12 million; Sleisenger ~15 million).
- High-endemic zones: **Mediterranean basin, Middle East, central/northern Asia, west & central Africa, Taiwan and the Amazon basin**; low in North America, northern Europe, Japan and Korea. Prevalence has fallen since the 1980s, largely due to **HBV vaccination**.
- **Two epidemiologic patterns** (Harrison):
  - *Endemic* (Mediterranean) — transmitted by **close personal/nonpercutaneous contact** among HBV carriers.
  - *Nonendemic* (USA, northern Europe) — confined to those with frequent blood exposure: **persons who inject drugs (PWID)** and **haemophiliacs**; in US HBsAg-positive PWID prevalence is 11–36%, haemophiliacs ~19%.
- **Routes** mirror HBV: parenteral (injection drug use), sexual and intrafamilial in endemic areas. Unlike HBV, **perinatal transmission is not a major route**.
- Explosive outbreaks of severe hepatitis occur (e.g., *"Lábrea fever"* / "black fever" in the Amazon basin — genotype 3).

Two patterns of infection: co-infection vs superinfection

Feature	HBV–HDV Co-infection	HDV Superinfection
Setting	Simultaneous acute HBV + HDV in a susceptible host	Acute HDV in an established **chronic HBV carrier**
Acute illness	Often **biphasic** ALT rise (1st = HBV, 2nd = HDV); usually self-limited	Severe acute hepatitis; may mimic a "flare" of chronic HBV
Chronicity	**Low (<5%)** — same as HBV alone; >90% resolve	**High (~90%)** progress to chronic HDV
Fulminant/ALF risk	Up to ~5%	Up to ~20% (highest of all viral hepatitides)
IgM anti-HBc	**Positive** (marker of acute HBV)	**Negative** (IgG anti-HBc positive) — *key discriminator*
Anti-HDV	IgM anti-HDV, often transient/low-titre	IgM + IgG anti-HDV, high and **sustained**

Feature	HBV–HDV Co-infection	HDV Superinfection
HBV DNA	Variable	**Low** — HDV suppresses HBV replication
Outcome	Generally good if resolves	Worsening liver disease; rapid cirrhosis

Diagnosis (serology and virology)

- **Screening is targeted, not routine** — test HBsAg-positive persons who: inject drugs, are from endemic regions, have an unexplained acute flare/severe or protracted hepatitis, are HBV DNA–negative yet have active liver disease, or show rapid progression to cirrhosis.
- **First-line test**: **total anti-HDV (IgM + IgG)** — invariably appears after exposure. **IgM anti-HDV** indicates current/recent infection and parallels disease activity (high titres ≈ serious liver damage). **IgG anti-HDV is not protective**.
- **HDV RNA by RT-PCR** is the **gold standard for current/active infection** and the only reliable way to distinguish chronic infection from recovery; a WHO international standard now aids quantification.
- **HDAg**: detectable transiently in early acute infection and in liver (immunohistochemistry); intrahepatic HDAg is a proposed histologic "gold standard" but is negative in up to 50% of long-standing cases.
- **Distinguishing co-infection from superinfection** rests on **IgM anti-HBc** (positive in co-infection, absent in superinfection) plus the HBV DNA trend (low in HDV superinfection vs rising in a true HBV flare).

Treatment

- **General principle**: HDV depends on **host RNA polymerase**, which cannot be targeted by standard nucleoside analogues; hence treatment is difficult and outcomes are modest.
- **Acute hepatitis D** — supportive; **liver transplantation** for acute liver failure.
- **Chronic hepatitis D**:
  - **Pegylated interferon-α (PegIFN-α)** is the only established/approved therapy — **180 µg subcutaneously weekly for ≥48 weeks (≈1 year)**; durable off-treatment HDV-RNA clearance in only ~**20–50%**, with frequent late relapse. High-dose conventional IFN-α (9 MU thrice weekly × 12 months) improves long-term survival in some.
  - **Nucleos(t)ide analogues (lamivudine, adefovir, tenofovir, entecavir) are ineffective against HDV** and add no benefit to PegIFN; reserve them to treat **underlying HBV if HBV DNA >2 × 10^3 IU/mL**.
  - **IFN is contraindicated in advanced/decompensated cirrhosis.**
- **Novel agents** (HDV-specific):
  - **Bulevirtide (Myrcludex B)** — myristoylated lipopeptide **NTCP entry inhibitor** blocking HBV/HDV hepatocyte entry; achieves significant HDV-RNA decline and ALT normalisation; granted **conditional EMA authorisation in 2020** (FDA review anticipated).

- **Lonafarnib — farnesyltransferase (prenylation) inhibitor** that blocks large-HDAg–HBsAg assembly; combined with **ritonavir** (CYP3A4 boost) ± PegIFN.
- **Nucleic-acid polymers (e.g., REP 2139)** — inhibit **HBsAg release**, producing marked HDV-RNA and HBsAg reduction (investigational).

- **Liver transplantation** is the option for HDV decompensated cirrhosis; outcome is **better than for HBV alone** and **graft reinfection is <10%** with HBV immunoglobulin (HBIG) ± nucleos(t)ide.

Prevention

- **HBV vaccination prevents HDV** in HBV-susceptible persons (no HBsAg → no HDV life cycle) — the cornerstone of prevention.
- **No specific HDV vaccine exists**, and the HBV vaccine **cannot protect existing HBV carriers**; such patients need behavioural counselling to avoid HDV exposure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HDV virion structure**: outer **HBsAg envelope** (label small/middle/large HBsAg); inner **ribonucleoprotein core**; **small & large HDAg**; **circular single-stranded (–)RNA genome (~1700 nt, rod-like)**; **NTCP receptor** on hepatocyte membrane with pre-S1 binding.
- **Serologic course — co-infection vs superinfection**: two timelines plotting **ALT, HBsAg, HDV RNA, IgM anti-HDV, total anti-HDV** and **IgM anti-HBc**; highlight the **biphasic ALT** of co-infection and **IgM anti-HBc positive (co-infection) vs negative (superinfection)** as the discriminator.

Clinical / Diagnostic significance

- Suspect HDV in any HBsAg-positive patient with **unexpectedly severe, fulminant, biphasic or rapidly progressive hepatitis**, or an unexplained flare of "stable" chronic hepatitis B.
- HDV suppresses HBV replication → **low/undetectable HBV DNA with active liver disease** is a clue to delta superinfection.
- Chronic HDV carries a **3–6 fold higher risk of HCC** and roughly **doubled mortality** versus HBV monoinfection; reported annual cirrhosis ~4% and HCC ~2.8%; 5-year survival after cirrhosis ~81–90%.
- Because therapy is unsatisfactory, **prevention via universal HBV vaccination** is the highest-yield intervention.

High-yield exam pointers

- HDV = **defective/satellite RNA virus**, genus *Deltavirus*, needs **HBsAg** helper; smallest human pathogen.
- Genome: **circular, ss, negative-sense ~1.7 kb RNA**, viroid-like, **ribozyme**, replicates via host **RNA pol II**.
- **HDAg** is the only viral protein — **small HDAg = replication**, **large HDAg = assembly (prenylated)**.
- **Entry via NTCP** → rationale for **bulevirtide**.

- **Co-infection** = self-limited, chronicity <5%, **IgM anti-HBc +**; **Superinfection** = ~90% chronic, severe, **IgM anti-HBc −**.
- **Highest fulminant-hepatitis risk** of all viral hepatitides (≈20% in superinfection).
- Diagnosis: **total/IgM anti-HDV + HDV RNA (RT-PCR, gold standard)**; IgG anti-HDV **not protective**.
- Treatment: **PegIFN-α ~48 weeks**; nucleos(t)ides **ineffective**; new drugs = **bulevirtide, lonafarnib, REP 2139**.
- Prevention: **HBV vaccine** (no separate HDV vaccine); cannot protect existing HBV carriers.
- **Lábrea fever** = severe Amazonian HDV genotype 3 outbreak.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Viral Hepatitis" (HDV virology, epidemiology, two epidemiologic patterns, serologic markers) and "Chronic Hepatitis" (chronic delta hepatitis, IFN/bulevirtide/lonafarnib therapy, transplantation).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Hepatitis D" (structure, life cycle, genotypes, pathogenesis, diagnostic serologic patterns, natural history, treatment and prevention) — primary subspecialty source.
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (current diagnosis and PegIFN-based management of chronic hepatitis D).

Coverage note: Corpus coverage is excellent and consistent; bulevirtide is recorded as conditionally EMA-approved (2020) with FDA review "anticipated" in this edition — quoted as such rather than asserting current FDA status.

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Hepatorenal syndrome

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Hepatorenal syndrome (**HRS**) is a *functional* form of acute kidney injury that develops in advanced cirrhosis (or acute/fulminant liver failure) with ascites, in which renal hypoperfusion arises from extreme splanchnic and systemic arterial vasodilatation rather than from any structural renal lesion — *the kidneys are histologically normal* and function can be restored by liver transplantation or by transplanting the same kidney into a non-cirrhotic recipient. It is essentially a diagnosis of exclusion, recognised after other causes of AKI are ruled out. The term was first coined in 1939; HRS complicates roughly **10% of patients with advanced cirrhosis** and carries a grave prognosis unless the underlying liver disease is reversed.

Epidemiology and Precipitants

- Acute renal dysfunction occurs in **15–25%** of hospitalised cirrhotics; HRS accounts for **10–30%** of these. The annual incidence of HRS in cirrhotics with ascites is ~8% (up to 40% in some series).

- HRS develops in ~**30%** of patients admitted with **spontaneous bacterial peritonitis (SBP)** or other infection, ~**25%** with severe alcohol-associated hepatitis, and ~**10%** of those undergoing serial large-volume paracentesis (LVP).
- **Common precipitants** (all reduce effective circulating volume or renal perfusion): bacterial infection/SBP and sepsis; GI/variceal haemorrhage; over-diuresis; diarrhoea from lactulose; LVP without colloid (albumin) replacement; and nephrotoxins — **NSAIDs, ACE inhibitors, ARBs**, and certain antibiotics.

Pathophysiology — the "three-hit" model

The current model (International Club of Ascites/Sleisenger) integrates three interacting components:

- **1. Splanchnic and systemic arterial vasodilatation** — the hallmark of progressive portal hypertension. Driven by endogenous vasodilators (**nitric oxide**, carbon monoxide, glucagon, prostacyclin, adrenomedullin, endogenous opiates), often amplified by bacterial translocation and inflammation. This pooling of blood in the splanchnic bed lowers the **effective arterial blood volume** and arterial pressure, creating a *hyperdynamic circulation* (high cardiac output, low systemic vascular resistance).
- **2. Compensatory renal vasoconstriction** — the fall in effective volume activates the **sympathetic nervous system**, the **renin–angiotensin–aldosterone system (RAAS)**, and non-osmotic release of **arginine vasopressin (ADH)**. Intrarenal mediators (endothelins, reduced vasodilatory prostaglandins, kallikreins, F2-isoprostanes) tip the balance toward intense renal vasoconstriction → rise in renal vascular resistance, fall in renal perfusion and **GFR**, with avid Na^+/water retention. Sustained vasoconstriction can eventually cause tubular damage, so a *functional* syndrome may evolve into an *organic* one.
- **3. Cardiac dysfunction (cirrhotic cardiomyopathy)** — a relatively low cardiac output fails to compensate for the fall in systemic vascular resistance, further reducing renal perfusion; an acute drop in cardiac output is often the precipitant of type 2 HRS.

Classification and Diagnostic Criteria

HRS is now classified by the **International Club of Ascites (ICA, 2015)** using AKI definitions, replacing the older "type 1 / type 2" terminology:

Old term	New term	Course / features
Type 1 HRS	**HRS–AKI**	Rapid, progressive impairment; ICA-AKI **stage 2 or 3**; classically ≥ doubling of creatinine to > **2.5 mg/dL** (or halving of CrCl to < 20 mL/min) in < **2 weeks**; poor prognosis
Type 2 HRS	**HRS–CKD (non-AKI)**	Slow, steady decline in GFR; moderate, *stable* creatinine rise; closely linked to **diuretic-resistant ascites**; better outcome than HRS-AKI

ICA-AKI definition and staging of AKI in cirrhosis:

Parameter	Definition
AKI	Rise in serum creatinine of **0.3 mg/dL (26.4 µmol/L) within 48 h**, OR a **≥ 50% rise from baseline** presumed to have occurred within the prior 7 days

Parameter	Definition
Stage 1	Rise of 0.3 mg/dL, or 1.5–2× baseline
Stage 2	> 2–3× baseline
Stage 3	> 3× baseline, OR creatinine ≥ **4 mg/dL** with an acute rise ≥ 0.3 mg/dL, OR initiation of **renal replacement therapy (RRT)**

ICA diagnostic criteria for HRS (Box 94.2):

- **Cirrhosis with ascites**
- Diagnosis of **AKI by ICA-AKI criteria**
- **No, or insufficient, response** after ≥ 2 days of **diuretic withdrawal** and **volume expansion with albumin 1 g/kg/day** (max 100 g/day)
- **Absence of shock**
- **No recent nephrotoxic drugs** (NSAIDs, aminoglycosides, contrast)
- **Absence of parenchymal kidney disease** — proteinuria < 500 mg/day, no microhaematuria (< 50 RBC/HPF), and normal renal ultrasound

Note on creatinine: because sarcopenic cirrhotics have low muscle mass and reduced urea synthesis, serum creatinine **underestimates** the true GFR — even small increases must be taken seriously. Oliguria is *not* used as a criterion in cirrhosis, since these patients are frequently oliguric with Na^+ retention despite a near-normal GFR.

Clinical features and differential diagnosis

- Usually **oligo/asymptomatic**; clues are progressive azotaemia, **oliguria, hyponatraemia (dilutional)** and a **very low urinary sodium (< 10 mmol/L)** with benign sediment in a patient with tense ascites and decompensated liver disease.
- HRS may present as new or worsening **hepatic encephalopathy** as urea/ammonia rise.
- **Differentials to exclude:** prerenal azotaemia/hypovolaemia (responds to volume), **acute tubular necrosis** (granular casts, FeNa often higher, fails albumin challenge), drug-induced acute interstitial nephritis, glomerulonephritis, and post-renal obstruction. Albumin volume challenge plus urinary biomarkers (e.g., **NGAL**, IL-18 — investigational) help separate ATN from HRS.

Management

Therapy aims to reverse splanchnic vasodilatation with **vasoconstrictors** and expand the central volume with **albumin**, as a bridge to definitive treatment (liver transplant) or until a precipitant (SBP, bleeding) resolves.

General / supportive: stop **diuretics, NSAIDs, ACEi/ARB** and all nephrotoxins; identify and treat infection (antibiotics, SBP); **IV albumin 1 g/kg/day** (max 100 g) on presentation, then **20–60 g/day** titrated to a CVP of ~10–15 cm H_2O (avoid pulmonary oedema).

Agent (always with albumin)	Mechanism	Dose / titration
Terlipressin *(preferred; FDA-approved)*	Selective **V1 vasopressin-receptor agonist** → splanchnic vasoconstriction	Sleisenger: **1 mg IV q4h**, ↑ to 2 mg IV q4h if creatinine not improved by 25% by day 3. CMDT: **0.85 mg IV q6h**, titrate by creatinine response; continuous infusion better tolerated than boluses
Midodrine + Octreotide	α1-agonist (midodrine) + somatostatin analogue suppressing vasodilators (octreotide)	Midodrine **7.5–15 mg PO TID** (to a max 15 mg TID) + octreotide **100–200 µg SC TID** (or 25 µg IV bolus then 25 µg/h); titrate MAP rise ≥ 15 mmHg
Norepinephrine	α1-adrenergic agonist	**0.1–0.7 µg/kg/min IV** infusion; titrate MAP rise ≥ 10 mmHg (requires ICU/central line)

- Vasoconstrictor therapy is given for a **maximum of ~7–14 days** until creatinine returns to within 0.3 mg/dL of baseline, or until transplant/TIPS. Pooled trials (**OT-0401, REVERSE**) showed terlipressin + albumin reversed HRS more often than albumin alone (**27% vs 14%**); head-to-head, terlipressin out-performed midodrine + octreotide (~70% vs ~29% renal recovery). Watch for **ischaemic/cardiovascular complications** of terlipressin.
- **TIPS** (transjugular intrahepatic portosystemic shunt) — most useful in **type 2 HRS / diuretic-resistant ascites**; improves creatinine and natriuresis but may worsen encephalopathy and hepatic function; not for advanced decompensation.
- **Liver transplantation** — the **definitive and only treatment that reverses both liver and renal failure**; HRS resolves in ~83% post-LT, 3-year survival ~60% (vs 70–80% without HRS); up to 35% need ongoing RRT.
- **RRT / MARS** (molecular adsorbent recirculating system) — temporising/experimental, of uncertain benefit; reserve dialysis as a bridge to transplant.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow chart of HRS** — boxes/arrows: *Cirrhosis + portal hypertension → splanchnic & peripheral arterial vasodilatation (NO, CO, glucagon, prostacyclin) → ↓ effective circulatory volume → ↓ arterial blood pressure → ↑ cardiac output (hyperdynamic) + activation of RAAS, SNS, ↑ ADH → renal vasoconstriction → ↓ renal perfusion → ↓ GFR → Hepatorenal syndrome*. **Add side-arrow** "triggers"**: SBP/sepsis, GI bleed, LVP, diuretics, diarrhoea, ACEi/ARB/NSAIDs; and** "cirrhotic cardiomyopathy (CCM)**" reducing cardiac output.
- **Management ladder** — *Stop diuretics & nephrotoxins → IV albumin 1 g/kg + treat infection → Vasoconstrictor (Terlipressin / Norepinephrine / Midodrine+Octreotide) + albumin → if refractory: TIPS or RRT bridge → Liver transplantation (definitive).*

Clinical / Diagnostic significance

- HRS is a **marker of end-stage liver disease** and a key driver of mortality in decompensated cirrhosis; its onset should trigger **transplant evaluation** and MELD recalculation (creatinine is a MELD component).

- **Prevention is paramount:** IV albumin with LVP, albumin in SBP (**1.5 g/kg day 1, 1 g/kg day 3** — reduces renal failure and improves survival), antibiotic prophylaxis for SBP/GI bleed, and pentoxifylline in severe alcohol-associated hepatitis.
- Always **exclude ATN and prerenal azotaemia** before labelling HRS — the albumin challenge (1 g/kg/day × 2 days after stopping diuretics) is both diagnostic and therapeutic.
- **Prognosis:** mortality correlates with **MELD score** and a systemic inflammatory response; AKI-HRS is often irreversible when a systemic infection is present. The **3-month survival** in cirrhotic HRS (~15%) is far worse than renal failure from infection (31%), hypovolaemia (46%) or parenchymal kidney disease (73%).

High-yield exam pointers

- HRS = **functional** AKI; kidneys are **histologically normal** and reverse with liver transplant.
- Central lesion = **splanchnic arterial vasodilatation (NO-mediated)** → ↓ effective volume → RAAS/SNS/ADH-driven **renal vasoconstriction**.
- **Type 1 = HRS-AKI** (rapid, creatinine usually > 2.5 mg/dL in < 2 weeks); **Type 2 = HRS-CKD** (slow, with refractory ascites).
- Diagnosis is by **ICA criteria** — cirrhosis + ascites + ICA-AKI, **no response to albumin 1 g/kg × 2 days**, no shock, no nephrotoxins, no parenchymal disease.
- Typical labs: **oliguria, hyponatraemia, urine Na^+ < 10 mmol/L**, benign sediment.
- **Terlipressin + albumin** is first-line and **FDA-approved**; alternatives = **noradrenaline + albumin** or **midodrine + octreotide + albumin**.
- **Liver transplantation is the only definitive cure**; TIPS helps mainly type 2 HRS; dialysis is a bridge.
- Best strategy is **prevention** — albumin with LVP and SBP, avoid NSAIDs/ACEi, treat infection early.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cirrhosis and Its Complications" (Hepatorenal Syndrome; portal hypertension and ascites sections; HRS-AKI/HRS-CKD terminology and treatment) — primary spine.
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Hepatic Encephalopathy, Hepatorenal Syndrome, Hepatopulmonary Syndrome, and Other Systemic Complications of Liver Disease" (Ch 94) — pathophysiology (three components), ICA-AKI staging (Table 94.2), ICA diagnostic criteria (Box 94.2), management with doses (Box 94.3), TIPS/LT data, OT-0401/REVERSE trials. *Dedicated subspecialty depth.*
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" — current management (terlipressin FDA-approved dosing, midodrine/noradrenaline regimens) and prognosis figures.

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Imaging in acute pancreatitis

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of peripancreatic and remote organ systems, ranging pathologically from self-limited *interstitial (oedematous)* disease to *necrotizing* pancreatitis. Diagnosis requires **two of three** criteria: (1) typical epigastric pain radiating to the back, (2) serum lipase/amylase >3× the upper limit of normal, and (3) characteristic findings on cross-sectional imaging. Imaging therefore serves three purposes — to **confirm the diagnosis** when clinical and biochemical features are equivocal, to **exclude alternative intra-abdominal catastrophes**, and crucially to **stage severity and detect local complications** (necrosis, fluid collections, vascular and ductal complications) that drive management. Imaging is interpreted within the framework of the **Revised Atlanta Classification (2012)**.

Indications and timing of imaging — "why and when"

- The **three main indications** for CT in AP (Sleisenger): (1) exclude other serious intra-abdominal conditions (perforated ulcer, mesenteric ischaemia); (2) **stage severity**; (3) detect **local complications** (necrosis, involvement of bowel/spleen/kidney, vascular complications).
- Routine **early CT is NOT recommended** — it is usually unnecessary or unhelpful in the first **48 hours** of admission. The diagnosis is most often clinical/biochemical.
- Contrast-enhanced CT is best performed **3–5 days into admission** in patients **not responding** to supportive care, because **necrosis (parenchymal perfusion defects) may not become apparent until 48–72 hours** after onset; imaging earlier underestimates necrosis.
- The **Revised Atlanta Criteria define two clinical phases** — *early* (<2 weeks, severity defined clinically by persistent organ failure) and *late* (>2 weeks, where imaging is needed to characterise evolving local complications).
- Caution: IV iodinated contrast should be avoided when serum **creatinine >1.5 mg/dL** (risk of AKI); some experimental/retrospective data suggest very early contrast may worsen necrosis, though human data are conflicting.

Imaging modalities — comparative overview

Modality	Primary role in AP	Key strengths / findings	Limitations
Transabdominal ultrasound (US)	**First-line** at admission	Detects **gallstones, CBD dilatation/choledocholithiasis, ascites**; pancreas diffusely enlarged, hypoechoic	Pancreas obscured by bowel gas in **25–35%**; poor for necrosis/extrapancreatic spread/severity
Plain abdominal radiograph	Excludes perforation/obstruction; supportive signs	*Sentinel loop*, *colon cut-off sign*, calcified gallstones, pancreatic calcification, retroperitoneal gas (abscess)	Non-specific, insensitive
Chest radiograph	Severity & pulmonary complications	Left/bilateral **pleural effusion**, raised hemidiaphragm, basal atelectasis, ARDS infiltrates	Indirect markers only

Modality	Primary role in AP	Key strengths / findings	Limitations
Contrast-enhanced CT (CECT)	**Reference standard** for staging & complications	Differentiates interstitial vs necrotizing; defines fluid collections; CTSI scoring	Avoid if creatinine >1.5 mg/dL; early scan underestimates necrosis
MRI / MRCP	Ductal anatomy; characterising collections	Superior depiction of **necrotic debris**, **pancreatic-duct disruption/disconnection**, ductal stones; equal to EUS/ERCP for choledocholithiasis	Less available, costlier, longer; gadolinium → nephrogenic systemic fibrosis (low risk with newer agents)
Endoscopic ultrasound (EUS)	Occult biliary disease; idiopathic AP	Detects **microlithiasis/sludge, small CBD stones**, small periampullary tumours; can predict necrosis	Operator-dependent; invasive
ERCP	**Therapeutic**, not diagnostic	Stone extraction in biliary AP with cholangitis/obstruction	Causes pancreatitis in **5–10%**; replaced diagnostically by EUS/MRCP

Contrast-enhanced CT — technique and Revised Atlanta morphology

- **Technique:** helical/MDCT after oral contrast followed by **rapid-bolus IV contrast**; *interstitial* pancreatitis shows **homogeneous parenchymal enhancement**, whereas *necrotizing* pancreatitis shows **lack of enhancement** (non-perfused parenchyma) ± peripancreatic necrosis.
- **Interstitial (oedematous) pancreatitis** occurs in **90–95%** of admissions: diffuse gland enlargement, homogeneous enhancement, mild peripancreatic stranding; usually resolves within a week.
- **Necrotizing pancreatitis** occurs in **5–10%**: lack of parenchymal enhancement and/or peripancreatic necrosis. Isolated **extrapancreatic** necrosis carries a more favourable prognosis than pancreatic necrosis. Necrosis is the radiological hallmark of severe disease and the lesion most associated with mortality.

Atlanta morphologic feature	Timing	Key CT appearance
Acute peripancreatic fluid collection (APFC)	<4 weeks, interstitial AP	Homogeneous fluid density, **no wall**, confined by fascial planes
Pancreatic pseudocyst	>4 weeks, interstitial AP	Encapsulated, **well-defined wall**, homogeneous fluid, **no solid component**
Acute necrotic collection (ANC)	<4 weeks, necrotizing AP	**Heterogeneous**, non-liquid + liquid density, **no encapsulating wall**, intra-/extrapancreatic
Walled-off necrosis (WON)	>4 weeks, necrotizing AP	Heterogeneous, **mature encapsulating wall**; loculations

CT Severity Index (Balthazar grade + necrosis score)

The **CT Severity Index (CTSI)** combines the Balthazar grade (A–E, based on inflammation/collections) with a necrosis score; **maximum = 10**. Higher scores correlate with local complications (pseudocyst, abscess) and mortality.

Balthazar grade	CT finding	Grade points
A	Normal pancreas	0
B	Focal/diffuse enlargement, contour irregularity, inhomogeneous attenuation; no peripancreatic inflammation	1
C	Grade B **plus** peripancreatic inflammation	2
D	Grade C **plus a single** peripancreatic fluid collection	3
E	Grade C **plus ≥2 collections** or **gas** in pancreas/retroperitoneum	4

Necrosis on CECT	Necrosis points
No necrosis	0
Up to 33%	2
33–50%	4
>50%	6

- **CTSI = Balthazar points + necrosis points** (0–10). Scores **0–3** = mild, **4–6** = moderate, **7–10** = severe. In Balthazar's data, grade D/E carried a 54% local-complication rate vs ~4% for A–C; mortality rose with CTSI (≈18% at scores 7–10 vs ≈4% at 0–6).
- A **Modified CTSI (Mortele)** simplifies inflammation/necrosis grading and adds **extrapancreatic complications** (pleural effusion, ascites, vascular/GI involvement), correlating better with outcome.
- **Newer CT techniques:** *perfusion CT* (day 3) detects ischaemia/necrosis earlier and predicts persistent organ failure; *subtraction CT* (colour map of unenhanced vs enhanced) also detects early necrosis.

MRI/MRCP, EUS and ERCP — special roles

- **MRCP** best delineates the **main pancreatic duct**, identifying **duct disruption/disconnection** (disconnected duct syndrome causing persistent fistula/recurrent collections) and intraductal stones; it characterises collections by showing necrotic **debris** better than CT. **Secretin-enhanced MRCP** improves duct visualisation, useful in idiopathic/recurrent AP.
- **EUS** is the most sensitive test for **occult biliary disease** (microlithiasis, sludge, small CBD stones) and small periampullary tumours; recommended after **8–12 weeks** in idiopathic AP and in patients **>40 years** to exclude malignancy. EUS at admission can detect CBD stones and triage the need for ERCP, avoiding unnecessary ERCP.
- **ERCP** is now primarily **therapeutic**: indicated within **24–48 h** in gallstone pancreatitis with **ascending cholangitis or persistent biliary obstruction**. It is the most sensitive test for bile-duct

stones but carries a 5–10% risk of post-ERCP pancreatitis (reduced by rectal indomethacin ± prophylactic pancreatic-duct stent).

- **CT-guided fine-needle aspiration** of a necrotic collection (after day 3) with Gram stain/culture can confirm **infected necrosis** (false-negative ~25%); **gas bubbles** on CT imply gas-forming organisms, though most infections occur without gas and gas may also accompany sterile necrosis with bowel microperforation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled CECT of necrotizing pancreatitis (axial):** label — *non-enhancing necrotic pancreatic body/tail*, *enhancing viable parenchyma (head/tail remnant)*, *peripancreatic acute necrotic collection*, *peripancreatic fat stranding*, *spleen*, *left pleural effusion*, *aorta/SMA*.
- **Flow/box diagram of the Revised Atlanta morphologic features:** two columns — *Interstitial AP* → **APFC (<4 wk)** → **Pseudocyst (>4 wk)**; *Necrotizing AP* → **ANC (<4 wk)** → **WON (>4 wk)**, with the dividing line at **4 weeks** and labels for "no wall" vs "encapsulated."

Clinical / Diagnostic significance

- Imaging **completes the diagnostic triad** and is decisive when pain or enzymes are equivocal (e.g., late presentation with normalised amylase, hypertriglyceridaemic AP with spuriously low amylase).
- **Severity stratification:** persistent organ failure (>48 h) defines *severe* AP clinically, but **CT-proven necrosis** and collections define the morphologic/anatomic severity that determines intervention. Single-organ failure carries 3–10% mortality, rising to ~50% with multiorgan failure in necrotizing disease.
- **Guides intervention:** sterile necrosis is managed conservatively; **infected necrosis/symptomatic WON** is treated by a **"step-up" approach** (percutaneous/endoscopic transgastric drainage → minimally invasive necrosectomy), ideally delayed 4–6 weeks to allow "walling-off."
- **Detects vascular/ductal complications:** CT/CT-angiography and MRI identify splanchnic (splenic/portal/SMV) thrombosis, **pseudoaneurysm** (treated by angioembolisation) and duct disruption (pancreatic ascites/pleural fistula — pleural fluid amylase markedly elevated).
- **Aetiology work-up:** US/EUS/MRCP identify gallstones and microlithiasis (the commonest cause), directing same-admission cholecystectomy in mild biliary AP.

High-yield exam pointers

- **Diagnosis = 2 of 3:** pain + lipase/amylase >3× ULN + imaging. Imaging is **not** mandatory if first two are met.
- **First-line modality = transabdominal ultrasound** (for gallstones/CBD), *not* CT.
- **Do not CT in first 48 h;** CECT best at **3–5 days** in non-responders — necrosis needs 48–72 h to appear.
- **Interstitial 90–95% vs necrotizing 5–10%;** necrosis = non-enhancement on CECT and is the key severity lesion.

- **Revised Atlanta collections:** APFC & pseudocyst (interstitial) vs ANC & WON (necrotizing); **4-week** cut-off separates acute (no wall) from walled-off (encapsulated).
- **CTSI = Balthazar (A–E, 0–4) + necrosis (0/2/4/6), max 10;** 7–10 = severe.
- **MRCP** best for **duct disruption** and ductal stones; **EUS** best for **microlithiasis/idiopathic AP**; **ERCP** is therapeutic (cholangitis/obstruction), not diagnostic.
- Avoid IV contrast if **creatinine >1.5 mg/dL;** gadolinium → nephrogenic systemic fibrosis.
- Plain film: **sentinel loop, colon cut-off sign;** CXR: **left pleural effusion** within 72 h signals severe disease.
- **Cullen's sign** (periumbilical) and **Grey Turner's sign** (flank) indicate haemorrhagic necrotizing pancreatitis.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute and Chronic Pancreatitis" (Revised Atlanta phases/morphology, interstitial vs necrotizing, CT timing, complications) and "Approach to the Patient with Pancreatic Disease" (EUS/ERCP/MRCP/secretin testing roles).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Acute Pancreatitis" (diagnostic imaging section: plain film/chest radiograph/US/EUS/CT, **Balthazar grading and CT Severity Index Table 58.1**, modified CTSI, perfusion/subtraction CT, MRI/MRCP).
- **CMDT 2026** — "Acute Pancreatitis" (imaging recommendations, CT-based severity/mortality table, contrast caution, EUS/ERCP indications).

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Irritable bowel syndrome

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Irritable bowel syndrome (IBS) is a chronic **functional bowel disorder** (a disorder of **gut–brain interaction**) characterised by **recurrent abdominal pain associated with altered bowel habits**, in the *absence of any detectable structural or biochemical abnormality*. No pathognomonic marker exists, so diagnosis is **symptom-based** (Rome IV criteria) after judicious exclusion of organic disease. It affects ~**10%** of adults and adolescents worldwide, is **2–3 times commoner in women** (who form ~80% of severe cases), and usually begins **before age 45**. Though benign, it markedly impairs quality of life and incurs high direct and indirect health-care costs.

Diagnostic criteria & classification

- **Rome IV criteria (2016):** *Recurrent abdominal pain, on average at least 1 day per week in the last 3 months, associated with ≥2 of:*
  - (1) related to **defecation**, (2) associated with a change in **frequency of stool**, (3) associated with a change in **form/appearance of stool**.
  - Criteria fulfilled for the last 3 months with **symptom onset ≥6 months** before diagnosis.

- **More stringent than Rome III** — pain must occur ≥ once/week and the term *"discomfort"* has been dropped. *Painless* diarrhoea or constipation does **not** qualify as IBS.
- **Supportive (non-diagnostic) symptoms:** straining, urgency, feeling of incomplete evacuation, passage of mucus, and bloating/distension.
- **Subtyping** by predominant stool form on the **Bristol Stool Form Scale** (≥25% of bowel movements rule):

Subtype	Stool pattern (≥25% of BMs)
IBS-C (constipation)	Hard/lumpy (Bristol 1–2) ≥25%; loose <25%
IBS-D (diarrhoea)	Loose/watery (Bristol 6–7) ≥25%; hard <25%
IBS-M (mixed)	Both hard and loose ≥25%
IBS-U (unsubtyped)	Insufficient abnormality to subtype

- Subtypes are **unstable** — over 1 year ~75% of patients switch subtype and ~29% switch between IBS-C and IBS-D.

Pathophysiology (multifactorial — disordered brain–gut axis)

- **Altered GI motility:** exaggerated, prolonged colonic motor response to meals and rectal distension; increased high-amplitude propagating contractions and rapid transit in IBS-D; slow transit/pelvic-floor dyssynergia in IBS-C.
- **Visceral hypersensitivity:** lowered thresholds for pain/discomfort on rectal balloon distension; *selective for visceral (not somatic) afferents*. **TRPV1 (vanilloid) channel** upregulation correlates with pain.
- **Central neural dysregulation:** functional MRI shows heightened activation of the **mid-cingulate** and **prefrontal cortex** (hypervigilance to visceral pain); stress and emotion alter sensory thresholds.
- **Psychological factors:** anxiety, depression, somatisation in up to 80% of referral patients; association with prior **physical/sexual abuse**.
- **Post-infectious IBS:** >10% develop IBS after infectious enteritis (≈**4-fold** risk); commoner in young women, after severe/bacterial/parasitic infection and with psychological comorbidity; mediated by residual enteroendocrine cells, T-lymphocytes and dysbiosis.
- **Low-grade immune activation/mucosal inflammation:** activated **mast cells** in proximity to nerves, raised IL-6, IL-1β, TNF; mast-cell mediators (histamine, proteases, PGE_2) drive hypersensitivity.
- **Altered intestinal permeability** ("leaky gut") — especially IBS-D and post-infectious IBS; reduced tight-junction proteins.
- **Gut dysbiosis:** reduced microbial diversity, ↓ *Bifidobacterium* and *Faecalibacterium*, ↑ Enterobacteriaceae; up to 4-fold higher odds of **SIBO** on breath testing (contested).
- **Serotonin (5-HT) pathways:** ↑ enterochromaffin cells and postprandial plasma 5-HT in IBS-D; **TPH1** polymorphism; downregulated mucosal **SERT** (serotonin reuptake transporter).
- **Bile-acid malabsorption:** in up to **25% of IBS-D** (reduced ileal **FGF-19**) → accelerated colonic transit.

- **Genetic:** twin studies and **SERT polymorphisms** support heritability.

Clinical features

- **Abdominal pain** (prerequisite): variable, often **crampy/episodic**, anywhere in the abdomen; *exacerbated by eating or stress, relieved by defecation or flatus*; worse premenstrually; **almost never nocturnal** and does not disturb sleep. Malnutrition is exceedingly rare.
- **Altered bowel habit** (most consistent feature): IBS-C — hard, narrow-calibre, infrequent stools (<3/week), straining, sense of anal blockage; IBS-D — small-volume loose stools (<200 mL), urgency, mucus, occasional incontinence.
- **Gas/bloating/distension** — common; most generate a *normal* amount of gas but tolerate gas loads poorly.
- **Upper-GI/extra-intestinal overlap:** dyspepsia, heartburn, nausea in 25–50%; overlap with fibromyalgia, chronic fatigue, headache, backache, urologic and gynaecologic symptoms.

Alarm ("red-flag") features that argue AGAINST IBS

- Onset after **age 40–45**, progressive course, **rectal bleeding/hematochezia**, **nocturnal** pain or diarrhoea, significant **weight loss**, fever, persistent diarrhoea after a 48-h fast, steatorrhoea.
- **Anaemia**, raised inflammatory markers, leucocytes/blood in stool, stool volume **>200–300 mL/day**.
- **Family history** of colorectal cancer, IBD or coeliac disease.
- *Any* alarm feature mandates targeted investigation (e.g. colonoscopy with random biopsies for microscopic colitis).

Investigations (diagnosis of positive features + limited exclusion)

- Diagnosis is **clinical**; over-testing in a young patient with typical symptoms and no alarm features is harmful and costly.
- **Baseline:** complete blood count; **CRP** and **faecal calprotectin** (or lactoferrin) to screen for IBD — IBD risk ≤1% if CRP ≤0.5 mg/dL or calprotectin ≤40 µg/g (>50 µg/g warrants endoscopy).
- **Coeliac serology** (tissue-transglutaminase IgA) in IBS-D.
- **Stool studies** for ova/parasites/*Giardia* only where prevalence is high or history suggestive.
- **Colonoscopy** if alarm features, onset >45 years, or failure of therapy — with **random biopsies** to exclude microscopic colitis; lactose/glucose **hydrogen breath test** selectively; **SeHCAT**/bile-acid testing in refractory IBS-D; **anorectal manometry + balloon expulsion** if pelvic-floor dyssynergia suspected.

Management (stepwise, severity- and symptom-directed)

- **Foundation (all patients):** strong **therapeutic relationship**, reassurance, explanation of the gut–brain nature, realistic goals, identifying triggers; regular **exercise**.
- **Diet:** eliminate identified food triggers (avoid nutritionally depleted diets); **soluble fibre** (psyllium 3–4 g BD — *not* insoluble wheat bran); **low-FODMAP diet** as a 3-step *restriction → reintroduction → personalised maintenance* protocol relieves symptoms in **50–80%** (avoid in eating disorders).

- **Antispasmodics** (pain/cramps): dicyclomine, hyoscyamine 30 min before meals; **enteric-coated peppermint oil** (superior to placebo for global symptoms/pain).
- **For IBS-D: loperamide** 2–4 mg (max 12 mg/day, prophylactic before stressful events; does not relieve pain); **bile-acid binders** (cholestyramine/colesevelam) for bile-acid diarrhoea; **eluxadoline** (mixed μ-/κ-agonist, δ-antagonist; contraindicated post-cholecystectomy, pancreatitis history or heavy alcohol use); **alosetron** (5-HT_3 antagonist; restricted to women with severe IBS-D — risk of **ischaemic colitis** ~1.03/1000 patient-years); **rifaximin** 550 mg TDS × 14 days (FDA-approved, especially bloating).
- **For IBS-C:** osmotic laxative **PEG 3350** (*avoid lactulose/sorbitol* — gas); **secretagogues** — lubiprostone (Cl^--channel ClC-2 activator), linaclotide and plecanatide (guanylate cyclase-C agonists), tenapanor (NHE3 inhibitor); **tegaserod** (5-HT_4 agonist) re-approved 2019 for women <65 without cardiovascular disease.
- **Neuromodulators (pain-predominant/severe):** low-dose **tricyclic antidepressants** (amitriptyline/nortriptyline/imipramine 10–50 mg at night — benefit independent of mood effect; TCAs favour IBS-D); **SSRIs** may help IBS-C and comorbid mood disorder. Avoid chronic anxiolytics.
- **Psychological therapies (refractory/severe): cognitive behavioural therapy** (NNT ≈ 3) and **gut-directed hypnotherapy** (NNT ≈ 4).
- **Severity spectrum: mild (~70%)** — primary care, education/diet; **moderate (~25%)** — gut-acting drugs; **severe (~5%)** — referral centres, constant pain + psychosocial difficulty, best managed with neuromodulators and psychological treatment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Brain–gut axis pathophysiology of IBS** (central hub "IBS" with radiating arrows): label *CNS hypervigilance — mid-cingulate/prefrontal cortex*, *Brain–gut axis — HPA axis, autonomic dysfunction*, *Visceral hypersensitivity (TRPV1)*, *Motility abnormalities*, *"Leaky" gut / altered permeability*, *Mast-cell activation & low-grade inflammation*, *Gut dysbiosis (↓Bifidobacterium, ↓Faecalibacterium, ↑Enterobacteriaceae)*, *Bile-acid malabsorption (↓FGF-19)*, *Serotonin/SERT polymorphism*, *Psychological — anxiety/depression/somatisation*, *Genetic — twin studies/SERT*.
- **Bristol Stool Form Scale & IBS subtyping graph:** Y-axis *% BM hard or lumpy (Bristol 1–2)*, X-axis *% BM loose or watery (Bristol 6–7)*, with **25% threshold** lines partitioning four quadrants labelled **IBS-C, IBS-D, IBS-M, IBS-U**; depict Bristol types 1–7 alongside.

Clinical / Diagnostic significance

- IBS is a **positive clinical diagnosis** by Rome IV plus *absence of red flags* — not purely a diagnosis of exclusion; limited testing avoids reinforcing illness behaviour.
- **Differential diagnosis** is broad: IBD (UC/Crohn, **microscopic colitis**), coeliac disease, bile-acid diarrhoea, lactase deficiency, SIBO, colorectal neoplasia, thyroid disease, carcinoid, endometriosis/ovarian cancer, and porphyria/lead poisoning (painful constipation).
- **Subtype-directed therapy** (pain vs constipation vs diarrhoea vs bloating) is the practical framework; agents are *adjunctive, not curative*.

- Failure to respond to a **2–4 week empiric trial** or emergence of alarm features should prompt further evaluation.

High-yield exam pointers

- **Rome IV:** abdominal pain ≥1 day/week × 3 months + ≥2 of (defecation-related / change in stool frequency / change in stool form); onset ≥6 months prior.
- **Subtypes** by Bristol scale, **25% rule**: IBS-C, IBS-D, IBS-M, IBS-U — *unstable over time*.
- Female:male ≈ **2–3:1**; prevalence ~**10%**; onset usually <45 years.
- **Pain is essential**, is **never nocturnal**, relieved by defecation — *painless* altered habit is not IBS.
- Up to **25% of IBS-D** have **bile-acid malabsorption**; >10% develop **post-infectious IBS** (4-fold risk).
- Screen IBS-D with **CRP + faecal calprotectin (>50 µg/g → scope)** and **coeliac serology**.
- **Low-FODMAP diet** helps 50–80%; **psyllium** (soluble) not wheat bran (insoluble).
- Drug pearls: **eluxadoline** contraindicated post-cholecystectomy/alcohol (pancreatitis); **alosetron** → ischaemic colitis (restricted); **rifaximin** for IBS-D/bloating; **linaclotide/plecanatide (GC-C agonists), lubiprostone (Cl^- channel), tenapanor (NHE3)** for IBS-C; **TCAs** for pain.
- **CBT (NNT 3)** and **gut-directed hypnotherapy (NNT 4)** for refractory disease.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Irritable Bowel Syndrome" (Owyang & Singh): Rome IV criteria, pathophysiology, drugs/doses, low-FODMAP protocol, severity spectrum.
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Irritable Bowel Syndrome": Bristol-scale subtyping, diagnostic algorithm, CRP/calprotectin thresholds, NNT for hypnotherapy/CBT.
- **CMDT 2026** — "Gastrointestinal Disorders: Irritable Bowel Syndrome": current pharmacologic management, drug doses, alarm features, FODMAP food groups.

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Chronic pancreatitis — complications and management

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Chronic pancreatitis (CP) is an irreversible inflammatory disease characterised histologically by chronic inflammation, fibrosis and progressive destruction (atrophy) of both the exocrine and endocrine pancreas, driven by stellate-cell activation, cytokine release and collagen deposition. Its cardinal manifestations are abdominal pain, steatorrhoea, weight loss and diabetes mellitus. Aetiology is summarised by the **TIGAR-O** system (Toxic-metabolic [alcohol, tobacco, hypercalcaemia, hypertriglyceridaemia], Idiopathic, Genetic [*PRSS1, SPINK1, CFTR, CTRC, CASR*], Autoimmune, Recurrent/severe acute pancreatitis, Obstructive). Because no therapy reverses the disease, **management is centred on screening for and treating its complications.**

Complications of chronic pancreatitis (Harrison Table 359-7)

Domain	Complication	Key facts
Pain	Chronic abdominal pain	Most common/disabling symptom; complex mechanism; narcotic dependence frequent
Exocrine	Exocrine pancreatic insufficiency (EPI) → steatorrhoea, malnutrition	Cumulative prevalence >80%; fat-soluble vitamin (A, D, E, K) deficiency; B12 malabsorption in ~40%
Endocrine	Pancreatogenic (**type 3c**) diabetes mellitus	Lifetime prevalence >80%; brittle, prone to **hypoglycaemia** (loss of glucagon reserve); ketoacidosis/end-organ damage uncommon
Ductal/ cystic	Pseudocyst; pancreatic duct stricture/stones	Pseudocyst in ~25% (commonest in alcoholic CP); ~70% communicate with the duct
Biliary	Distal CBD stricture → jaundice, cholangitis, secondary biliary cirrhosis	Symptomatic in ~10%; long tapered stenosis of intrapancreatic CBD
Luminal	Duodenal (gastric-outlet) obstruction	~5%; from head fibrosis/inflammatory mass
Vascular	Splanchnic (splenic > portal) vein thrombosis; pseudoaneurysm	Splenic-vein thrombosis → **left-sided ("sinistral") portal hypertension** + gastric varices; pseudoaneurysm (splenic artery commonest)
Haemorrhagic	GI bleeding	Pseudoaneurysm, ruptured varices, hemosuccus pancreaticus, peptic ulcer
Fistula	External (pancreaticocutaneous); internal (pancreatic ascites, pancreaticopleural effusion)	High-amylase ascites/effusion; from duct disruption/pseudocyst rupture
Skeletal	Metabolic bone disease	Osteopenia/osteoporosis in **~65%** (alcohol, smoking, vitamin-D deficiency, inflammation)
Malignant	Pancreatic adenocarcinoma	~4–5% cumulative risk at 20 yr; hereditary *PRSS1* ~10% (rising to ~19% by age 70)

General principles of management

- **Remove the driver:** absolute **alcohol abstinence** and **smoking cessation** (both are independent, dose-dependent drivers of progression, fibrosis and calcification).
- **Diet:** a low-fat or heart-healthy/Mediterranean diet; avoid very-low-fat diets that worsen fat-soluble-vitamin deficiency.
- **Treat the specific complication** (below); refer all CP patients to a centre offering endoscopic/surgical therapy.

Management of pain

- **Stepwise analgesia:** acetaminophen and NSAIDs first; **tramadol** if an opioid is needed; *avoid strong opioids* where possible (addiction is common).
- **Adjuvant pain-modifiers: pregabalin** (RCT-proven to reduce pain and opioid need) or gabapentin, tricyclic antidepressants, SSRIs. Antioxidants give mixed results; pancreatic enzymes do **not** reliably relieve pain.
- **Coeliac plexus block** (CT- or EUS-guided): relief in ~50% but typically **short-lived** — a conditional, low-evidence recommendation.
- **Endoscopic therapy** for a dominant duct stricture/obstructing stone: pancreatic sphincterotomy, stone extraction ± **ESWL**, and ductal stenting; successful in ~50%.
- **Surgery for a dilated duct:** ductal decompression by **lateral pancreaticojejunostomy (modified Puestow)** relieves pain in ~80%; head-resecting variants (**Frey / Beger** — duodenum-preserving pancreatic head resection) for an inflammatory head mass. Two RCTs show **surgery is superior to endoscopy** for pain/quality of life in dilated-duct disease, and early surgery may give superior short-term relief.
- **Total pancreatectomy with islet autotransplantation (TPIAT):** last resort for intractable **small-duct** or hereditary CP; benefits those with shorter symptom duration and low opioid use.

Management of exocrine insufficiency / steatorrhoea

- **Pancreatic enzyme replacement therapy (PERT)** is the cornerstone — diagnosis of EPI confirmed by **faecal elastase-1 <100 µg/g** (200 = normal; 100–200 = mild-moderate).
- Start **25,000–50,000 units of lipase with each meal**, titrating up to **90,000–100,000 units/meal**; aim for adequate lipase across the prandial/postprandial phase. Take enzymes spread throughout the meal.
- Add **acid suppression** (PPI or H2-blocker) — *mandatory* with non-enteric-coated preparations and useful to improve response with enteric-coated preparations.
- Judge response clinically (stool consistency, visible fat, weight gain). If refractory: increase dose/change formulation, exclude **coeliac disease / SIBO**, and substitute **medium-chain triglycerides** (lipase-independent absorption).
- **Monitor and replace** fat-soluble vitamins (esp. vitamin D) and zinc; check body weight and **bone mineral density (DEXA)** — treat osteopenia/osteoporosis.

Management of endocrine insufficiency (type 3c diabetes)

- Annual **fasting glucose and HbA1c** screening; C-peptide estimates residual β-cell mass.

- **Metformin** preferred (associated with lower secondary pancreatic-cancer risk); **insulin** is frequently required, but requirements are lower than in type 1 DM.
- **Avoid over-tight glycaemic control** — brittle diabetes with impaired glucagon reserve and malnutrition predisposes to dangerous treatment-induced **hypoglycaemia**.

Management of structural / vascular complications

- **Pseudocyst:** observe if asymptomatic. Drain if symptomatic, complicated, rapidly enlarging or generally >6 cm — preferred is **EUS-guided endoscopic cystogastrostomy/cystojejunostomy** (success 80–90%); surgical drainage (often with a Puestow) where endoscopy fails; **percutaneous drainage is discouraged** (downstream duct stricture → fistula/recurrence). Address an associated duct stricture/disruption (bridging stent) to prevent recurrence.
- **Biliary obstruction: cholangitis is an absolute indication** for intervention. **Surgical biliary bypass** (choledochojejunostomy/choledochoduodenostomy ± Whipple/head resection) is definitive; endoscopic stenting (multiple plastic stents or a fully-covered SEMS for 6–12 months) is a temporising option with lower long-term success. A new stricture may signal malignancy — assess with EUS.
- **Duodenal obstruction:** trial of conservative therapy (inflammation may settle); **gastrojejunostomy** (± duct drainage) or head resection if it fails.
- **Pseudoaneurysm / haemorrhage:** the **splenic artery** is most often involved; beware a **sentinel bleed** preceding exsanguination, and **hemosuccus pancreaticus** (bleeding via the ampulla/duct). CT angiography then **angiographic embolisation or covered stent-graft** is first-line (has replaced surgery); treat once identified even if not yet bleeding — mortality after bleeding is ~40%.
- **Splenic-vein thrombosis with gastric varices:** therapy only if bleeding (risk ~10%) — **splenectomy is curative**; endoscopic cyanoacrylate injection controls acute bleeding.
- **Pancreatic fistula:** internal (pancreatic ascites/pleural effusion) or external — bowel rest, parenteral nutrition and **octreotide** (100 µg SC 8-hourly), with **endoscopic transpapillary/bridging stent** across the duct disruption; surgery (distal resection or fistulojejunostomy) if endoscopy fails.
- **Autoimmune pancreatitis** (a treatable cause/mimic): **prednisone 40 mg/day** for 4 weeks then taper; **rituximab** (or azathioprine/MMF) for relapse.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Complications map of the pancreas in CP":** outline the pancreas (atrophic, with punctate parenchymal calcifications) and label: *dilated main pancreatic duct with intraductal calculus*, *pancreatic-duct stricture*, *pseudocyst (tail)*, *distal common bile duct stricture → biliary dilatation*, *duodenal compression*, *splenic-vein thrombosis with gastric (fundal) varices*, *splenic-artery pseudoaneurysm*.
- **Diagram 2 — "Pain-management ladder in CP":** stacked steps labelled *Abstinence (alcohol + tobacco) → Acetaminophen/NSAID → tramadol + pregabalin/TCA → Coeliac plexus block → Endoscopy (sphincterotomy, ESWL, stent) → Surgery (Puestow / Frey-Beger) → TPIAT*.

Clinical / Diagnostic significance

- **Diagnosis of CP:** CT/MRI is first-line (calcifications, ductal dilatation, atrophy); MRCP/EUS for early disease (≥5 of 9 EUS / Rosemont features); the **secretin test** (most sensitive functional test) becomes abnormal once **≥60%** of exocrine function is lost.
- **Steatorrhoea appearing in CP** strongly implies EPI; **a new biliary stricture or unexplained weight loss** must trigger exclusion of **pancreatic cancer** (tumefactive CP can mimic carcinoma).
- **Any GI bleed or unexplained anaemia** in a CP patient mandates urgent search for a **pseudoaneurysm**.
- **Surveillance bundle:** annual HbA1c (diabetes), periodic fat-soluble vitamins/zinc and DEXA (bone disease, EPI), and cancer vigilance — especially in hereditary *PRSS1*/tropical CP.

High-yield exam pointers

- **TIGAR-O** classifies aetiology; alcohol + smoking drive progression — **abstinence is therapy.**
- EPI prevalence **>80%**; diagnose with **faecal elastase-1 <100 µg/g**; treat with **PERT 25,000–50,000 → 90,000–100,000 U lipase/meal + PPI**.
- **Type 3c (pancreatogenic) diabetes** is *brittle* — guard against **hypoglycaemia**; **metformin** preferred.
- **Pseudocyst (~25%)** → EUS-guided endoscopic drainage; **percutaneous drainage discouraged.**
- **Splenic-vein thrombosis → sinistral portal hypertension + gastric varices → splenectomy is curative.**
- **Pseudoaneurysm** (splenic artery) — **sentinel bleed**, **hemosuccus pancreaticus**, mortality ~40% — treat by **angioembolisation/stent-graft.**
- Biliary stricture (~10%): **cholangitis = absolute indication**; surgical bypass is definitive.
- **Dilated duct + pain → surgery (Puestow) beats endoscopy** (RCT evidence); intractable small-duct/hereditary → **TPIAT**.
- Pancreatic cancer cumulative risk **~4–5% at 20 yr** (≈10–19% in hereditary CP); **~65% have metabolic bone disease.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute and Chronic Pancreatitis" (chronic pancreatitis pathophysiology, TIGAR-O classification, complications [Table 359-7], steatorrhoea/PERT, pain and surgical therapy, hereditary pancreatitis).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Chronic Pancreatitis" (deep detail on pseudocyst, GI bleeding, pseudoaneurysm, splenic-vein thrombosis/varices, bile-duct and duodenal obstruction, pancreatic fistulas, diabetes management).
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (current management: enzyme [pancrelipase] dosing, pain pharmacotherapy, endoscopic/surgical algorithm — Puestow/Beger/Frey, autoimmune pancreatitis steroids/rituximab, cancer risk).

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Portosystemic anastomosis — sites and clinical relevance

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — A **portosystemic (porto-systemic) anastomosis** is a site where tributaries of the valveless **portal venous system** communicate with veins of the **systemic (caval) circulation**. In health these channels carry negligible flow *towards* the portal vein. When the **hepatic venous pressure gradient (HVPG)** rises (portal hypertension is defined as HVPG >5 mmHg; *clinically significant* portal hypertension is HVPG ≥10 mmHg), flow **reverses**, the collaterals dilate, and varices form as decompressing channels. They are the anatomical basis of the lethal complication of cirrhosis — **variceal haemorrhage** (20–30% mortality per episode).

Anatomy of the normal portal circulation (orientation)

- The **portal vein** is formed behind the neck of the pancreas by union of the **superior mesenteric vein** and the **splenic vein**; it is ~7.5 cm long, runs dorsal to the hepatic artery and bile duct, and divides at the hilum into right and left branches.
- The **inferior mesenteric vein** usually drains into the splenic vein; the **left gastric (coronary) vein** drains into the portal vein near the splenomesenteric confluence; the **umbilical vein** drains into the *left* portal branch.
- The portal system drains capillary blood from the **oesophagus, stomach, small and large intestine (to the upper anal canal), pancreas, gallbladder and spleen**, and supplies ~75% of total hepatic blood flow. Being **valveless**, it permits pressure to be transmitted retrogradely into collaterals.

Sites of portosystemic anastomosis (core of the answer)

Site	Portal (visceral) tributary	Systemic vein	Clinical lesion / sign
Lower oesophagus / gastro-oesophageal junction	Left gastric (coronary) & short gastric veins → splenic/portal	Oesophageal tributaries of the **azygos/hemiazygos** (perioesophageal) veins → SVC	**Oesophageal & gastro-oesophageal varices** — the principal, bleeding collateral
Gastric fundus / cardia	Short gastric & posterior gastric → splenic vein	Left renal vein via **spontaneous spleno-renal shunt**	**Fundal (gastric) varices**; isolated in splenic-vein thrombosis
Anal canal / rectum	Superior rectal vein (from inferior mesenteric)	Middle & inferior rectal veins → internal iliac / internal pudendal → IVC	**Ano-rectal varices** (to be distinguished from haemorrhoids)
Peri-umbilical anterior abdominal wall	**Para-umbilical veins** in the falciform/round ligament (from left portal vein)	Superficial & inferior epigastric / thoraco-epigastric veins	**Caput medusae**; *Cruveilhier–Baumgarten* venous hum
Retroperitoneum (veins of *Retzius*)	Colonic & other splanchnic veins; ovarian veins (esp. in women)	Retroperitoneal, renal, lumbar and iliac veins	Ectopic / retroperitoneal varices; rarely bleed
Bare area of liver / diaphragm (veins of *Sappey*)	Hepatic capsular & diaphragmatic portal twigs	Phrenic veins → IVC	Adhesion collaterals; clinically silent
Patent / recanalised ductus venosus	Left portal vein	IVC	Rare congenital shunt

- **Mechanistic note (Sleisenger):** the GE-junction collaterals (left gastric/coronary + short gastric draining to the azygos system) are the dominant route in *intra-hepatic* portal hypertension; an increase in azygos blood flow is a hallmark. The fundus drains via short gastric veins into the splenic vein, hence **splenic-vein thrombosis ("left-sided" portal hypertension)** produces *isolated* fundal varices, often with a spleno-renal shunt.

Four venous zones at the gastro-oesophageal junction (why varices bleed here)

- **Gastric zone** (2–3 cm below junction) — submucosal longitudinal veins draining to short/left gastric veins.
- **Palisade zone** (2–3 cm of distal oesophagus) — the **dominant portosystemic watershed**; perforating veins do *not* connect to peri-oesophageal veins, so these varices **cannot decompress** and are **most prone to rupture**.
- **Perforating zone** — network of veins connecting submucosal and external (peri-oesophageal) veins.
- **Truncal zone** (~10 cm, proximal) — 4 longitudinal veins; communicate with peri-oesophageal veins (which drain to the azygos), so they decompress and **rarely bleed**.

Pathophysiology — pressure thresholds and rupture

- Collaterals form because portal pressure **exceeds** systemic venous pressure → flow reverses out of the portal bed.
- **Gradient thresholds:** varices develop at an HVPG **≥10 mmHg**; bleeding requires a gradient **≥12 mmHg** (reducing HVPG <12 mmHg almost abolishes bleeding risk).
- Rupture follows **Laplace's law**: *wall tension* $T = (P \times r)/w$ — large varices (r), thin wall (w), and high transmural pressure (P), with limited soft-tissue support at the GE junction, predispose to rupture. Endoscopic risk stigmata: **red wale signs, cherry-red spots, haematocystic spots, white-nipple sign**.

Gastric varices — Sarin classification

Type	Location	Association
GOV1	Extend 2–5 cm below GE junction, contiguous with oesophageal varices	Commonest (~70% of gastric varices); intra-hepatic portal HTN
GOV2	Cardia/fundus, contiguous with oesophageal varices	Intra-hepatic portal HTN
IGV1	Isolated fundal varices, no oesophageal varices	**Splenic-vein thrombosis** (left-sided) / cirrhosis
IGV2	Isolated, gastric body/antrum/pylorus	Least common

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Sites of portosystemic anastomosis."** Draw the portal vein (SMV + splenic vein confluence), spleen and gut. Label the four classic sites with their venous pairs: (i) *Lower oesophagus* — left gastric/coronary vein ↔ azygos vein; (ii) *Rectum* — superior rectal vein ↔ middle/inferior rectal veins; (iii) *Umbilicus* — para-umbilical veins ↔ epigastric veins (caput medusae); (iv) *Retroperitoneum* — colonic/splanchnic veins ↔ renal/lumbar veins (veins of Retzius). Mark **arrows showing reversed (hepatofugal) flow** and the resulting lesion at each site.
- **Diagram 2 — "Four zones of the gastro-oesophageal junction."** Vertical strip of distal oesophagus/cardia labelled **gastric → palisade (watershed, bleeds) → perforating → truncal**, with the palisade zone starred as the rupture site and peri-oesophageal veins draining to the azygos system.

Clinical / Diagnostic significance

- **Oesophageal/gastric varices:** life-threatening upper-GI bleed; screen at diagnosis of cirrhosis by endoscopy (skip if liver stiffness <20 kPa and platelets normal). **Primary prophylaxis** = non-selective β-blocker (**carvedilol** preferred; or propranolol/nadolol titrated to HR 55–60, SBP >90 mmHg) **or** endoscopic variceal ligation.
- **Acute variceal bleed:** restrictive transfusion (transfuse at Hb <7 g/dL, target 7–9), **vasoactive drug** (somatostatin/octreotide/terlipressin), **prophylactic ceftriaxone**, urgent endoscopic band

ligation; **balloon tamponade** (Sengstaken–Blakemore/Minnesota tube) or self-expanding metal stent as a bridge to **TIPS** (transjugular intrahepatic portosystemic shunt) on endoscopic failure.

- **Gastric (fundal) varices:** cyanoacrylate glue injection; **BRTO** (balloon-occluded retrograde transvenous obliteration) when a spleno-renal shunt is present, ± TIPS. **Isolated fundal varices → exclude splenic-vein thrombosis → splenectomy is curative** for that pattern.
- **Caput medusae & Cruveilhier–Baumgarten hum:** clinical bedside signs of a recanalised umbilical/para-umbilical collateral — distinguish radiating peri-umbilical veins of portal hypertension from the **"flow away from umbilicus"** of IVC obstruction.
- **Ano-rectal varices** occur in 10–40% of cirrhotics at colonoscopy: they are dilated **superior and middle rectal (haemorrhoidal) veins**, **collapse with digital pressure**, and must not be confused with haemorrhoids (which do not collapse and are cushions in the anal canal).
- **Ectopic varices** (duodenum, peristomal after proctocolectomy, biliary) cause <5% of variceal bleeds but are easily missed; suspect with obscure GI bleed or bloody ascites.
- **Encephalopathy:** large spontaneous or surgical/TIPS shunts divert nitrogenous blood past the liver → portosystemic (hepatic) encephalopathy (occurs in up to ~20% after TIPS).

High-yield exam pointers

- **Four classic sites:** lower oesophagus, ano-rectum, peri-umbilicus, retroperitoneum (add fundus, bare area of liver).
- **Most clinically important & dangerous collateral = gastro-oesophageal varices** (left gastric/coronary + short gastric ↔ azygos).
- **Palisade zone** of the distal oesophagus is the watershed that **cannot decompress** → commonest bleeding site.
- **HVPG ≥10 mmHg → varices form; ≥12 mmHg → varices bleed.** Laplace's law governs rupture.
- **Caput medusae** = recanalised para-umbilical veins (left portal vein); a venous hum = **Cruveilhier –Baumgarten** sign.
- **Rectal varices ≠ haemorrhoids:** varices collapse on digital pressure and connect superior↔middle rectal veins.
- **Isolated gastric fundal varices (IGV1)** → think **splenic-vein thrombosis**; treat with splenectomy/BRTO, *not* β-blockers alone.
- **Sarin classification:** GOV1 (commonest), GOV2, IGV1, IGV2.
- **"Downhill" oesophageal varices** (upper third, from SVC obstruction) are NOT portal-hypertensive — a key differential.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cirrhosis and Its Complications" (portal hypertension definition, HVPG thresholds, classification of portal hypertension, complications, variceal-bleed management, TIPS).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Portal Hypertension and Variceal Bleeding" (normal portal anatomy; the four sites of porto-systemic collateral formation; the four gastro-oesophageal venous zones; Laplace's law; Sarin classification of gastric varices; ectopic and ano-rectal varices) and used for collateral/watershed detail.
- **CMDT 2026** — Gastrointestinal & Liver disorders (current management of variceal bleeding; haemorrhoids vs rectal varices).

Coverage note: The named venous eponyms **veins of Retzius** (retroperitoneal), **veins of Sappey** (bare area/diaphragm), the **Cruveilhier–Baumgarten** hum, and **"downhill" varices** are standard, universally accepted internal-medicine/anatomy facts included to satisfy the "list the sites" phrasing; the corpus describes the corresponding retroperitoneal (ovarian–iliac) and para-umbilical collaterals but does not use these eponyms verbatim. Harrison Ch 355's coverage of collateral *anatomy* is thin (as flagged in the spec); the anatomical depth here is drawn chiefly from Sleisenger.

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Active ulcerative colitis

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Ulcerative colitis (UC) is a chronic, relapsing, idiopathic inflammatory bowel disease characterised by *continuous*, diffuse mucosal inflammation that invariably involves the rectum and extends proximally in an uninterrupted fashion to involve part or all of the colon. The hallmark of active disease is **bloody diarrhoea** with tenesmus, urgency, passage of mucus and crampy lower-abdominal pain. Management of the *active* attack is governed by two axes — the **anatomical extent** (proctitis / left-sided / extensive) and the **severity of the flare** (mild, moderate, severe/fulminant) — and follows a "step-up / accelerated step-up" strategy with three goals: terminate the acute attack, achieve steroid-free clinical and endoscopic (mucosal) remission, and prevent recurrence.

Assessment of disease activity & severity (basis of all treatment decisions)

Severity is graded clinically (*Truelove & Witts*, refined as the *Montreal S-classification*) and endoscopically (*Mayo subscore*), supported by labs (Hb, albumin, ESR, CRP, faecal calprotectin).

Parameter	Mild (S1)	Moderate (S2)	Severe (S3)
Stools/day	≤4	4–6	>6, bloody
Blood in stool	intermittent	frequent	continuous
Pulse	normal	normal	≥90/min

Parameter	Mild (S1)	Moderate (S2)	Severe (S3)
Temperature	normal	normal	≥37.5°C
Haemoglobin	normal	≥10.5 g/dL	<10.5 g/dL
ESR	<30 mm/h	≤30	≥30 mm/h
Mayo endoscopic subscore	1	2–3	3 (ulceration, spontaneous bleeding)

- **Montreal extent:** *E1* — proctitis; *E2* — left-sided (distal to splenic flexure); *E3* — extensive/pancolitis (proximal to splenic flexure). Extent dictates whether topical, oral or systemic therapy is appropriate.
- **Truelove & Witts severe attack** = ≥6 bloody stools/day **plus ≥1** systemic sign (pulse >90, temp >37.8°C, Hb <10.5 g/dL, ESR >30) — the classic trigger for hospital admission.
- Before treating, **exclude infective mimics**: stool for *Salmonella, Shigella, Campylobacter,* Shiga-toxin *E. coli*, *Clostridioides difficile* toxin, ova/parasites (multiplex PCR preferred); consider **CMV superinfection** (mucosal biopsy) in steroid-refractory immunosuppressed patients.

Mild–moderate disease (out-patient, oral/topical therapy)

- **Proctitis / proctosigmoiditis (distal):** topical **mesalamine is the drug of choice** — suppository **1 g at bedtime** (proctitis) or enema **4 g at bedtime** (proctosigmoiditis) for 4–8 weeks (~75% improve). Topical mesalamine is *superior to* topical steroids and to oral 5-ASA for distal disease.
- **Extensive (above sigmoid):** combine **oral mesalamine 2–4.8 g once daily** with a nightly mesalamine enema/suppository; 50–75% improve, dose-response continues to 4.8 g/day. **Sulfasalazine 3–6 g/day** (acute) is effective but limited by sulfapyridine intolerance — give **folic acid** supplementation.
- **Oral budesonide MMX (Uceris) 9 mg/day for 4–8 weeks** (colonic release, minimal systemic steroid effect, no taper needed) or **oral prednisone** if no response to 5-ASA within 4–8 weeks.
- 5-ASA achieves clinical improvement in ~75% and remission in 20–30%; **maintenance 5-ASA reduces 12-month relapse from 75% to <40%**.

Moderate–severe disease (oral/systemic immunosuppression & biologics)

- **Oral corticosteroids: prednisone 40 mg/day** (Harrison: 40–60 mg/day); rapid response in ~2 weeks, then taper **5 mg/week** (slower, 2.5 mg/week below 20 mg). Steroids **induce but never maintain** remission; up to 30% become steroid-dependent/refractory.
- **Thiopurines** (steroid-sparing maintenance, not for induction — slow onset 3–6 months): **azathioprine 2–3 mg/kg/day** or **6-mercaptopurine 1–1.5 mg/kg/day**. Check/keep in mind **TPMT** status (1 in 300 deficient → marrow toxicity); monitor CBC and LFTs; ~4-fold lymphoma risk.
- **Biologics / small molecules** are increasingly used early ("treat-to-target", aiming for deep remission). Choice depends on prior biologic exposure, severity, comorbidity and route preference.

Agent	Class / target	Induction dosing
Infliximab	anti-TNF (chimeric IgG1)	5 mg/kg IV at 0, 2, 6 wk → q8 wk (↑10 mg/kg q4 wk by trough)
Adalimumab	anti-TNF (human IgG1, SC)	160 mg day 0, 80 mg day 14, then 40 mg q2 wk
Golimumab	anti-TNF (human IgG1, SC)	approved for moderate–severe UC
Vedolizumab	anti-α4β7 integrin (gut-selective)	IV; preferred first-line in older/comorbid patients; superior to adalimumab
Ustekinumab	anti-IL-12/23 (p40)	IV induction → SC maintenance
Mirikizumab / risankizumab	anti-IL-23 (p19)	injectable; 2nd/3rd-line
Tofacitinib	pan-JAK inhibitor (oral)	10 mg BID × 8–16 wk
Upadacitinib	selective JAK1 (oral)	45 mg/day × 8 wk
Ozanimod / etrasimod	S1P-receptor modulator (oral)	once-daily (ozanimod needs dose escalation)

- **Combination therapy** (anti-TNF + immunomodulator) is superior to either alone for moderate–severe UC and reduces anti-drug antibody formation; do **proactive trough/antibody monitoring**.
- **JAK-inhibitor caution:** boxed warning — thrombosis, MACE, malignancy, serious infection, herpes zoster (give Shingrix); relegated to 2nd-line, avoid in >50 y, smokers, cardiovascular risk.
- **Pre-biologic screening:** latent TB (PPD/QuantiFERON-TB Gold) and hepatitis B (HBsAg/HBsAb/HBcAb) before anti-TNF.

Acute severe ulcerative colitis (ASUC) — a medical emergency

A hospitalised severe attack (Truelove–Witts criteria) carries real risk of toxic megacolon, perforation and death; **up to 30% require colectomy**. Managed jointly with surgery from day 1.

- **General measures:** admit; IV fluids and electrolyte correction; transfuse if Hct <25–28%; **stop opioids/anticholinergics/antidiarrhoeals** (precipitate toxic megacolon); plain AXR/CT on admission; stool studies + *C. difficile*; nutritional support (TPN only if malnourished/prolonged NPO — enteral/elemental diets do **not** treat active UC). **VTE pharmacological prophylaxis for ALL hospitalised IBD patients** (high thrombotic risk).
- **First-line: IV corticosteroids** — methylprednisolone **40–60 mg/day** or hydrocortisone **300 mg/day**; ± hydrocortisone enema for tenesmus. Assess response at **day 3**.
- **Day-3 non-response (Oxford/Travis criteria) = >8 stools/day, OR 3–8 stools/day with CRP >45 mg/L** → escalate to **rescue therapy** or surgery.
- **Rescue (salvage) therapy:**
  - **Infliximab 5–10 mg/kg IV** — colectomy at 3 months fell from 69% (placebo) to 47%; intensive/accelerated dosing for hospitalised patients (low albumin → faecal drug loss).

- **IV cyclosporine 2–4 mg/kg/day continuous infusion** — ~82% respond; trough **150–350 ng/mL** (Harrison) / 200–400 ng/mL (Sleisenger). A *bridge* to thiopurine/vedolizumab maintenance or to surgery.
- **CYSIF & CONSTRUCT trials:** infliximab and cyclosporine are **equally effective** as rescue therapy — choice rests on local expertise and comorbidity.
- Add PCP prophylaxis (co-trimoxazole) and monitor renal function/electrolytes/Mg/cholesterol with cyclosporine (seizure risk if cholesterol <120 mg/dL).

- **Toxic megacolon** (transverse/right colon >6 cm with loss of haustration): NG suction, roll-over manoeuvre, serial films; **colectomy if no improvement in 48–72 h** to pre-empt perforation (perforation mortality ~15%).

Surgery

- Surgery is **curative** in UC. **Indications:** intractable/steroid-refractory disease, fulminant colitis/toxic megacolon unresponsive to medical therapy (48–72 h), colonic perforation, massive haemorrhage, and dysplasia/carcinoma (cancer prophylaxis).
- **Operation of choice = restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA)** preserving the sphincter; ~6–10 (typically 5–7) bowel motions/day.
- **Pouchitis** complicates ~30–50% (up to 80% long-term); responds to **metronidazole or ciprofloxacin**. Emergency/fulminant cases are usually staged (subtotal colectomy with end ileostomy first).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **ASUC management algorithm (flowchart):** Box 1 "Severe UC — Truelove & Witts: ≥6 bloody stools/day + pulse >90 / temp >37.8°C / Hb <10.5 / ESR >30" → "Admit; IV fluids, stop opioids/anticholinergics, VTE prophylaxis, AXR/CT, stool + C. difficile/CMV, surgical referral" → "**IV methylprednisolone 40–60 mg/day**" → **Day 3 assessment**: branch (a) *Responds* → switch to oral prednisone, taper, start maintenance (5-ASA/thiopurine/biologic); branch (b) *No response (>8 stools/day OR 3–8 + CRP >45)* → "**Rescue: infliximab 5–10 mg/kg OR IV cyclosporine 2–4 mg/kg/day**" → response → maintenance; no response → "**Colectomy (IPAA)**".
- **Treatment pyramid by severity:** base "Topical/oral 5-ASA (mesalamine, sulfasalazine)" → "Budesonide MMX / oral prednisone" → "Thiopurines (AZA/6-MP)" → "Biologics (anti-TNF, vedolizumab, ustekinumab) & small molecules (JAK-i, S1P modulators)" → apex "IV steroids → rescue therapy → colectomy".

Clinical / Diagnostic significance

- **Severity assessment is the single most important determinant of therapy** — distal mild disease is treated topically, whereas severe disease mandates hospitalisation and parenteral therapy.
- **Faecal calprotectin >150 mcg/g or CRP >5 mg/L** in a previously remitting patient strongly suggests relapse and warrants endoscopic confirmation; calprotectin tracks mucosal healing and predicts pouchitis.

- **Avoid colonoscopy in fulminant disease/toxic megacolon** (perforation risk) — flexible sigmoidoscopy suffices to confirm activity.
- **Cancer surveillance:** colonoscopy from **8 years after diagnosis**, then every 1–5 years (chromoendoscopy enhances dysplasia detection); cumulative cancer risk ~3–4.8% at 20 y, 7–13.9% at 30 y.
- Antibiotics have **no role** in active or quiescent UC (unlike pouchitis); diet/TPN does not induce remission in UC.

High-yield exam pointers

- UC is **continuous, mucosal, rectum-upward**; treatment is by **extent × severity**.
- **Topical mesalamine = drug of choice for distal/mild-moderate UC**, superior to topical steroids.
- **Oral mesalamine 2–4.8 g/day** for extensive mild-moderate disease; combine oral + rectal for best effect.
- **Steroids induce, never maintain**; budesonide MMX 9 mg/day spares systemic effects.
- **ASUC: IV steroids → reassess day 3 → rescue with infliximab or cyclosporine → colectomy**; CYSIF/CONSTRUCT = equal efficacy.
- **VTE prophylaxis for every hospitalised IBD patient**; stop opioids/anticholinergics.
- **Toxic megacolon = colon >6 cm + loss of haustration**; colectomy if no response in 48–72 h.
- **Screen for TB and hepatitis B before anti-TNF**; JAK inhibitors carry thrombosis/MACE warnings.
- **IPAA is the curative operation of choice**; pouchitis (30–50%) responds to metronidazole/ciprofloxacin.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Inflammatory Bowel Disease" (clinical activity/Montreal classification, drug classes and doses, biologics/small-molecules table, indications for surgery, IPAA, toxic megacolon).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Management of Inflammatory Bowel Diseases" (acute severe UC algorithm, cyclosporine dosing/trough, CYSIF and CONSTRUCT rescue-therapy trials, thiopurine/methotrexate data).
- **CMDT 2026** — "Gastrointestinal Disorders: Ulcerative Colitis" (Table 17–12 activity assessment, mild-moderate/severe-fulminant management, day-3 Oxford non-response criteria, VTE prophylaxis, surgery and cancer-surveillance figures).

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Ulcerative colitis

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Ulcerative colitis (UC) is a chronic, relapsing idiopathic inflammatory bowel disease limited to the colon, with diffuse mucosal inflammation beginning in the rectum and extending proximally in a continuous manner. It presents chiefly with bloody diarrhea, urgency, tenesmus, mucus, and crampy lower abdominal pain. Management is extent- and severity-based, with the aims of terminating the acute attack, achieving steroid-free clinical and endoscopic remission, preventing relapse, and avoiding cancer, toxic megacolon, and unnecessary colectomy.

Initial assessment and treatment targets

- **Confirm diagnosis before escalation**: exclude infectious colitis with stool testing for *Salmonella*, *Shigella*, *Campylobacter*, Shiga-toxin-producing *E. coli*, *C. difficile*, and amebiasis; consider CMV on biopsy in corticosteroid-exposed or immunosuppressed patients.
- **Define extent**: **E1 proctitis** is limited to rectum; **E2 left-sided/distal UC** extends distal to the splenic flexure; **E3 extensive UC/pancolitis** extends proximal to the splenic flexure.
- **Grade severity**: **mild** ≤4 stools/day, no systemic illness, normal inflammatory markers; **moderate** ≥4 stools/day with minimal systemic toxicity; **severe** ≥6 bloody stools/day with pulse ≥90/min, temperature ≥37.5°C, hemoglobin <10.5 g/dL, and ESR ≥30 mm/hour.
- **Baseline activity work-up**: stool frequency and bleeding diary, fever/pulse/BP and volume status, abdominal tenderness or peritonism, Hb, WBC, platelets, ESR/CRP, serum albumin, electrolytes, renal and liver tests, fecal calprotectin/lactoferrin, and flexible sigmoidoscopy with biopsy.
- **Endoscopy**: sigmoidoscopy is preferred in acute colitis; avoid full colonoscopy in fulminant disease because of perforation risk. Mild endoscopy shows erythema and reduced vascular pattern; severe disease shows spontaneous bleeding and ulceration.
- **Targets**: symptom control alone is insufficient; aim for **steroid-free remission**, mucosal healing, normalization of CRP/fecal calprotectin, restored nutrition, preserved quality of life, and prevention of dysplasia.

General and supportive measures

- Explain the chronic relapsing course, adherence, drug adverse effects, need for surveillance, and early reporting of fever, increasing bleeding, distension, or severe pain.
- Avoid precipitating or worsening factors during acute attacks: **NSAIDs**, opioids, anticholinergics, unnecessary antidiarrheals in severe colitis, dehydration, hypokalemia, and delayed surgical review.
- Treat anemia, iron deficiency, hypoalbuminemia, fluid and electrolyte depletion, malnutrition, osteoporosis risk, anxiety/depression, and extraintestinal manifestations.
- Before immunosuppression or biologics: screen for **latent TB** and **hepatitis B**, update inactivated vaccines including influenza, pneumococcal and recombinant zoster vaccine where indicated, and avoid live vaccines once immunosuppressed.
- Antibiotics have **no routine role** in active or quiescent uncomplicated UC; use them for documented infection, perioperative indications, or pouchitis.

- All hospitalized severe UC patients require **VTE prophylaxis**, because active IBD is prothrombotic even when rectal bleeding is present.

Induction therapy by extent and severity

Clinical setting	Preferred induction	Escalation / notes
Mild proctitis	Mesalamine suppository **1 g nightly** for 4-8 weeks	If inadequate, add oral 5-ASA or topical steroid.
Mild proctosigmoiditis / left-sided UC	Mesalamine enema **4 g nightly**; suppository treats only distal 15-20 cm	Topical 5-ASA is superior to topical steroid; oral + rectal 5-ASA is better than either alone.
Mild-moderate extensive UC	Oral mesalamine **2-4.8 g/day** plus rectal mesalamine	Most improve in 4-8 weeks; sulfasalazine **3-6 g/day** works but intolerance is common; give folate with sulfasalazine.
5-ASA inadequate after 4-8 weeks	Budesonide MMX **9 mg/day** for 8 weeks or oral prednisone	Budesonide has lower systemic exposure; no role for budesonide or prednisone as maintenance.
Moderate nonhospitalized UC	Prednisone **40 mg/day** (or 40-60 mg/day equivalent)	Taper after response, usually 5 mg/week, slower below 20 mg if needed.

- Monitor 5-ASA toxicity with renal function and urinalysis periodically; recognize paradoxical 5-ASA worsening, pancreatitis, nephritis, headache, nausea, and rash.
- Requiring repeated corticosteroids, inability to taper, severe endoscopic ulceration, low albumin, anemia, or high CRP indicates high-risk disease and should prompt steroid-sparing therapy.

Moderate-to-severe steroid-sparing therapy

- **Thiopurines**: azathioprine **2-3 mg/kg/day** or 6-mercaptopurine **1-1.5 mg/kg/day** are slow-onset agents used mainly for maintenance or with anti-TNF therapy. Check TPMT activity if available; monitor CBC and liver tests. Pancreatitis, myelosuppression, hepatotoxicity, infection, lymphoma, HPV-related cervical dysplasia, and nonmelanoma skin cancer are key risks.
- **Anti-TNF agents**: infliximab **5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks** is useful for moderate-severe UC and rescue in acute severe UC; adalimumab and golimumab are subcutaneous alternatives for moderate disease. Combination infliximab + azathioprine improves steroid-free remission and reduces antidrug antibodies in selected patients.
- **Vedolizumab**: **300 mg IV at 0, 2, 6 weeks then every 8 weeks**; gut-selective anti-alpha4beta7 therapy, useful first-line in moderate-severe UC, especially in older patients or those at higher infection risk.
- **Anti-IL therapy**: ustekinumab **weight-based IV induction then 90 mg SC every 8 weeks**; IL-23 agents such as mirikizumab, risankizumab, and guselkumab are options after biologic failure or when safety profile is favored.
- **JAK inhibitors**: tofacitinib **10 mg twice daily induction, then 5 mg twice daily**; upadacitinib **45 mg daily for 8 weeks, then 15 or 30 mg daily**. Reserve especially after TNF-blocker failure; avoid in high cardiovascular/thrombosis risk when possible, vaccinate against zoster, and monitor CBC, lipids, liver tests, and infections.

- **S1P receptor modulators**: ozanimod is titrated **0.23 mg days 1-4, 0.46 mg days 5-7, then 0.92 mg daily**; etrasimod **2 mg daily**. Check ECG/cardiac risk, CBC and liver tests; watch for bradycardia, AV block, hypertension, macular edema, lymphopenia, and herpes reactivation.
- For anti-TNF loss of response, measure trough and antidrug antibodies: low trough without antibodies needs dose escalation/shorter interval; high antibodies need switch; active disease with therapeutic trough needs another class.

Acute severe UC, fulminant colitis and toxic megacolon

- **Admit immediately** if ≥6 bloody stools/day with systemic toxicity, severe anemia, hypoalbuminemia, fever, tachycardia, weight loss, dehydration, or abdominal tenderness.
- Initial care: bowel rest for 24-48 hours if very ill, IV fluids, correction of potassium/magnesium, transfusion for significant anemia, stool pathogen testing, CMV assessment if refractory, abdominal radiograph/CT for dilatation, daily labs, strict stool chart, stop opioids/anticholinergics, VTE prophylaxis, and early colorectal surgical consultation.
- **IV corticosteroid**: methylprednisolone **40-60 mg/day** or hydrocortisone **300 mg/day**. Clinical improvement should be evident within **3 days**.
- Non-response predictors include **>8 stools/day** or **3-8 stools/day with CRP >45 mg/L** after IV steroids; do not continue ineffective steroids.
- **Rescue therapy**: infliximab **5-10 mg/kg IV** or cyclosporine **2-4 mg/kg/day IV**. Cyclosporine requires renal, BP, electrolyte, magnesium/cholesterol and drug-level monitoring; give Pneumocystis prophylaxis when using combined intense immunosuppression.
- **Toxic megacolon**: colonic dilatation **>6 cm** with systemic toxicity; manage with intensive monitoring, serial abdominal films, correction of electrolytes, decompression measures, antibiotics if sepsis/perforation is suspected, and urgent surgery if worsening or no improvement in **48-72 hours**.
- Colectomy is mandatory for perforation, uncontrolled hemorrhage, peritonitis, progressive distension, hemodynamic instability, carcinoma, or failed steroid/rescue therapy.

Maintenance, monitoring and cancer prevention

- Continue the drug that achieved remission: oral mesalamine usually **2-4 g/day**; topical mesalamine may be nightly to every 3 days for distal disease. Maintenance 5-ASA reduces relapse substantially; topical steroids are ineffective for maintenance.
- **Never use corticosteroids for maintenance**. Steroid-dependence, steroid-refractoriness, or >1 steroid course every 1-2 years requires thiopurine, biologic, or small-molecule therapy.
- Follow remission with stool frequency/bleeding, Hb, albumin, CRP, fecal calprotectin, and proctoscopy/endoscopy when relapse or treatment target assessment is needed. CRP >5 mg/L or fecal calprotectin >150 mcg/g during relapse suggests active inflammation.
- Cancer surveillance is required for UC proximal to the rectum: begin colonoscopy **8 years after diagnosis**, then every **1-5 years** according to extent, activity, scarring, pseudopolyps, dysplasia, PSC, and family history. Use high-definition colonoscopy with chromoendoscopy or electronic enhancement when available.

- Endoscopically resectable visible dysplasia can be removed with close surveillance; invisible high-grade dysplasia, multifocal low-grade dysplasia, unresectable lesions, carcinoma, or suspicious strictures generally require colectomy.

Surgery and pouch care

- Indications include **intractable disease**, fulminant colitis, toxic megacolon, perforation, massive hemorrhage, obstruction/stricture suspicious for cancer, dysplasia/carcinoma, recurrent unmanageable systemic complications, growth failure, and intolerable drug toxicity.
- Emergency setting: subtotal colectomy with end ileostomy and rectal stump/mucus fistula is safest and allows later reconstruction.
- Elective operation of choice for most fit patients is **restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA)**; expected function is about 5-10 stools/day, with possible nocturnal seepage early.
- Total proctocolectomy cures colitis and removes colorectal cancer risk, but pouch patients still need assessment of retained cuff/pouch symptoms.
- **Pouchitis** presents with increased stool frequency, watery stool, urgency, cramping, nocturnal leakage, fever/malaise/arthralgia, or bleeding; confirm endoscopically and treat usually with ciprofloxacin or metronidazole. Chronic refractory pouchitis may need rotating antibiotics, budesonide/mesalamine, biologics, or pouch revision/removal.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Extent-severity-treatment flowchart**: E1 proctitis, E2 left-sided colitis, E3 extensive colitis; mild/moderate/severe; arrows to rectal 5-ASA, oral + rectal 5-ASA, steroids, biologic/small molecule, IV steroid, infliximab/cyclosporine, colectomy.
> - **Toxic megacolon algorithm**: severe UC → abdominal X-ray showing transverse colon >6 cm → stop opioids/anticholinergics, fluids/electrolytes, IV steroids, serial films, rescue therapy, surgery at 48-72 hours or earlier for perforation/peritonitis.

Clinical / Diagnostic significance

- UC is a diagnosis of exclusion during first presentation and relapse; missing *C. difficile*, CMV, ischemic colitis, STI proctitis, amebiasis, or Crohn colitis leads to dangerous steroid escalation.
- Severe UC is a medical-surgical emergency: early surgical consultation is good practice, not treatment failure.
- Extraintestinal disease may determine drug choice: peripheral arthritis, erythema nodosum and pyoderma often parallel colitis; axial spondyloarthritis may need anti-TNF therapy; PSC increases colorectal cancer risk and needs close surveillance.
- Pregnancy planning: aim remission for 3-6 months before conception; 5-ASA, many biologics and corticosteroids when indicated are generally usable, whereas methotrexate is teratogenic and JAK inhibitors should be avoided.

High-yield exam pointers

- Write the **three treatment objectives**: stop attack, achieve clinical/endoscopic remission, prevent relapse.
- Always classify by **extent + severity** before treatment.
- **Topical mesalamine is first-line and superior to topical steroid** for distal mild-moderate UC.
- **Oral + rectal mesalamine** is better than either alone for left-sided or extensive mild-moderate UC.
- **Steroids induce but never maintain remission**.
- Acute severe UC: reassess after **3 days** of IV steroids; rescue with **infliximab or cyclosporine**, or operate.
- Toxic megacolon is **colon >6 cm + toxicity**; no improvement by **48-72 hours** means colectomy.
- Screen for **TB, hepatitis B, vaccination status, zoster risk, skin cancer, CBC/LFT/renal toxicity** before and during immunosuppressive therapy.
- Surveillance colonoscopy starts **8 years** after diagnosis for colitis beyond rectum.

> **SOURCE & COVERAGE**
> Harrison 22e — "Inflammatory Bowel Disease"; Sleisenger & Fordtran's GI & Liver 11e — "Management of Inflammatory Bowel Diseases"; CMDT 2026 — "Gastrointestinal Disorders".

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Non-alcoholic fatty liver disease

Asked in: Paper II Sep 2025 · Paper II Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — Non-alcoholic fatty liver disease (NAFLD) is excess macrovesicular triglyceride accumulation in **>5% of hepatocytes** in a person who drinks little to no alcohol and has no competing cause of steatosis. It is regarded as the **hepatic manifestation of the metabolic syndrome** and is now the commonest cause of chronic liver disease worldwide. In 2023 a multi-society consensus replaced the stigmatising terms NAFLD/NASH with **MASLD** (metabolic dysfunction–associated steatotic liver disease) and **MASH** (steatohepatitis) under the umbrella of *steatotic liver disease (SLD)* — with **≥98% population overlap** between the old and new definitions. It spans a dynamic spectrum from benign **simple steatosis (MASL)** → **steatohepatitis (MASH)** → **fibrosis** → **cirrhosis / hepatocellular carcinoma (HCC)**.

Nomenclature & Diagnostic Criteria

- **Steatotic liver disease (SLD)** is the new umbrella term for excess hepatic fat; its two main causes are alcohol-associated and metabolic.
- **MASLD** = hepatic steatosis + drinks little alcohol + **≥1 cardiometabolic risk factor** (overweight/obesity, hypertension, dyslipidaemia, insulin resistance/T2DM — i.e. ≥1 of the 5 metabolic-syndrome criteria).

- A new intermediate category **MetALD** captures metabolic-risk patients who also drink "social" amounts of alcohol; higher intake regardless of metabolic factors is **ALD** (alcohol-associated liver disease).

Category	Alcohol intake (women / men)	Metabolic risk factor
MASLD	<20 g/d / <30 g/d	≥1 present
MetALD	20–50 g/d / 30–60 g/d	present
ALD	≥50 g/d / ≥60 g/d	irrelevant to definition

- Reference: 10 g alcohol ≈ one can beer / 4 oz wine / 1.5 oz (one shot) spirits. A diagnosis of MASLD still requires **exclusion** of other causes of steatosis (Table below).

Epidemiology & Risk Factors

- **Prevalence:** ~25–30% of US adults (global ~30%); **MASH in 3–6%**. Highest in **Hispanics and Asian-Indians (~50%)**, intermediate in whites (~30%), lowest in African-Americans (~25%). Highest regional prevalence: Latin America (44%), MENA (36.5%), South Asia (33.8%).
- **Lean MASLD** (BMI <25, or <23 in Asians) occurs in 4% (US) to 19% (Asia) — driven by visceral adiposity, insulin resistance and sarcopenia despite normal BMI.
- **Type 2 diabetes mellitus is the strongest risk factor** for acquisition, fibrosis progression and HCC; the MASLD–T2DM relationship is **bidirectional** (MASLD raises incident T2DM 2–5 fold). Screen every diabetic for MASLD and every MASLD patient for T2DM.
- Other associations: central (android) obesity, dyslipidaemia, hypertension, **PCOS**, hypothyroidism, hypogonadism, GH deficiency, **obstructive sleep apnoea (OSA)** and cardiovascular disease (CVD).
- **Genetics: PNPLA3 I148M** (adiponutrin, rs738409) — the strongest variant, increases steatosis, MASH and fibrosis; **TM6SF2** and **MBOAT7** also raise risk; **HSD17B13** loss-of-function is *protective*. First-degree relatives of MASH-cirrhosis probands carry a **12-fold** higher risk of advanced fibrosis; twin studies attribute ~half of cirrhosis risk to heritability.

Pathogenesis (Multiple-Hit Model)

- The old "**two-hit hypothesis**" (Day & James) is now a **multiple-parallel-hit** model: *first hit* = hepatic steatosis from insulin resistance; *subsequent hits* = lipotoxic, oxidative and inflammatory insults causing hepatocyte injury and fibrosis.
- **Steatosis** results when free fatty acid (FFA) supply exceeds disposal — from (1) dietary fat uptake, (2) adipose lipolysis (driven by peripheral **insulin resistance**), and (3) hepatic **de novo lipogenesis (DNL)**. **Dietary fructose** is delivered directly via the portal vein and activates ChREBP/SREBP-1 to drive DNL. Triglyceride storage *per se* is a relatively safe, benign biomarker of metabolic dysfunction.
- **Steatohepatitis** is defined by **lipotoxicity** — toxic lipid intermediates (palmitate, cholesterol, lysophosphatidylcholine, ceramides) cause ER and oxidative stress, hepatocyte apoptosis/ballooning and **hepatic stellate-cell activation** → fibrosis.
- **Adipokine imbalance:** ↑leptin, TNF-α, IL-6, resistin, PAI-1 with ↓**adiponectin**. Obesity-related **gut dysbiosis** increases intestinal permeability and energy harvest, exposing the liver to

inflammatory gut-derived products. Cirrhosis is the result of **futile/maladaptive repair** replacing parenchyma with scar.

Histopathology, Staging & Natural History

- **Macrovesicular steatosis in >5% hepatocytes** is the minimum. **MASH** additionally requires **hepatocyte ballooning + lobular (mixed) inflammation**; *Mallory-Denk bodies*, glycogenated nuclei, megamitochondria and lipogranulomas may be seen.
- Fibrosis is characteristically **perisinusoidal/pericellular "chicken-wire" fibrosis in acinar zone 3**, later becoming portal and bridging.
- **NAFLD Activity Score (NAS, NASH-CRN/Brunt):** unweighted sum of steatosis (0–3) + lobular inflammation (0–3) + ballooning (0–2) = **0–8**; ≤2 "not-NASH", ≥5 "likely NASH". Fibrosis is **staged separately F0–F4** (F0 none → F1 mild → F2 significant → F3 advanced/bridging → F4 cirrhosis).

Fibrosis stage	Description	Fibrosis progression rate
Simple steatosis (MASL)	fat only, no injury	~1 stage / **14 years**
MASH (steatohepatitis)	ballooning + inflammation	~1 stage / **7 years**
"At-risk MASH"	MASH + fibrosis ≥**F2**	high-risk; warrants therapy
F4 cirrhosis	bridging + nodules	decompensation 3–20%/yr; **HCC 1–2%/yr**

- **Fibrosis stage is the single strongest predictor of liver-related morbidity and mortality.** Most patients are asymptomatic until cirrhosis; the leading overall cause of death is **cardiovascular disease**, not liver disease.

Diagnosis & Non-Invasive Staging

- Usually an **incidental finding** — raised ALT or steatosis on imaging. Exclude alternatives: alcohol, hepatitis C (esp. genotype 3), autoimmune hepatitis, Wilson disease, haemochromatosis, α1-antitrypsin deficiency, drugs (amiodarone, methotrexate, tamoxifen, valproate, glucocorticoids, NRTIs).
- **Biochemistry:** mild aminotransferase rise; **ALT/AST ratio is usually >1 in MASLD** (reverses to <1 with advanced fibrosis — contrast with the AST>ALT of alcohol). *Normal ALT does not exclude MASLD* (up to 80% have normal enzymes). ANA/SMA and ferritin may each be mildly raised in ~30%.
- **Two-step non-invasive testing (NITs):**
  - **Step 1 – FIB-4 index** (age, AST, ALT, platelet count): <1.3 → low risk, manage/recheck in primary care; ≥2.67 → high risk, refer.
  - **Step 2 – VCTE (transient elastography) liver stiffness:** <8 kPa rules out advanced fibrosis; 8–12 kPa = possible fibrotic MASH; **>12 kPa** = high likelihood advanced fibrosis. **ELF panel** (hyaluronic acid + TIMP-1 + PIIINP; FDA-approved, **≥9.8** = high progression risk) is an alternative blood-based test.
  - Other scores/tools: NAFLD Fibrosis Score, **CAP** (steatosis quantitation with VCTE), **MRI-PDFF** (most accurate fat quantitation) and **MRE** (most accurate fibrosis tool).

- **Liver biopsy** (gold standard, NAS + fibrosis stage) is now reserved for diagnostic uncertainty, discordant/indeterminate NITs, or suspected competing diagnosis — limited by sampling error and inter-observer variability.

Treatment

- **Lifestyle modification is foundational for all patients:** graded weight loss — **5% reduces steatosis, 7–10% reduces inflammation/MASH, >10% can regress fibrosis**. **Mediterranean diet**, avoid saturated fat / refined carbohydrate / sugar-sweetened (fructose) beverages; **≥150 min/week** moderate exercise (aerobic and resistance both effective); **coffee ≥3 cups/day** lowers fibrosis/HCC risk; abstain from alcohol.
- **Pharmacotherapy** is reserved for **at-risk MASH (≥F2)** without cirrhosis — *not* for simple steatosis:

Agent	Class / mechanism	Evidence
Resmetirom	Selective **THR-β agonist**	**FDA accelerated approval (2024)** for non-cirrhotic at-risk MASH; *MAESTRO-NASH* — NASH resolution 26–30% vs 10%, fibrosis improvement 24–26% vs 14%
Pioglitazone (30 mg/d)	TZD, PPAR-γ ligand	*PIVENS* — NASH resolution 47% vs 21%; weight gain, fracture, bladder-cancer/CHF caution
Vitamin E (RRR-α-tocopherol 800 IU/d)	Antioxidant	*PIVENS* — histologic improvement 43% vs 19% (**non-diabetics**); caution: haemorrhagic stroke, ? prostate cancer
GLP-1 RA (semaglutide, liraglutide); **tirzepatide** (GLP-1/GIP)	Incretin mimetics	NASH resolution (semaglutide 0.4 mg 59% vs 17%); weight loss, CV benefit; fibrosis benefit not yet proven
SGLT-2 inhibitors	Glycosuric	↓ALT and steatosis; histologic benefit unproven
Statins	—	**Safe** in MASLD/compensated cirrhosis; treat dyslipidaemia, lower portal pressure, ?↓HCC

- **Not recommended / no benefit:** metformin (no histologic benefit – TONIC study; may ↓HCC risk), ursodeoxycholic acid, betaine, silymarin.
- **Bariatric surgery** for BMI ≥40, or ≥35 with comorbidity — resolves MASH and improves fibrosis in ~80% at 1 year; avoid in decompensated cirrhosis.
- **Liver transplantation** for decompensated MASH cirrhosis/HCC; MASLD is now a leading transplant indication and **may recur** in the graft.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spectrum/natural-history flow diagram:** *Normal liver → Simple steatosis (MASL) → Steatohepatitis (MASH: ballooning + inflammation) → Fibrosis (F1→F2→F3 bridging) → Cirrhosis (F4) → HCC.* Label progression rates (1 stage/14 yr for steatosis, 1 stage/7 yr for MASH) and mark "**at-risk MASH = MASH + ≥F2**".
- **Two-step risk-stratification algorithm:** Box 1 *FIB-4* (<1.3 low / ≥2.67 high) → Box 2 *VCTE* (<8 / 8–12 / >12 kPa) or *ELF* → "refer to hepatology / consider biopsy". Label axes "Primary care → Specialist".

Clinical / Diagnostic significance

- **CVD is the leading cause of death** in MASLD — aggressive cardiovascular risk reduction (statins, BP, glycaemic control) is central, not optional.
- MASLD is an independent risk factor for **incident T2DM, CKD, colorectal cancer and metabolic syndrome**; it can cause **HCC even without cirrhosis**, complicating surveillance.
- Once **cirrhosis** is diagnosed: 6-monthly **HCC surveillance (USS ± AFP)**, endoscopic **variceal screening per Baveno**, and monitoring for decompensation.
- A large share of "**cryptogenic cirrhosis**" is burnt-out MASH (steatosis disappears as fibrosis advances).
- Targeted (not universal) screening of high-risk groups — T2DM, obesity-with-metabolic-complications, family history of cirrhosis — using FIB-4 is cost-effective.

High-yield exam pointers

- **New nomenclature (2023): SLD umbrella → MASLD / MetALD / MASH**; ~98% overlap with old NAFLD/NASH.
- MASLD = steatosis + **≥1 cardiometabolic risk factor** + alcohol <20 g/d (F) / <30 g/d (M).
- **>5% steatotic hepatocytes** = minimum; **MASH = ballooning + lobular inflammation**; "chicken-wire" zone-3 fibrosis.
- **T2DM = strongest risk factor**; **PNPLA3 I148M** = key gene; **HSD17B13** protective.
- **Fibrosis stage = best prognostic marker**; **CVD = commonest cause of death**.
- **NAS 0–8** (steatosis+inflammation+ballooning); fibrosis staged separately **F0–F4**.
- **FIB-4 then VCTE/ELF** is the non-invasive pathway; FIB-4 <1.3 excludes advanced fibrosis.
- **Weight loss 5/7/10%** = steatosis/MASH/fibrosis benefit; **resmetirom (THR-β agonist)** = first FDA-approved drug (2024); pioglitazone & vitamin E from PIVENS.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Metabolic Dysfunction–Associated Steatotic Liver Disease and Steatohepatitis" (primary spine: nomenclature, criteria, pathogenesis, FIB-4/VCTE/ELF staging, resmetirom/PIVENS, bariatric surgery, transplant).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Nonalcoholic Fatty Liver Disease" (two-hit/multiple-hit pathogenesis, NAS/Brunt histology, PNPLA3/MBOAT7 genetics, natural history).
- **CMDT 2026** — "Metabolic Dysfunction–Associated Steatotic Liver Disease" (ALT/AST ratio, weight-loss thresholds, current drug regimens, prognosis).

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Portal hypertension — portocaval anastomosis and management

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — **Portal hypertension** is defined as elevation of the **hepatic venous pressure gradient (HVPG)** to **>5 mmHg**. The portal venous system normally drains blood from the stomach, small and large intestines, spleen, pancreas, and gallbladder into the liver. When portal pressure rises, blood is diverted through **portosystemic (portocaval) collateral channels** — pre-existing communications between the portal and systemic venous systems that dilate to decompress the hypertensive portal bed; these collaterals are the anatomical basis of **varices, caput medusae and shunt-related complications**. The three primary clinical consequences are **gastroesophageal varices with haemorrhage, ascites, and splenomegaly with hypersplenism**.

Sites of portosystemic (portocaval) anastomosis

- **Lower oesophagus / gastro-oesophageal junction** — left gastric (coronary) and short gastric veins (portal) anastomose with the azygos/hemiazygos system (systemic) → **oesophageal and gastric varices** (the most dangerous, cause variceal haemorrhage).
- **Anorectal junction** — superior rectal vein (portal, via inferior mesenteric vein) anastomoses with middle and inferior rectal veins (systemic) → **anorectal varices** (distinct from haemorrhoids).
- **Periumbilical / anterior abdominal wall** — recanalised paraumbilical vein (via left branch of portal vein) anastomoses with superficial epigastric veins → **caput medusae**; a venous hum over it = *Cruveilhier–Baumgarten murmur*.
- **Retroperitoneal / bare areas** — veins of *Retzius* and *Sappey* between gut/liver and retroperitoneal systemic veins.
- **Spontaneous splenorenal shunt** — splenic vein to left renal vein; relevant to gastric varices and amenable to BRTO.

Classification of portal hypertension (Harrison Table 355-3)

Anatomical level	Site relative to sinusoid	Representative causes
Prehepatic	—	Portal vein thrombosis; splenic vein thrombosis; massive splenomegaly (*Banti's syndrome*)
Intrahepatic — presinusoidal	Before sinusoid	Schistosomiasis; congenital hepatic fibrosis
Intrahepatic — sinusoidal	At sinusoid	**Cirrhosis (many causes)**; alcoholic hepatitis
Intrahepatic — postsinusoidal	After sinusoid	Hepatic sinusoidal obstruction (veno-occlusive syndrome)
Posthepatic	Hepatic veins → heart	Budd-Chiari syndrome; IVC webs; restrictive cardiomyopathy; constrictive pericarditis; severe congestive heart failure

- **Intrahepatic causes account for >95% of cases**, and **cirrhosis is overwhelmingly the most common cause** of portal hypertension.

Pathophysiology and haemodynamic staging

- Portal hypertension results from **two simultaneous processes**: (1) **increased intrahepatic resistance** to blood flow (cirrhosis, regenerative nodules, microthrombi), and (2) **increased splanchnic blood flow** from splanchnic vasodilation (mediated by nitric oxide and other vasodilators).
- In advanced disease, **neurohumoral activation** (renin-angiotensin-aldosterone and sympathetic systems) causes sodium/water retention, expanded blood volume, and a **hyperdynamic circulation** that further raises portal pressure.
- **Compensated cirrhosis**: HVPG **5–10 mmHg** — may be asymptomatic for ≥10 years.
- **Clinically significant portal hypertension (CSPH)**: HVPG **≥10 mmHg** — substantial risk of decompensation (variceal bleed, ascites, encephalopathy).
- **Variceal haemorrhage risk**: HVPG / gradient **>12 mmHg**. After decompensation, median survival is **<2 years**.

Clinical features and diagnosis

- **Three primary complications**: gastroesophageal varices ± haemorrhage; ascites with peripheral oedema; congestive splenomegaly with **hypersplenism** (thrombocytopenia, leukopenia) — often the *first* indication of portal hypertension.
- **Variceal haemorrhage** carries a **20–30% mortality per bleeding episode**; ~5–15% of cirrhotics develop varices per year, and ~one-third of those with varices will bleed.
- **Predictors of bleeding**: severity of cirrhosis (Child-Pugh class, MELD score), height of wedged-hepatic-vein pressure, varix size and location, tense ascites, and endoscopic stigmata — *red wale signs, hematocystic spots, diffuse erythema, bluish colour, cherry-red spots, white-nipple spots*.

- **Diagnosis**: suggested by thrombocytopenia, splenomegaly, ascites, encephalopathy or varices. **Endoscopy** identifies varices; **contrast CT/MRI** shows nodular liver and intra-abdominal collateral circulation; **HVPG** can rarely be measured by interventional radiology.
- **Ascites work-up**: diagnostic paracentesis with **SAAG** — a **SAAG >1.1 g/dL** indicates portal hypertension as the cause; ascitic neutrophils **>250/μL** indicate spontaneous bacterial peritonitis.

Management of variceal haemorrhage

A. Primary prophylaxis (no prior bleed)

- Surveillance **endoscopy** at diagnosis of compensated cirrhosis, then every 2 years if liver disease is active or every 3 years if inactive; screening can be omitted if no thrombocytopenia and transient elastography liver stiffness **<20 kPa**.
- High-risk varices = medium/large varices, or small varices with high-risk stigmata or decompensated cirrhosis.
- **Nonselective beta-blockers (NSBB)** — propranolol or nadolol titrated to **heart rate 55–60 beats/min** with systolic BP >90 mmHg. **Carvedilol** is the NSBB of choice (added anti-α1 vasodilation lowers portal pressure more, needs no HR goal, may prevent decompensation and improve survival in CSPH).
- **Endoscopic variceal ligation (EVL)** has equivalent efficacy to NSBB for primary prophylaxis; once prophylaxis is started, surveillance endoscopy is unnecessary.

B. Acute variceal bleeding

- **Resuscitate**: fluid and red-cell replacement using a **restrictive transfusion** strategy (start at Hb <7 g/dL, goal 7–9 g/dL) — reduces rebleeding and mortality. Do **not** correct prolonged PT with FFP unless there is active coagulopathic bleeding.
- **Vasoconstrictors — somatostatin or octreotide** improve initial bleeding control, reduce transfusion needs and all-cause mortality.
- **Prophylactic antibiotics — ceftriaxone** before endoscopy reduces infection, rebleeding and mortality.
- **Urgent upper endoscopy** is first-line — diagnoses and controls bleeding with **EVL**.
- **Balloon tamponade** (*Sengstaken-Blakemore* or *Minnesota* tube) or self-expandable metal stents can stabilise the patient as a **bridge to TIPS** after endoscopic failure.

C. TIPS and shunts (portal decompression)

- **Transjugular intrahepatic portosystemic shunt (TIPS)** is created percutaneously: an expandable metal stent is advanced under angiographic guidance into the hepatic vein and through the hepatic parenchyma to form a **direct portocaval shunt** that decompresses the portal system.
- Indications: failure of/ineligibility for endoscopic therapy; gastric or proximal-stomach varices where band ligation often fails; refractory recurrent bleeding; bridge to transplant.
- **Hepatic encephalopathy occurs in up to 20%** after TIPS, especially in the elderly and those with pre-existing encephalopathy.
- **Gastric varices fed by a splenorenal shunt** can be treated with **balloon-occluded retrograde transvenous obliteration (BRTO)**, sometimes combined with TIPS.

- Monitor TIPS patency with **Doppler ultrasound** for stenosis; all TIPS candidates should undergo transplant evaluation.

D. Recurrent bleeding (Harrison Fig. 355-3)

- Endoscopic therapy + pharmacologic therapy to control bleeding, then risk-stratify by Child class: **Child A** → consider **TIPS** and transplant evaluation; **Child B/C** → transplant evaluation with endoscopic therapy/beta-blockers and consideration of TIPS, progressing to **liver transplantation**.

Management of other portal-hypertensive complications

- **Ascites**: dietary **sodium restriction (2 g/day)**; **spironolactone 100 mg/d ± furosemide 40 mg/d**, escalating to spironolactone 400 mg/d and furosemide 160 mg/d. **Refractory ascites** → large-volume paracentesis (give **IV 25% albumin 6–8 g per L** removed if ≥5 L) or TIPS (effective but does *not* improve survival and increases encephalopathy). Avoid NSAIDs and aminoglycosides; use ACEi/ARB cautiously.
- **Spontaneous bacterial peritonitis**: ascitic neutrophils >250/μL; commonest organism *E. coli*; treat with **IV third-generation cephalosporin × 5 days** plus **albumin (1.5 g/kg day 1, 1.0 g/kg day 3)** to prevent renal failure; **quinolone prophylaxis** after an episode and at presentation with GI bleeding.
- **Hepatorenal syndrome**: stop diuretics, give albumin 1 g/kg/d; treat with **terlipressin** (or low-dose norepinephrine); midodrine + octreotide + albumin are third-line; **liver transplantation** is definitive.
- **Hepatic encephalopathy**: treat precipitants; **lactulose** titrated to 2–3 soft stools/day; **rifaximin 550 mg twice daily** (has replaced neomycin/metronidazole); closure of large portosystemic shunts in refractory cases; avoid protein restriction.
- **Portal hypertensive gastropathy**: *snakeskin mosaic* mucosa; treat with NSBB + iron; refractory bleeding → TIPS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sites of portosystemic anastomosis** — outline the portal vein with collaterals labelled: *Oesophageal varices (left gastric/coronary ↔ azygos)*, *Anorectal varices (superior ↔ middle/inferior rectal)*, *Caput medusae (paraumbilical ↔ epigastric)*, *Retroperitoneal veins of Retzius*, *Splenorenal shunt (splenic ↔ left renal vein)*.
- **TIPS schematic** — label: *Jugular vein → IVC → Hepatic vein*, *Expandable metal stent through hepatic parenchyma*, *Portal vein*, *Direct portocaval shunt*.

Clinical / Diagnostic significance

- **HVPG** is the gold-standard measure of portal pressure and stratifies risk: >5 = portal hypertension, ≥10 = CSPH/decompensation risk, >12 = variceal bleeding risk.
- **SAAG >1.1 g/dL** confirms portal hypertension as the cause of ascites; ascitic protein <1.5 g/dL flags increased SBP risk.
- Endoscopic surveillance and **NSBB/carvedilol or EVL** prevent first bleeds; **vasoconstrictor + antibiotic + endoscopic** therapy is the acute bleeding bundle.

- **TIPS** is the key non-surgical portal decompression but precipitates encephalopathy; **liver transplantation** is the definitive treatment for decompensated portal hypertension.

High-yield exam pointers

- Portal hypertension = **HVPG >5 mmHg**; variceal bleeding risk at **>12 mmHg**; CSPH = **≥10 mmHg**.
- **Cirrhosis (sinusoidal, intrahepatic) >95%** of cases; classify pre-/intra-/post-hepatic.
- Three complications: **varices, ascites, hypersplenism**; variceal bleed mortality **20–30%/episode**.
- Acute bleed bundle: **restrictive transfusion (Hb 7–9), octreotide/somatostatin, ceftriaxone, urgent EVL**.
- **Carvedilol** is now the NSBB of choice for primary prophylaxis of variceal bleeding.
- **TIPS = direct portocaval shunt**; complication = encephalopathy in **up to 20%**; bridge to transplant.
- *Sengstaken-Blakemore / Minnesota* tube = balloon tamponade rescue; **BRTO** for splenorenal-shunt gastric varices.
- Ascites: **spironolactone + furosemide**, albumin after LVP ≥5 L; SBP = **neutrophils >250/µL**.
- HE: **lactulose + rifaximin 550 mg BD**; *caput medusae* with a hum = **Cruveilhier-Baumgarten** sign.

SOURCE & COVERAGE

Harrison 22e — Ch 355 "Cirrhosis and Its Complications" (Tables 355-2/355-3; Figs 355-3, 355-4, 355-5). **Coverage note**: Harrison Ch 355 covers the definition, HVPG thresholds, classification, pathophysiology and full management of portal hypertension and its complications, and names gastroesophageal varices, the splenorenal shunt, intra-abdominal collateral circulation and the TIPS portocaval shunt. The detailed *named anatomical sites of portosystemic anastomosis* (caput medusae / Cruveilhier-Baumgarten, anorectal varices, periumbilical and retroperitoneal veins of Retzius/Sappey, splenorenal shunt drainage) are universally accepted standard anatomy supplied to satisfy the "portocaval anastomosis" phrasing, as this anatomical detail is thin in the provided chapter.

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Serological and virological markers of hepatitis B

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Hepatitis B virus (HBV) is a 42-nm, enveloped, partially double-stranded DNA hepadnavirus with an outer **hepatitis B surface antigen (HBsAg)** coat, an inner **hepatitis B core antigen (HBcAg)**, secreted **hepatitis B e antigen (HBeAg)**, and circulating **HBV DNA**. Serologic and virologic markers diagnose acute HBV, distinguish natural recovery from vaccination, define chronic infection beyond 6 months, assess infectivity and replication, and identify clinically important mutant or occult infection.

Virologic basis and chronology

- **HBsAg** is the envelope protein of virions and abundant noninfectious spherical/tubular particles; routine assays detect all forms. It is the **first serum marker**, detectable **1-12 weeks after exposure**, usually **8-12 weeks**, and precedes ALT rise and symptoms by **2-6 weeks**.
- **HBcAg** remains intracellular or within HBsAg-coated nucleocapsids; naked core antigen does not circulate, so **HBcAg is not a routine serum diagnostic test**. Its antibody, **anti-HBc**, is therefore more useful clinically.
- **HBeAg** is a secreted nucleocapsid protein from the precore/core gene. It appears with or shortly after HBsAg and is a **qualitative marker of replication, intact virions, high infectivity, and usually detectable HBV DNA**.
- **HBV DNA** is the direct virologic marker of replication and is more sensitive and precise than HBeAg; it is essential in chronic HBV, pregnancy transmission risk, antiviral decisions, and follow-up.
- **Anti-HBc** appears **1-2 weeks after HBsAg**. **IgM anti-HBc** predominates for the first **6 months** after acute infection; **IgG anti-HBc** persists indefinitely after either recovery or chronicity.
- **Anti-HBs** appears after HBsAg clearance, usually weeks to months after anti-HBc, persists long-term, and is the **protective neutralizing antibody** after natural infection or vaccination.
- **Anti-HBe** appears after HBeAg loss and usually indicates lower replication and reduced infectivity, but it does not exclude HBeAg-negative chronic hepatitis due to precore or basal core promoter mutants.

Individual markers and interpretation

Marker	What it detects	High-yield interpretation
HBsAg	Surface/envelope antigen in virions and subviral particles	Current HBV infection; persistence **>6 months** = chronic HBV. In self-limited acute HBV it disappears 1-2 months after jaundice and rarely persists beyond 6 months.
Anti-HBs	Antibody to HBsAg	Recovery, noninfectivity, and immunity when it follows natural infection; isolated anti-HBs indicates vaccination. Protective vaccine response is commonly taken as **>=10 mIU/mL**.

Marker	What it detects	High-yield interpretation
Total anti-HBc	IgM + IgG antibody to core antigen	Marker of natural exposure; **not produced by vaccination**. Persists after recovery and in chronic HBV.
IgM anti-HBc	Recent anti-core response	Best marker of acute/recent HBV; sole marker in the **window period**; may reappear during severe flares/reactivation of chronic HBV.
IgG anti-HBc	Remote or chronic anti-core response	Past natural infection or chronic HBV; predominates beyond 6 months.
HBeAg	Secreted e antigen	High replication and infectivity; persistence **>3 months** after acute HBV suggests higher likelihood of chronic infection.
Anti-HBe	Antibody to e antigen	Seroconversion marker, usually lower infectivity; can coexist with active HBV DNA replication in precore/core promoter mutant disease.
HBV DNA by PCR	Viral nucleic acid	Quantitative replication marker; correlates with infectivity, liver injury, progression, cirrhosis, HCC risk, and treatment response.
Quantitative HBsAg	Serum HBsAg level	Specialist follow-up marker; serial use may help distinguish inactive carrier state from HBeAg-negative active disease.

Acute hepatitis B: serologic sequence

- **Early incubation:** HBV DNA and HBsAg appear before clinical hepatitis; HBeAg follows shortly and indicates high infectivity. ALT rises later, with symptoms and jaundice.
- **Symptomatic/icteric phase:** HBsAg remains detectable; **IgM anti-HBc** is present and confirms acute HBV. HBeAg usually disappears near peak ALT before HBsAg clearance.
- **Resolution:** HBsAg becomes negative, **anti-HBe** appears first, then **anti-HBs** appears and persists. Anti-HBc switches from predominantly IgM to predominantly IgG.
- **Window period:** HBsAg has disappeared but anti-HBs is not yet detectable; **IgM anti-HBc may be the only serologic evidence** of current or recent infection. More sensitive modern HBsAg and anti-HBs assays make this less common.
- **Rare HBsAg-negative acute HBV:** in up to **1-5%** of acute infections, HBsAg may be below assay detection; **IgM anti-HBc establishes the diagnosis**.
- **Progression to chronicity:** persistence of **HBsAg >6 months** or **HBeAg >3 months** after acute illness suggests chronic HBV. Immunocompetent adults usually recover; chronicity is far more common after neonatal, childhood, or immunosuppressed infection.

Common serologic patterns

HBsAg	Anti-HBs	Anti-HBc	HBeAg / anti-HBe	HBV DNA	Interpretation
-	-	-	-	-	Susceptible, no evidence of prior infection or vaccination.

HBsAg	Anti-HBs	Anti-HBc	HBeAg / anti-HBe	HBV DNA	Interpretation
-	+	-	-	-	**Vaccinated immune**; anti-HBs alone.
-	+	IgG +	Usually anti-HBe + or -	Usually undetectable	**Recovered natural infection**; immune due to past HBV.
+	-	IgM +	HBeAg often + early	+	**Acute hepatitis B**.
-	-	IgM +	Variable	Variable	**Window period** or rare HBsAg-negative acute HBV.
+ >6 months	-	IgG +	**HBeAg +**	High	**HBeAg-positive chronic HBV/chronic hepatitis**; high replication and infectivity.
+ >6 months	-	IgG +	HBeAg -, anti-HBe +	Low or undetectable, usually **<2000 IU/mL**	**Inactive carrier / HBeAg-negative chronic HBV infection**, if ALT normal and stable over serial follow-up.
+ >6 months	-	IgG +	HBeAg -, anti-HBe +	Detectable/high, often fluctuating	**HBeAg-negative chronic hepatitis B** from precore/core promoter mutant or reactivation; ALT often elevated or fluctuating.
-	-	IgG +	-	Usually negative; occasionally low-level positive	**Isolated anti-HBc**: remote infection with lost anti-HBs, false-positive, window period if IgM, or occult/low-level infection.
+	+	IgG +	Variable	Variable	Chronic HBV with low-affinity/nonneutralizing anti-HBs or heterotypic anti-HBs; **not** proof of imminent clearance.

Chronic HBV phases and virologic classification

- **HBeAg-positive chronic HBV infection** (*immune-tolerant phase*): HBeAg positive, very high HBV DNA, commonly **>=10^7 IU/mL**, normal or low ALT, and minimal necroinflammation/fibrosis; typical after perinatal or early-childhood infection.
- **HBeAg-positive chronic hepatitis B** (*immune-active/clearance phase*): HBeAg positive, HBV DNA high or intermediate, ALT elevated, and active necroinflammation. Harrison emphasizes that DNA is often well above **10^3-10^4 IU/mL** and may exceed **10^9 IU/mL**.
- **HBeAg-negative chronic HBV infection** (*inactive carrier state*): HBsAg positive, IgG anti-HBc positive, HBeAg negative, anti-HBe positive, normal ALT, minimal histologic activity, and HBV DNA undetectable or low, usually **<2000 IU/mL**.
- **HBeAg-negative chronic hepatitis B** (*reactivation phase*): HBeAg negative but HBV DNA detectable, ALT elevated or fluctuating, and active liver injury. It is usually due to **precore stop-codon** or **basal core promoter** mutations, so absence of HBeAg does not prove inactive disease.

- **HBsAg-negative phase / functional cure:** HBsAg negative, anti-HBc positive, anti-HBs present or absent, normal ALT, and serum HBV DNA usually undetectable; intrahepatic cccDNA may persist, so reactivation remains possible under intense immunosuppression.
- The distinction between inactive carrier state and HBeAg-negative chronic hepatitis requires **serial ALT and HBV DNA monitoring over months**, because both DNA and aminotransferases may fluctuate.

Special patterns, mutants, and pitfalls

- **Precore mutation:** classically G1896A creates a stop codon and prevents HBeAg synthesis; patients have **anti-HBe with detectable HBV DNA** and may have progressive HBeAg-negative chronic hepatitis.
- **Basal core promoter mutations:** reduce HBeAg production while maintaining replication; they are associated with HBeAg-negative active disease and have been linked with more severe infection and HCC risk in specialist texts.
- **Occult HBV infection: HBsAg negative with detectable HBV DNA**, often low level, and sometimes without anti-HBc; important in cryptogenic liver disease, blood/organ donation, and immunosuppression.
- **Isolated anti-HBc** should not be equated automatically with active replication; common explanations are remote resolved infection with loss of anti-HBs, false positivity, window-period acute HBV if IgM, or rarely low-level occult infection.
- **HBsAg escape mutants** may alter the surface antigen "a" determinant, causing failure of commercial HBsAg detection or reduced neutralization by vaccine/HBIG-derived anti-HBs.
- **IgM anti-HBc is not always de novo acute HBV:** it may reappear in severe flares or spontaneous/reactivation episodes of chronic HBV; clinical history, old records, HBsAg duration, and serial follow-up are essential.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Acute HBV timeline:** x-axis weeks after exposure; label HBV DNA/HBeAg early, HBsAg first antigen, ALT and jaundice peak, IgM anti-HBc, IgG anti-HBc, anti-HBe, anti-HBs, and the **window period** between HBsAg loss and anti-HBs appearance.
- **Chronic HBV phase chart:** label immune-tolerant HBeAg-positive infection, immune-active HBeAg-positive hepatitis, inactive carrier HBeAg-negative infection, HBeAg-negative chronic hepatitis/reactivation, and HBsAg-negative functional cure; show ALT and HBV DNA trends.

Clinical / Diagnostic significance

- **Acute HBV diagnosis:** HBsAg plus **IgM anti-HBc** confirms acute infection; IgM anti-HBc is decisive in the window period and in rare low-HBsAg acute disease.
- **Chronic HBV diagnosis:** HBsAg persistence beyond 6 months with IgG anti-HBc establishes chronic HBV; HBeAg, anti-HBe, HBV DNA, ALT, and fibrosis assessment classify activity.
- **Infectivity and transmission:** HBeAg-positive, high-DNA serum is highly infectious; HBeAg-positive mothers transmit HBV to offspring far more often than anti-HBe-positive mothers.

Maternal HBV DNA >=**200,000 IU/mL** supports third-trimester antiviral prophylaxis in addition to neonatal HBIG plus vaccine.

- **Treatment and prognosis:** HBV DNA is the key quantitative marker for antiviral decisions and monitoring; persistent high replication predicts cirrhosis and HCC risk. Short-term treatment endpoints include HBV DNA suppression, HBeAg loss/seroconversion, ALT normalization, and ideally HBsAg loss.
- **Screening before immunosuppression:** HBsAg and anti-HBc, often with anti-HBs, should be checked before chemotherapy, B-cell-depleting agents, transplantation, or prolonged immunosuppression because resolved or inactive HBV can reactivate.
- **Vaccination and postexposure care:** isolated anti-HBs indicates vaccine immunity; postvaccination anti-HBs testing is useful in high-risk adults, dialysis, immunosuppression, and occupational exposure decisions. HBIG provides immediate anti-HBs, while vaccine provides durable active immunity.
- **Blood and organ safety:** screening of donated blood for HBsAg and anti-HBc has markedly reduced transfusion-associated HBV; isolated anti-HBc or occult HBV can still be clinically relevant in donors and immunosuppressed recipients.

High-yield exam pointers

- **HBsAg first, anti-HBs last** is the simplest acute HBV chronology.
- **IgM anti-HBc = acute/recent HBV** and is the marker of the **window period**.
- **IgG anti-HBc = natural exposure**, not vaccination.
- **Anti-HBs alone = vaccination**; anti-HBs plus IgG anti-HBc = recovered natural infection.
- **HBsAg >6 months = chronic HBV**; **HBeAg >3 months** after acute infection predicts chronicity.
- **HBeAg = replication/infectivity**, but **HBV DNA is the best quantitative replication marker**.
- **HBeAg-negative does not mean inactive**; check HBV DNA and ALT for precore/core promoter mutant disease.
- **Inactive carrier:** HBsAg positive, anti-HBe positive, normal ALT, low/undetectable HBV DNA, usually **<2000 IU/mL**.
- **Isolated anti-HBc** needs interpretation: remote infection, false-positive, window period, or occult/low-level HBV.

SOURCE & COVERAGE

Harrison 22e — "Acute Viral Hepatitis"; Harrison 22e — "Chronic Hepatitis"; Sleisenger & Fordtran's Gastrointestinal and Liver Disease — "Hepatitis B"; CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders".

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Tropical sprue

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Tropical sprue (TS) is a **primary, acquired malabsorption syndrome** affecting residents of, or visitors to, endemic tropical regions, characterised by chronic diarrhoea, steatorrhoea, weight loss and multiple nutrient deficiencies (classically **both folate and vitamin B12**). The term "primary" implies that all other recognised causes of malabsorption have been excluded. By the **Baker–Klipstein definition (1970)**, diagnosis requires malabsorption of **at least two unrelated nutrient groups** (e.g. fat, carbohydrate, vitamins), an abnormal small-bowel mucosal biopsy, and exclusion of celiac disease, parasitic infection, SIBO and pancreatic insufficiency. It is regarded by many as a **post-infectious complication** of acute enteritis and responds to broad-spectrum antibiotics plus folic acid.

Historical note & epidemiology

- **History:** Malabsorption in the tropics is described in the *Charaka Samhita* as **"Grahani"** (loss of "digestive fire"). First English description by **William Hillary (1759, Barbados)** as *aphthoides chronica*; the word "sprue" derives from the Dutch *sprouw* (aphthous mouth ulceration); **Manson** coined "sprue" in 1880.
- **Geography:** Endemic in **South & South-East Asia (southern India, Pakistan), the Philippines, the Caribbean (Puerto Rico, Haiti, Cuba), Central/South America and parts of tropical Africa/Australia**. Notably **rare in Africa, Jamaica and parts of South-East Asia** — distribution is patchy, suggesting different aetiologies in different regions.
- **Burden:** Occurs in **8–20%** of people after an attack of infectious gastroenteritis in India. **Adults > children** (opposite to celiac disease). **Epidemic TS** occurred in WWII soldiers/POWs and in South India in the 1960s–70s (responsible for **30,000–40,000 deaths**); epidemic disease is **no longer reported**, but **sporadic TS** remains a leading cause of adult malabsorption in South Asia. Seasonal clustering was noted in Puerto Rico (first 3 months of the year).
- **Declining incidence** over recent decades — attributed to improved sanitation and wider antibiotic use in acute diarrhoea.

Aetiopathogenesis

- The aetiology is **uncertain**; no single causative agent has ever been isolated despite extensive search. Because TS **responds to antibiotics**, an **infectious/post-infectious basis** is favoured.
- **Post-infectious trigger:** In travellers/expatriates, an antecedent gastroenteritis (enteropathogenic *E. coli*, *Giardia*, *Cyclospora*) greatly raises risk — in US military personnel, prior infectious gastroenteritis increased the odds of TS ~**36.6-fold** and of intestinal malabsorption ~3.9-fold.
- **Small-intestinal bacterial overgrowth (SIBO):** Overgrowth of **enterotoxigenic coliforms** (*Klebsiella*, *Enterobacter cloacae*, *E. coli*) in the upper small bowel. Unabsorbed luminal fat activates the **"ileal brake"** (peptide YY, neurotensin) → slowed small-bowel transit → perpetuation of SIBO.
- **Other agents:** Coronavirus-like viral particles seen in jejunal enterocytes in some series (inconsistent).

- **Mucosal injury model:** Microbial toxins damage **intestinal crypt stem cells** → immature enterocytes, villous shortening and increased permeability → mucosal inflammation with a marked rise in **intraepithelial lymphocytes (IELs)** (predominantly CD8+ αβ-T cells; innate signalling via NOD-2/TLR-2, IL-15, T-bet). The difference between symptomatic TS and asymptomatic tropical enteropathy may reflect host innate immune response.

Clinical features

- **Cardinal triad:** chronic diarrhoea, **sore red tongue (glossitis)** and weight loss; stools are **pale, bulky, frothy, foul-smelling (steatorrhoea)** with abdominal distension and borborygmi; nocturia.
- **Onset:** In southern India often follows an **acute enteritis**; in expatriates/epidemics begins with fever and watery (rarely bloody) diarrhoea, then lingering diarrhoea with weight loss. Course shows **exacerbations and remissions**.
- **Deficiency signs:** pallor (iron, folate, B12 anaemia); **angular stomatitis, cheilitis, glossitis** (B-complex); **hyperpigmentation of palms, knuckles and buccal mucosa** (attributed to B12 deficiency — may be the only presenting sign); pedal oedema, leukonychia, koilonychia and hair/skin changes (hypoproteinaemia/iron).
- **Late/severe:** gross emaciation with proximal muscle weakness; **night blindness, Bitot spots, corneal xerosis** (vitamin A); tetany/carpopedal spasm (Ca/Mg); haemorrhagic diathesis (vitamin K); metabolic bone disease (vitamin D); peripheral neuropathy. *Subacute combined degeneration of the cord* (historical) and **"sprue coma"** (apathy/listlessness from magnesium depletion) are now rare. A rare **Ogilvie-like colonic pseudo-obstruction** may occur.
- **Clubbing is NOT a feature** — its presence should suggest an alternative (e.g. IPSID/lymphoma).

Histopathology & pathophysiology

- Biopsy from distal duodenum/proximal jejunum (now standard at upper GI endoscopy) shows **partial villous atrophy with crypt elongation/hyperplasia**; villi may appear fused; lamina propria infiltrated by lymphocytes/plasma cells with **markedly increased IELs** (reported mean ~77 IELs/100 enterocytes); an eosinophilic infiltrate may be seen.
- The normal **villous-to-crypt ratio of 4:1–5:1 falls to ~2:1 or 1:1**. *Complete/flat (total) villous atrophy as in celiac disease is NOT seen in TS.*
- **Whole small-bowel involvement** (ileum often more affected than duodenum) — distinguishing it from the proximal-predominant celiac disease. Changes are of **similar severity throughout** the small bowel, and a **gluten-free diet does NOT improve** TS.
- **Electron microscopy:** degenerating/dead cells in the **basal crypt region** (a feature resembling radiation/chemotherapy enteritis) — supports a **primary stem-cell** lesion; *this differs from celiac disease*.
- **Functional consequences:** ↓ absorptive surface → ↓ **D-xylose** absorption; **fat malabsorption** with secondary *functional* pancreatic insufficiency (abnormal Lundh/pancreolauryl test, but **normal secretin response**); **B12 and bile-acid malabsorption** from terminal-ileal involvement; folate/iron malabsorption from proximal involvement → **combined folate + B12 deficiency** is characteristic.

Feature	Tropical sprue	Celiac disease
Distribution in small bowel	Entire small bowel (ileum ≥ duodenum)	Proximal (duodenum/jejunum) predominant
Villous atrophy	Partial; ratio 2:1–1:1; never totally flat	May be total/flat (Marsh III)
Vitamin pattern	**Folate AND B12 both low**	Folate low, **B12 usually normal**
Serology (anti-tTG/EMA)	Negative	Positive
Response to gluten-free diet	None	Clinical & histologic improvement
Response to antibiotics + folate	Curative	No response
EM crypt change	Degenerating basal crypt (stem-cell) cells	Absent

Diagnosis

- **No single diagnostic test** — diagnosis rests on **multiple nutrient deficiencies + abnormal small-bowel biopsy + exclusion** of other causes (Baker–Klipstein).
- **Mandatory exclusions:** *Giardia* and other parasites (≥3 stool samples with modified acid-fast stains — TS should not be entertained until cysts/trophozoites excluded), **celiac disease** (negative anti-tTG/EMA serology), SIBO and chronic pancreatitis.
- **Malabsorption tests (endemic-area data):** abnormal **D-xylose** ~99%, **steatorrhoea** ~90%, **B12 malabsorption** 60–90%; a **5-g** (rather than 25-g) D-xylose dose is used in the tropics to avoid vomiting/diarrhoea. Serum **folate and B12 both low**; raised methylmalonic acid confirms B12 deficiency.
- **Endoscopy: scalloping** of duodenal folds and **mosaic/"mosaiform" mucosa** of the terminal ileum (better seen with narrow-band/magnification imaging); jejunal aspirate culture **>10^5 organisms/mL** indicates SIBO.
- **Imaging:** barium follow-through shows **thickened mucosal folds, loss of the feathery jejunal pattern, dilated atonic loops and delayed transit**; CT mainly excludes mesenteric masses/lymphadenopathy (TB, lymphoma).

Treatment

- **Specific therapy: Tetracycline 250 mg QID (or doxycycline 100 mg OD) for 3–6 months** *plus* **folic acid** — usually **curative**, with clinical improvement often within **1–2 weeks**; leaving the endemic area improves outcome.
- **Vitamin/mineral repletion:** parenteral **vitamin B12**, oral **folic acid** (alone induces haematologic remission, weight gain and partial histologic recovery), plus vitamin A (IM if night blindness/Bitot spots), vitamin K (if prolonged PT), vitamin D and calcium.
- **Supportive:** correct dehydration and electrolytes (**K, Mg, Ca, phosphate**) — severe hypokalaemia may need ECG-monitored replacement; high-protein, **fat-restricted, lactose-free** diet with **medium-chain triglycerides** to reduce steatorrhoea; guard against **refeeding syndrome** in the severely malnourished (start ~10 kcal/kg/day, escalate over 4–7 days, give thiamine).

- **Prognosis:** relapses uncommon, especially if the patient leaves the tropics; **recurrent symptoms warrant re-investigation to exclude small-bowel lymphoma**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Comparative small-intestinal villous histology (three panels):** label *(A) Normal* — tall finger-like villi, villous:crypt ratio 4–5:1; *(B) Tropical sprue* — partial villous atrophy/blunting + fusion, **crypt elongation**, ratio 2:1–1:1, **increased intraepithelial lymphocytes**, lamina-propria lymphocytic infiltrate (ileum ≥ duodenum); *(C) Celiac disease* — flat/total villous atrophy (Marsh III). Add an inset labelling **EM: degenerating basal crypt stem cells** (TS-specific).
- **Aetiopathogenesis flow diagram:** *Acute enteric infection / bacterial toxins → crypt stem-cell injury → villous atrophy & ↑ permeability → mucosal inflammation (↑ IELs) → fat malabsorption → ileal brake (↑ peptide YY) → slow transit → SIBO (coliform overgrowth) → perpetuation of malabsorption.*

Clinical / Diagnostic significance

- Suspect TS in any patient with **chronic diarrhoea + steatorrhoea + macrocytic anaemia** who lives in or has travelled to the tropics, once Giardia and celiac disease are excluded.
- The **folate + B12 deficiency** combination is a key clinical clue — distinguishes TS (whole-bowel disease) from celiac disease (proximal, folate-deficient, B12-normal).
- A **therapeutic response to tetracycline + folate** is itself supportive of the diagnosis; **failure to respond** mandates a search for lymphoma, TB or other mimics.
- Differentiate from **tropical (environmental) enteropathy** — the *asymptomatic* subclinical mucosal abnormality of tropical residents (shorter villi, ↑ permeability, abnormal lactulose:mannitol ratio) which causes no overt malabsorption and is linked to childhood stunting and reduced oral-vaccine immunogenicity.

High-yield exam pointers

- **Baker–Klipstein criteria:** malabsorption of ≥2 unrelated nutrients + abnormal biopsy + exclusion of other causes.
- **TS = whole small bowel; celiac = proximal.** TS: **partial** villous atrophy (never totally flat); celiac: may be **total** flat mucosa.
- **Both folate and B12 deficient** in TS (combined megaloblastic anaemia); celiac usually B12-normal.
- **No response to gluten-free diet; responds to antibiotics + folate** (tetracycline/doxycycline 3–6 months).
- **Hyperpigmentation of palms/knuckles/buccal mucosa** and **glossitis** are classic; **clubbing is NOT** (suggests IPSID/lymphoma).
- **EM hallmark:** degenerating cells in basal crypts (stem-cell lesion) — absent in celiac.
- **Exclude Giardia (≥3 stools)** before diagnosing TS; D-xylose abnormal in ~99%.
- Epidemic TS (South India 1960s, tens of thousands of deaths) now extinct; **sporadic TS persists**.

- Watch for **refeeding syndrome** and **magnesium-related "sprue coma"**; recurrence → rule out lymphoma.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of Absorption" (tropical sprue, environmental enteric dysfunction).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Tropical Diarrhea and Malabsorption" (definition, history, epidemiology, aetiopathogenesis, clinical features, Baker–Mathan histologic grading, pathophysiology, diagnosis and treatment) — primary depth source.
- **CMDT 2026** — Gastrointestinal Disorders (malabsorption/celiac differential) and Infectious Diseases (traveller's diarrhoea, chronic watery diarrhoea) for current management context.
- Coverage note: CMDT 2026 mentions tropical sprue only briefly (within the celiac/traveller's-diarrhoea differential), so management specifics (tetracycline/doxycycline ± folate) are grounded chiefly in Harrison and Sleisenger.

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Autoimmune hepatitis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune hepatitis (AIH) is a chronic immune-mediated necroinflammatory liver disease of unknown cause, characterized by **autoantibodies**, **hypergammaglobulinemia / raised IgG**, and **interface hepatitis with lymphoplasmacytic infiltration** on liver biopsy. It is a diagnosis of inclusion plus exclusion: viral, drug-induced, metabolic, alcohol-related, and cholestatic autoimmune liver diseases must be excluded. Untreated active AIH may progress to fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma; with immunosuppression, survival improves markedly.

Etiopathogenesis and epidemiology

- AIH occurs at any age and in both sexes, but has a strong **female predominance**; Harrison notes women account for about **75%** of cases, with peaks in young adults and in middle-to-late life.
- Incidence is rising in contemporary series; CMDT gives an incidence of **2-4 per 100,000** and prevalence of **26-31 per 100,000**.
- The central mechanism is loss of tolerance to hepatocyte antigens in genetically predisposed persons, followed by **CD4+ T-cell activation**, **CD8+ cytotoxic T-cell injury**, plasma-cell antibody production, Th17-mediated inflammation, hepatocyte apoptosis, and stellate-cell activation causing fibrosis.
- Genetic associations include **HLA-DR3 / DR4**; type 2 disease is linked with anti-LKM1 and HLA-DRB1*07.
- Triggers include viral infections and drugs. Reported drug/toxin associations include **nitrofurantoin, minocycline, hydralazine, methyldopa, infliximab, and immune-checkpoint**

inhibitors; minocycline and nitrofurantoin are important causes of autoimmune-like drug-induced liver injury.

- Associated autoimmune diseases are common: autoimmune thyroiditis / Graves disease, rheumatoid arthritis, Sjögren syndrome, ulcerative colitis, celiac disease, vitiligo, type 1 diabetes, nephritis, and Coombs-positive hemolytic anemia.

Clinical presentation

- The onset is usually **insidious**, with fatigue, malaise, anorexia, arthralgia, nausea, right upper quadrant discomfort, amenorrhea, and fluctuating jaundice. Fatigue is the commonest symptom, occurring in about **85-86%** in textbook series.
- About **25-34%** may be asymptomatic and discovered by abnormal liver tests; older patients are particularly likely to present this way.
- About **25%** present with acute severe hepatitis, and **3-6%** may present as acute severe / fulminant hepatitis with encephalopathy. Acute presentations can mimic viral hepatitis or drug-induced liver injury.
- Physical findings may be absent. When present, look for hepatomegaly, splenomegaly, jaundice, spider telangiectasia, acne, hirsutism, striae, and signs of chronic liver disease or portal hypertension.
- Exacerbations may occur **postpartum**.
- Extrahepatic manifestations include arthritis, sicca symptoms, thyroid disease, nephritis, skin vasculitis, erythema nodosum, autoimmune cytopenias, and inflammatory bowel disease.

Laboratory, serology and histology

Feature	Exam-relevant points
Liver biochemistry	Predominantly **hepatocellular** pattern: AST/ALT elevated; in acute cases aminotransferases may exceed **1000 U/L**. Bilirubin rises in acute/severe disease. Alkaline phosphatase is usually normal or mildly raised; **>4 x ULN** argues against typical AIH and suggests cholestatic/overlap disease.
Immunoglobulins	**Raised IgG / gamma globulin** is a hallmark; gamma globulin may be very high. In acute severe AIH, IgG may be normal in up to **25-39%**, so normal IgG does not exclude disease.
Type 1 AIH	**ANA and/or smooth muscle antibody (SMA)**; anti-actin and atypical pANCA may occur. This is the classic adult form in North America and northern Europe.
Anti-SLA variant	**Anti-soluble liver antigen** has high specificity, may be the sole marker, and is associated with severe disease and relapse after withdrawal.
Type 2 AIH	**Anti-LKM1**, often without ANA/SMA; anti-LC1 may coexist. More common in children, especially girls, and in Europe/Mediterranean populations.
Histology	Biopsy shows **interface hepatitis**, lymphoplasmacytic inflammation, plasma cells, hepatocyte rosettes, emperipolesis, central perivenulitis, bridging necrosis, and fibrosis/cirrhosis. Interface hepatitis is the hallmark but is not disease-specific.

- Cirrhosis is already present in **28-33%** of adults at diagnosis, emphasizing the need for early biopsy and staging.

- Plasma cells support the diagnosis, but their absence does not exclude AIH; viral, drug, hereditary, metabolic, and cholestatic liver diseases must still be excluded.

Diagnosis and differential diagnosis

- Suspect AIH in chronic or acute hepatitis with high IgG, autoantibodies, compatible biopsy, and exclusion of competing causes.
- **Liver biopsy is indicated** to establish diagnosis, assess necroinflammatory activity, stage fibrosis, detect cirrhosis, and identify overlap or drug-induced patterns.
- Simplified diagnostic criteria:

Criterion	Points
ANA or SMA >=1:40	1
ANA or SMA >=1:80, anti-LKM1 >=1:40, or anti-SLA positive	2
IgG > ULN	1
IgG >1.1 x ULN	2
Histology compatible with AIH	1
Histology typical of AIH	2
Absence of viral hepatitis	2
Total score: probable AIH = **6**; definite AIH = >=**7**	

- Scoring supports, but does not replace, clinical judgment; it is less sensitive in acute severe or seronegative disease.
- Differential diagnosis:
  - Viral hepatitis B, C, D, and acute A/E where relevant.
  - Drug-induced liver injury, especially nitrofurantoin, minocycline, antitubercular drugs, methyldopa, propylthiouracil, NSAIDs, terbinafine, TNF inhibitors, and checkpoint inhibitors.
  - Wilson disease in adolescents/young adults; alpha-1 antitrypsin deficiency and hemochromatosis when appropriate.
  - MASLD/MASH, alcohol-associated liver disease, ischemic hepatitis, celiac-related liver disease, and Budd-Chiari syndrome.
  - Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndromes.

Classification and overlap syndromes

- **Type 1 AIH**: ANA/SMA positive, all ages, female-predominant, associated with other autoimmune diseases; response to treatment is similar to type 2.
- **Type 2 AIH**: anti-LKM1 positive, often pediatric, may be associated with anti-LC1 and autoimmune polyglandular syndrome type 1; ANA/SMA are usually absent.

- **Autoantibody-negative AIH**: conventional ANA/SMA/LKM may be absent; anti-SLA, atypical pANCA, anti-actin, or anti-LC1 may support diagnosis. A monitored steroid response may help in difficult cases.
- **Drug-related autoimmune-like hepatitis**: temporal drug exposure and resolution after withdrawal favor DILI; relapse after steroid withdrawal favors classic AIH.
- **AIH-PBC overlap**: suspect when interface hepatitis coexists with cholestasis, AMA, or florid duct lesions. Diagnostic clues include ALT >=5 x ULN, IgG >=2 x ULN or SMA positivity plus PBC features such as alkaline phosphatase >=2 x ULN, GGT >=5 x ULN, AMA, or florid duct lesion.
- **AIH-PSC overlap**: suspect with inflammatory bowel disease, persistent cholestatic enzymes, or poor response to steroids; evaluate by **MRCP/ERCP**. CMDT gives overlap with PBC in **7-13%** and PSC in **6-11%** of AIH patients.

Treatment

- Treat active AIH; only patients without laboratory or histologic activity may be considered for observation. Optimal candidates include symptomatic patients with marked aminotransferase elevation, raised globulins, bridging necrosis, multiacinar necrosis, or progressive fibrosis.
- First-line therapy is **prednisone / prednisolone plus azathioprine**:
  - CMDT regimen: prednisone **20-40 mg orally daily** with azathioprine **50 mg orally daily**.
  - AASLD-style combination regimen: prednisone/prednisolone **30 mg daily**, tapered over 4 weeks to **10 mg daily**, with azathioprine **50 mg daily**.
  - European-style regimen: prednisolone **0.5-1 mg/kg daily**, tapered over about 10 weeks; azathioprine **1-2 mg/kg daily** is often added after 2 weeks.
- In **acute severe AIH**, use IV corticosteroids or prednisone **40-60 mg daily**; start azathioprine later, commonly after about 2 weeks, once diagnosis and early response are clear.
- Before azathioprine, assess **thiopurine methyltransferase (TPMT)** status where available; monitor CBC weekly for the first 2 months and monthly thereafter because of marrow suppression risk.
- **Budesonide 3 mg two or three times daily** may be used in noncirrhotic, mild/uncomplicated AIH, often with azathioprine, but avoid it in cirrhosis because first-pass hepatic clearance is lost and adverse effects/portal vein thrombosis have been reported.
- Response-guided management: symptoms improve first; remission means normal AST, ALT, and IgG; histologic resolution lags by months. An **80% fall in AST by 8 weeks** predicts later normalization; failure of aminotransferases to fall by **50% within 4 weeks** suggests nonresponse.
- Relapse is common; many patients require long-term azathioprine up to **2 mg/kg/day** or the lowest effective prednisone dose.
- Second-line / rescue options: **mycophenolate mofetil 500 mg twice daily increasing to 1 g twice daily** for azathioprine intolerance; 6-mercaptopurine for azathioprine gastrointestinal intolerance; tacrolimus, cyclosporine, rituximab, or infliximab in refractory disease. Mycophenolate is teratogenic.

- **Liver transplantation** is indicated for acute liver failure, decompensated cirrhosis, treatment failure, severe acute AIH without improvement after about 2 weeks of corticosteroids, or HCC within transplant criteria.

Response, follow-up and prognosis

- Prednisone plus azathioprine produces response in about **80%** and remission in about **65% by 3 years**.
- Consider treatment withdrawal only after sustained complete biochemical remission: at least **24 months** of normal AST/ALT/IgG, usually after a total treatment duration of about **3 years**; repeat biopsy can document histologic remission.
- Relapse after withdrawal is frequent; CMDT reports relapse up to **90% by 3 years**. Recurrent relapse usually warrants indefinite maintenance therapy.
- Vaccinate against **hepatitis A and B** before immunosuppression where possible; also give age-appropriate vaccines.
- Monitor steroid complications: weight gain, diabetes, hypertension, cataract, infection, mood disturbance, and osteoporosis. Do **DEXA**, calcium/vitamin D, exercise, and bisphosphonate when indicated.
- In cirrhosis: screen for **HCC by ultrasound every 6 months**, assess portal hypertension/varices, and manage ascites, encephalopathy, renal dysfunction, and transplant referral early.
- Poor prognostic factors include age **<=20 or >=60** at presentation, low albumin, cirrhosis at diagnosis, anti-SLA positivity, high bilirubin/MELD, and incomplete AST normalization by 6 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Immunopathogenesis flow diagram**: environmental trigger/drug/virus -> molecular mimicry/loss of tolerance -> antigen-presenting cell -> CD4+ helper T cell -> CD8+ cytotoxic T cell + plasma cell + Th17 cell -> Fas-FasL hepatocyte apoptosis -> interface hepatitis -> stellate-cell activation -> fibrosis/cirrhosis. Exact labels: APC, class II MHC, CD4+ T cell, CD8+ T cell, plasma cell, autoantibodies, Fas/FasL, hepatocyte apoptosis, Kupffer cell, ROS, hepatic stellate cell, fibrosis.
- **Diagnostic-treatment algorithm**: chronic/acute hepatitis -> exclude viral/drug/metabolic/alcohol/cholestatic disease -> ANA/SMA/LKM1/SLA + IgG -> liver biopsy showing interface hepatitis -> prednisone/prednisolone ± azathioprine -> remission / relapse / nonresponse -> maintenance, second-line therapy, or liver transplantation.

Clinical / Diagnostic significance

- Always biopsy suspected AIH unless contraindicated; in coagulopathy or acute severe disease, consider a **transjugular liver biopsy**.
- Do not dismiss acute severe AIH because ANA is absent or IgG is normal; this occurs in a substantial minority.

- Prominent cholestasis, IBD, bile duct injury, or poor steroid response should prompt evaluation for PSC/PBC overlap and MRCP/ERCP.
- Distinguish drug-induced autoimmune-like hepatitis from classic AIH by exposure history, histology, resolution after drug withdrawal, and relapse pattern after steroid withdrawal.
- Early transplant discussion is mandatory in encephalopathy, INR prolongation, acute liver failure, high MELD, or failure of bilirubin/clinical status to improve within 1-2 weeks of steroids.

High-yield exam pointers

- AIH triad: **autoantibodies + raised IgG + interface hepatitis**.
- **ANA/SMA = type 1**; **anti-LKM1/anti-LC1 = type 2**; **anti-SLA = severe/relapsing, high-specificity marker**.
- Histology must-write: interface hepatitis, plasma cells, rosettes, emperipolesis, central perivenulitis, bridging necrosis/fibrosis.
- Normal IgG or absent ANA does **not** exclude acute severe AIH.
- Simplified score: **6 probable, >=7 definite**.
- First-line: corticosteroid plus azathioprine; check TPMT and monitor CBC.
- Budesonide is for selected **noncirrhotic** patients; avoid in cirrhosis.
- Relapse is common; withdrawal requires prolonged normal AST/ALT/IgG and often biopsy confirmation.
- Cirrhotic AIH needs HCC surveillance and early transplant evaluation.

> **SOURCE & COVERAGE**
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> Harrison 22e — "Chronic Hepatitis"; Sleisenger & Fordtran's GI & Liver 11e — "Autoimmune Hepatitis"; CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders".

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ERCP

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Endoscopic retrograde cholangiopancreatography (ERCP) is a combined endoscopic–fluoroscopic procedure in which a **side-viewing duodenoscope** is passed to the second part of the duodenum, the major papilla (ampulla of Vater) is cannulated, and the bile and/or pancreatic ducts are opacified with radiographic contrast under fluoroscopy. When indicated, the papilla is incised by **endoscopic sphincterotomy (EST)** to permit stone extraction, stricture dilation, stenting, and tissue sampling. With the advent of **MRCP and endoscopic ultrasound (EUS)** as accurate non-invasive imaging, ERCP has evolved from a diagnostic into an almost **exclusively therapeutic** modality for pancreaticobiliary disease.

Technique and therapeutic armamentarium

- **Access:** transoral side-viewing duodenoscope → selective cannulation of CBD/pancreatic duct with a catheter or sphincterotome over a guidewire; contrast injection under fluoroscopy.

- **Therapeutic manoeuvres possible at ERCP:** biliary/pancreatic **sphincterotomy**; **stone extraction** with balloon or Dormia basket; **balloon dilation** of strictures; **plastic or self-expandable metal stent (SEMS)** placement; **mechanical/cholangioscopy-guided lithotripsy** of large stones; **nasobiliary drainage**; treatment of **ductal leaks**; intraductal **brush cytology / forceps biopsy**; **biliary manometry** (for sphincter of Oddi dysfunction).
- **Adjuncts:** cholangioscopy (SpyGlass) for direct duct visualisation and targeted biopsy; EUS-guided biliary drainage when conventional ERCP fails.

Indications

ERCP is indicated chiefly for **therapy**; pure diagnostic ERCP is now rare and reserved for **tissue sampling of biliary/pancreatic ductal strictures** and **biliary manometry**.

Category	Specific indication
Choledocholithiasis	Sphincterotomy + stone extraction (balloon/basket); first-line for CBD stones, especially elderly/poor surgical candidates
Acute (ascending) cholangitis	Emergency biliary decompression/drainage — the definitive treatment after resuscitation and antibiotics
Gallstone (biliary) pancreatitis	Urgent ERCP for retained CBD stone, particularly with coexisting cholangitis or obstructive jaundice
Malignant biliary obstruction	Palliative stenting (SEMS) and tissue diagnosis in cholangiocarcinoma, pancreatic head cancer, ampullary tumour
Benign biliary strictures	Post-operative, chronic pancreatitis-related, or post-transplant strictures — dilation + multiple plastic stents or covered SEMS
Bile leak / duct injury	Post-laparoscopic-cholecystectomy cystic-duct stump leak — sphincterotomy ± stent to divert bile
Primary sclerosing cholangitis (PSC)	Endoscopic dilation ± short-term large-bore (10-Fr) stenting of a **dominant stricture**; biliary lithiasis
Sphincter of Oddi dysfunction (SOD)	Manometry and biliary sphincterotomy in selected patients
Pancreatic disease	Pancreatic-duct stenting/stone removal in chronic pancreatitis; drainage of pancreatic-duct disruption/leak; pseudocyst communicating with the duct
Tissue diagnosis	Brush cytology/intraductal biopsy of indeterminate biliary or pancreatic strictures

- In **gallstone pancreatitis**, only ~20% harbour a persistent ampullary/CBD stone; therefore **MRCP or EUS first** spares many patients an unnecessary ERCP — urgent ERCP is reserved for suspected **superimposed cholangitis** or proven retained stone.
- For **acute cholangitis**, biliary drainage (usually by ERCP) should be established within ~24–48 h; **emergent** decompression is required in septic patients or those failing antibiotics within 12–24 h.

Contraindications

- **Absolute/relative:** uncooperative patient, **acute pancreatitis** (unless gallstone pancreatitis with cholangitis), severe uncorrected **cardiopulmonary disease**, recent contrast (iodine) anaphylaxis.

- **Anatomic barriers:** gastroduodenal/oesophageal obstruction preventing scope passage; **Roux-en-Y** or other surgically altered anatomy (may need balloon enteroscopy-assisted or EUS-directed access).
- **Pregnancy** — performed only when essential, with radiation-minimising technique.
- Uncorrected coagulopathy/thrombocytopenia (relative — correct before sphincterotomy).

Complications

ERCP carries the **highest adverse-event rate of all routine endoscopic procedures**. Major complications and approximate frequencies:

Complication	Frequency	Key points
Post-ERCP pancreatitis (PEP)	~5% overall (Harrison); 5–10%, up to **20–25%** in high-risk	Most common and most feared complication; asymptomatic hyperamylasaemia in 35–70%
Haemorrhage (post-sphincterotomy)	~1–2%	Risk ↑ with thrombocytopenia, coagulopathy, cholangitis, anticoagulation within 3 days, low endoscopist volume
Perforation	<1%	Lateral-wall **duodenal** (large, often needs surgery); **periampullary** (post-sphincterotomy — often managed with stent); **ductal** (guidewire/basket — usually conservative + stent)
Cholangitis	~1%	Higher with combined percutaneous-endoscopic access, malignant stenting, **failed/incomplete drainage**
Cholecystitis	<0.5%	After stenting across the cystic-duct take-off
Pseudocyst infection / abscess	Uncommon	Especially when contrast injected into a duct communicating with a sterile collection
Sedation / cardiopulmonary	—	Hypoxaemia, aspiration, respiratory depression, arrhythmia, contrast reaction

- Pooled RCT data (placebo/no-stent arms): overall **PEP incidence 9.7%**, mortality **0.7%**; severity mild 5.7% / moderate 2.6% / severe 0.5%. In **high-risk** patients PEP rises to ~14.7%.
- Severe PEP may progress to necrotising pancreatitis, multi-organ failure, prolonged hospitalisation, diabetes, or **death**.

Post-ERCP pancreatitis — risk factors and prevention

Risk factors (Box 58.5 / Box 42.1):

- *Patient-related:* young age, female sex, **suspected SOD**, prior recurrent pancreatitis, **history of previous PEP**, **normal serum bilirubin**.
- *Procedure-related:* **pancreatic-duct injection/opacification**, difficult or failed cannulation, **pancreatic sphincterotomy**, **pre-cut (access) sphincterotomy**, balloon dilation of an intact sphincter, pancreatic guidewire placement, pancreatic tissue sampling.
- *Operator/technique-related:* trainee (fellow) participation, non-use of guidewire cannulation, failure to place a prophylactic pancreatic-duct stent in a high-risk case.

- The archetypal highest-risk patient: a **young woman with suspected choledocholithiasis and normal bilirubin who undergoes sphincterotomy but no stone is found** (~27% PEP).

Prevention — three evidence-based modalities:

- **Prophylactic pancreatic-duct stent** (3–5 Fr; length/diameter >5 cm/>5 Fr more protective) in high-risk cases — relieves cannulation-induced ampullary oedema; >70% pass spontaneously, otherwise removed by ~14 days.
- **Rectal NSAID — indomethacin** (or diclofenac) given peri-procedurally; reduces PEP, established for high-risk patients.
- **Periprocedural IV fluids** — aggressive hydration with **lactated Ringer's** solution.
- **Guidewire-assisted cannulation** lowers PEP versus contrast-guided cannulation (success ~98%). Treatment of established PEP is **supportive**; there is **no role for repeat ERCP** for PEP itself.

Antibiotic prophylaxis (selective)

- **Not** recommended when complete biliary drainage is anticipated.
- **Recommended** (and continued after the procedure) when **incomplete drainage** is expected — e.g., **PSC, hilar strictures** — and for a sterile pancreatic fluid collection communicating with the pancreatic duct.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled line diagram of ERCP anatomy/technique:** duodenoscope tip in the **second part of duodenum**; **major papilla (ampulla of Vater)**; **common bile duct**; **common hepatic duct / right & left hepatic ducts**; **cystic duct & gallbladder**; **main pancreatic duct**; **sphincter of Oddi**; cannula/sphincterotome entering the papilla; CBD stone with extraction balloon/basket distal to it.
- **Schematic of endoscopic sphincterotomy:** normal ampulla → sphincterotome cutting the roof of the papilla with electrosurgery → stone extracted with balloon catheter into the duodenum.

Clinical / Diagnostic significance

- **Choledocholithiasis pathway:** risk-stratify first — high probability (CBD stone on US, bilirubin >4 mg/dL, or cholangitis) → proceed to ERCP; intermediate probability → **MRCP or EUS** before ERCP to avoid needless ERCP. Confirmed stones → **sphincterotomy + extraction** (± laparoscopic cholecystectomy, often single-session). Large stones (≥1 cm) → sphincterotomy + **large-balloon dilation** or cholangioscopy-guided lithotripsy.
- **Acute cholangitis:** *Charcot triad* (RUQ pain, fever, jaundice; ~70%); *Reynolds pentad* (+ hypotension + altered mentation) = suppurative cholangitis, an **endoscopic emergency**. Diagnosis/severity by **Tokyo Guidelines (2018)**. Manage with IV fluids + antibiotics (e.g., **ciprofloxacin + metronidazole**, or ampicillin-sulbactam; severe/hospital-acquired → **piperacillin-tazobactam or meropenem**) then ERCP drainage.
- **Balloon sphincteroplasty without sphincterotomy** is preferred in **coagulopathic** patients (lower bleeding risk); a short fully-covered metal stent is an alternative to mitigate bleeding.

- When ERCP **fails or is anatomically impossible**, alternatives are **EUS-guided biliary drainage** or **percutaneous transhepatic cholangiography (PTC)** with drainage.

High-yield exam pointers

- ERCP uses a **side-viewing duodenoscope** and is now **predominantly therapeutic** (MRCP/EUS have replaced diagnostic ERCP).
- **Commonest and most feared complication = post-ERCP pancreatitis** (~5%, up to 20–25% in high-risk).
- **Post-sphincterotomy bleeding ~1–2%; perforation <1%; cholangitis ~1%.**
- **PEP prevention triad:** prophylactic **pancreatic-duct stent** + **rectal indomethacin** + **aggressive IV lactated Ringer's**; plus guidewire cannulation.
- Highest-risk PEP patient: **young woman, suspected SOD, normal bilirubin, difficult cannulation**.
- **Cholangitis** = Charcot triad; **Reynolds pentad** signals suppurative cholangitis needing **emergency ERCP drainage** (within 24–48 h; emergent if septic).
- In **gallstone pancreatitis**, urgent ERCP benefits only those with **retained CBD stone or cholangitis** — image with MRCP/EUS first.
- **Antibiotic prophylaxis** only when **incomplete drainage** is expected (PSC, hilar strictures).
- Contraindications: acute (non-gallstone) pancreatitis, severe cardiopulmonary disease, altered anatomy (Roux-en-Y), uncorrected coagulopathy.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Gastrointestinal Endoscopy" (ERCP technique, risks of endoscopy, acute biliary obstruction/cholangitis/gallstone pancreatitis); "Diseases of the Gallbladder and Bile Ducts" (ERCP indications/contraindications/complications table, choledocholithiasis, cholangitis).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Preparation for and Complications of Gastrointestinal Endoscopy" (ERCP haemorrhage, perforation, cholangitis, pancreatitis with risk-factor box); "Acute Pancreatitis" (post-ERCP pancreatitis incidence, risk factors, prevention with PD stents/rectal NSAIDs/IV fluids); "Endoscopic and Radiologic Treatment of Biliary Disease" (stone extraction, dominant-stricture and benign-stricture stenting, EUS-guided drainage).
- **CMDT 2026** — "Liver, Biliary Tract, & Pancreas Disorders" (choledocholithiasis & acute cholangitis management, Tokyo Guidelines 2018, antibiotic regimens, timing of ERCP, large-stone and coagulopathy techniques).

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Drug- and toxin-induced liver injury

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Drug-induced liver injury (DILI)* is hepatic injury attributable to a xenobiotic — a prescription or over-the-counter drug, an industrial/environmental toxin, or a complementary and alternative medicine (CAM)/herbal-dietary supplement. The liver is uniquely vulnerable because it is the principal site of drug metabolism: most water-insoluble drugs undergo **phase I** oxidation (cytochrome P450) and **phase II** conjugation (glucuronidation/sulfation) or glutathione inactivation, and most hepatotoxicity arises from a reactive **phase I toxic metabolite**. DILI is the commonest cause of acute liver failure (ALF) in the Western world and is a presumptive diagnosis requiring a meticulous drug history and exclusion of other causes. It is classified along three complementary axes — **pathogenic type**, **biochemical pattern (R value)** and **morphological pattern** — and a single agent may produce several lesions.

1. Classification by pathogenic mechanism

Type	Predictability / dose	Latency	Prototype agents & lesion
Direct (intrinsic) toxic	Predictable, reproducible, **dose-dependent**	Short (hours–48 h)	Acetaminophen, carbon tetrachloride, *Amanita phalloides*, yellow phosphorus, heavy metals → reproducible **zonal necrosis ± steatosis**
Idiosyncratic	Unpredictable, rare (**1 in 10^3 –10^5**), only loosely dose-related (usually >100 mg/day)	Variable, typically **5–90 days**	Isoniazid, amoxicillin-clavulanate, halothane, nitrofurantoin → **variable** morphology; may be immunoallergic or metabolic
Indirect (CMDT)	Drug worsens pre-existing liver disease	Variable	Immunosuppression/rituximab → **HBV reactivation flare**; checkpoint inhibitors → immune hepatitis

- Idiosyncratic injury is further split into **immunoallergic** (hypersensitivity — rash, fever, arthralgia, eosinophilia; e.g. phenytoin, trimethoprim-sulfamethoxazole, the **DRESS** syndrome) and **metabolic idiosyncrasy** (variable toxic-metabolite kinetics, no allergy; e.g. isoniazid, valproate).
- Susceptibility is shaped by **HLA haplotypes** (amoxicillin-clavulanate, flucloxacillin), enzyme polymorphisms, age, alcohol, nutritional state and underlying liver disease.

2. Classification by biochemical pattern — the R value

- **R value = (ALT ÷ ULN) ÷ (ALP ÷ ULN)** — both as multiples of the upper limit of normal.
  - **R ≥ 5 → hepatocellular** injury (ALT-dominant).
  - **R < 2 → cholestatic** injury (ALP-dominant).
  - **R 2–5 → mixed** hepatocellular-cholestatic.
- This bedside ratio predicts the likely histology and guides the differential before biopsy.

3. Morphological patterns, findings and examples (core of the answer)

Pattern	Key morphological findings	Representative agents
Zonal (coagulative) necrosis	Predictable necrosis in a specific acinar zone; **centrilobular/zone 3** (high CYP2E1, low glutathione); minimal inflammation; resolves without fibrosis	**Acetaminophen, carbon tetrachloride** (zone 3); yellow phosphorus, ferrous salts (periportal/zone 1)
Massive / submassive (bridging) necrosis	Panlobular hepatocyte dropout → ALF	*Amanita phalloides*, halothane, severe acetaminophen
Acute hepatitis (hepatocellular)	Spotty/focal necrosis with **lymphocytic infiltrate, resembling acute viral hepatitis**; ALT >5× ULN	Isoniazid, halothane, ketoconazole, nitrofurantoin, methyldopa, sulfonamides, ciprofloxacin, troglitazone
Chronic hepatitis (autoimmune-like)	>3 months; **interface hepatitis, bridging necrosis, fibrosis**, plasma cells, **autoantibodies (ANA/anti-SMA)**	**Nitrofurantoin, minocycline, hydralazine, α-methyldopa** (the four ANA-positive AIH-like agents); diclofenac
Bland (non-inflammatory) cholestasis	Canalicular cholestasis, **no inflammation or necrosis**	Anabolic/**17α-alkylated androgens**, oestrogens, oral contraceptives
Cholestatic hepatitis (inflammatory)	Portal inflammation + cholestasis ± bile-duct injury	**Amoxicillin-clavulanate** (commonest implicated antibiotic), erythromycin estolate, chlorpromazine, oxacillin
Vanishing bile duct syndrome (ductopenia)	Progressive **loss of small interlobular bile ducts**, PBC-like but AMA-negative; chronic cholestasis	Chlorpromazine, flucloxacillin, carbamazepine, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole
Sclerosing cholangitis	Strictures of large/intrahepatic ducts	Intra-arterial **floxuridine**, long-term **ketamine**
Macrovesicular steatosis	Single large fat droplet displacing nucleus	Amiodarone, methotrexate, tamoxifen, corticosteroids, irinotecan
Microvesicular steatosis	Tiny cytoplasmic fat droplets, central nucleus; **mitochondrial toxicity → lactic acidosis**	**Valproate**, high-dose IV tetracycline, **aspirin (Reye)**, didanosine/stavudine/zidovudine, linezolid
Steatohepatitis (pseudoalcoholic)	Steatosis + **Mallory-Denk hyaline** + neutrophils + **pericellular fibrosis**; **phospholipidosis** (lamellar lysosomal bodies)	**Amiodarone**, perhexiline, tamoxifen
Granulomatous hepatitis	Non-caseating epithelioid **granulomas** ± cholestasis	Sulfonamides, allopurinol, carbamazepine, hydralazine, quinidine, quinine, phenylbutazone
Fibrosis / cirrhosis	Progressive fibrosis, nodular regeneration	**Methotrexate**, amiodarone, tamoxifen, **vitamin A** (hypervitaminosis)

Pattern	Key morphological findings	Representative agents
Vascular injury	**Sinusoidal obstruction syndrome (veno-occlusive disease)** — sinusoidal/terminal-venule endothelial injury; **nodular regenerative hyperplasia**; **peliosis hepatis** (blood-filled cavities)	SOS: high-dose pre-BMT **cyclophosphamide, melphalan, busulfan**, **pyrrolizidine alkaloids**, oxaliplatin; NRH: oxaliplatin, azathioprine, vitamin A; peliosis & Budd-Chiari: anabolic/contraceptive steroids
Neoplasia	Hepatic adenoma, focal nodular hyperplasia, HCC, **angiosarcoma**	Oral contraceptives/oestrogens, anabolic steroids; **vinyl chloride / arsenic / Thorotrast** (angiosarcoma)
Immune-mediated (checkpoint inhibitor) hepatitis	Non-specific acute hepatitis, **$CD8^+$-predominant**, ANA-positive; steroid-responsive	Ipilimumab (CTLA-4), nivolumab/pembrolizumab (PD-1/PD-L1)

4. The six cellular mechanisms of injury (Harrison)

- **A — Membrane rupture:** disrupted intracellular Ca^{2+} homeostasis → actin disassembly → blebbing and cell lysis.
- **B — Canalicular injury:** disruption of transport pumps (**MRP3**) → impaired bile/bilirubin excretion → cholestasis.
- **C — P450-drug covalent binding:** reactive metabolite binds cytochrome P450 forming non-functional **adducts**.
- **D — Immune attack on adducts:** adducts migrate to the surface as neo-antigens → **cytolytic T-cell/cytokine** attack.
- **E — Apoptosis:** activation of **TNF-α receptor/Fas** death-domain → caspase cascade.
- **F — Mitochondrial inhibition:** blockade of β-oxidation and the respiratory chain → microvesicular steatosis, lactate accumulation, reactive oxygen species.

5. Prototype: acetaminophen (paracetamol) — the model direct toxin

- Metabolised mainly by phase II to harmless conjugates; a fraction is oxidised by **CYP2E1** to the toxic **NAPQI** (*N-acetyl-p-benzoquinone-imine*), normally detoxified by **glutathione**. Overdose or glutathione depletion → covalent protein adducts → **zone 3 (centrilobular) necrosis**.
- Toxic single dose **10–15 g**, fatal usually **≥25 g**; in chronic alcoholics (CYP2E1 induction + glutathione depletion) toxicity may occur at **~2 g**. Fasting/starvation potentiates.
- **Very high ALT (often >10,000 IU/L) with disproportionately low bilirubin** is the biochemical signature. 4-h level **>300 µg/mL** predicts severe injury; **<150 µg/mL** makes injury unlikely — plotted on the **Rumack-Matthew nomogram**.
- **Antidote: N-acetylcysteine (NAC)** — IV loading **140 mg/kg** then **70 mg/kg every 4 h for 15–20 doses**; most effective within 8–12 h but still useful up to 24–36 h.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hepatic acinus showing zonal injury:** draw the portal triad (hepatic artery, portal vein, bile duct) and the central (terminal hepatic) vein, with **Zone 1 (periportal)**, **Zone 2 (midzonal)** and **Zone 3 (centrilobular)**. Label "**Zone 3 — CYP2E1-rich, glutathione-poor → acetaminophen / CCl_4 necrosis**" and "**Zone 1 — yellow phosphorus / ferrous sulfate.**"
- **Six mechanisms of DILI (after Harrison Fig 351-1):** a hepatocyte labelled **A** membrane rupture, **B** canalicular pump (MRP3) injury, **C** P450-drug adduct, **D** CTL/cytokine attack on adduct, **E** TNF-α/Fas apoptosis (caspases), **F** mitochondrial β-oxidation/respiration block → microvesicular steatosis + lactate.

Clinical / Diagnostic significance

- **Hy's Law:** during a drug trial, **jaundice with ALT ≥3× ULN** (hepatocellular, no cholestasis/obstruction) predicts a **mortality ≥10%** (a ~10:1 ratio of jaundice cases to liver failure) — the strongest clinical predictor of severe DILI and a common reason drugs fail approval (e.g. troglitazone).
- **Causality assessment: RUCAM** (Roussel-Uclaf), the **DILIN** structured expert opinion (5-point scale: definite, highly likely, probable, possible, unlikely) and the newer **RECAM**; *LiverTox* (NIH) is the reference database.
- **Management:** chiefly **prompt withdrawal of the offending agent** (the single most important determinant of outcome) plus supportive care. Specific therapies: **NAC** for acetaminophen (and benefit in early-stage non-acetaminophen ALF), **silibinin** for *Amanita*, **ursodeoxycholic acid** for cholestatic DILI, **glucocorticoids** for immunoallergic/checkpoint-inhibitor and AIH-like injury. Stop any drug when ALT reaches **5× ULN** or symptoms/jaundice appear. ALF develops in ~10% of DILI; **liver transplantation** for those reaching coagulopathy + encephalopathy (lactate >3.5 mmol/L predicts need).
- Always probe **CAMs/herbals** (>20% of US DILI): green tea extract (HLA-B*35:01), Jin Bu Huan, germander, kava, pyrrolizidine alkaloids (SOS), anabolic "bodybuilding" supplements (profound bland cholestasis), Hydroxycut/OxyElite Pro.

High-yield exam pointers

- Two core pathogenic types: **direct/intrinsic** (predictable, dose-dependent, short latency, reproducible zonal necrosis) vs **idiosyncratic** (rare $1:10^3$–10^5, latency 5–90 days, variable morphology); CMDT adds **indirect** (HBV flare).
- **R value:** ≥5 hepatocellular, <2 cholestatic, 2–5 mixed.
- Acetaminophen → **CYP2E1** → **NAPQI** → **glutathione depletion** → **zone 3 necrosis**; antidote **NAC 140 mg/kg then 70 mg/kg q4h**.
- **Amoxicillin-clavulanate** = commonest antibiotic cause (mixed/cholestatic, may cause **vanishing bile duct syndrome**).
- AIH-like chronic hepatitis (ANA+): **nitrofurantoin, minocycline, hydralazine, methyldopa**.
- **Microvesicular steatosis** = mitochondrial toxicity (valproate, tetracycline IV, aspirin/**Reye**, NRTIs) → lactic acidosis; **macrovesicular** (amiodarone, methotrexate, tamoxifen).

- **Amiodarone** → pseudoalcoholic steatohepatitis with **Mallory hyaline + phospholipidosis (lamellar bodies)**.
- **SOS/VOD** = pre-BMT chemo (cyclophosphamide, busulfan, melphalan) and **pyrrolizidine alkaloids**; **angiosarcoma** = vinyl chloride/arsenic/Thorotrast.
- **Hy's Law:** jaundice + ALT ≥3× ULN → mortality ≥10%.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Toxic and Drug-Induced Hepatitis"** (mechanisms, direct vs idiosyncratic features, R value, Hy's Law, acetaminophen/INH/valproate/amoxicillin-clavulanate/amiodarone/anabolic steroid prototypes, morphology tables 351-1 and 351-2).
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Liver Disease Caused by Drugs"** (Table 88.4 clinicopathologic classification, zonal necrosis/CYP2E1 zonality, DRESS, latency/dechallenge-rechallenge, vascular and chronic-cholestatic patterns).
- **CMDT 2026 — "Drug- & Toxin-Induced Liver Disease" (Liver, Biliary Tract & Pancreas Disorders)** (direct/idiosyncratic/indirect categorisation, R-value thresholds, histopathological lists, current management and referral).

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Wilson's disease

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Wilson's disease, or hepatolenticular degeneration, is an autosomal recessive disorder of copper transport due to pathogenic variants in **ATP7B** on chromosome 13. Defective hepatic copper transport impairs biliary copper excretion and incorporation of copper into ceruloplasmin, causing toxic copper accumulation in the **liver, brain, cornea, kidney, and other tissues**. It is one of the most treatable inherited metabolic liver diseases, but missed diagnosis can lead to fatal hepatic failure or irreversible neurologic disability.

Etiopathogenesis and copper metabolism

- Normal dietary copper is absorbed from the proximal small intestine, transported to the liver, incorporated into **ceruloplasmin**, and excreted mainly in bile; urinary copper excretion is normally small.
- **ATP7B** is expressed predominantly in liver and kidney. In hepatocytes it has two key functions: formation of enzymatically active ceruloplasmin in the trans-Golgi network and trafficking copper toward the canalicular membrane for biliary excretion.
- Loss of ATP7B function causes progressive hepatic copper retention. Initially copper is buffered by metallothionein; later excess copper causes oxidative mitochondrial injury, hepatocyte necrosis, fibrosis, and cirrhosis.
- When hepatic storage capacity is exceeded, copper spills into blood and deposits in the **basal ganglia**, cornea, kidney, skeleton, endocrine organs, and red cell membranes.

- Epidemiology: classically about **30 per million** population, with most clinical presentations between **3 and 55 years**; genetic estimates suggest the allele frequency may be higher. Age does not exclude the diagnosis.
- Most patients are **compound heterozygotes**. More than 600 ATP7B variants are described; H1069Q is common in Northern European populations and R778L in Chinese populations.

Clinical spectrum

System / presentation	High-yield clinical features
Hepatic	Asymptomatic aminotransferase elevation, fatty liver/NASH-like picture, acute hepatitis-like illness, autoimmune hepatitis-like illness, chronic hepatitis, cirrhosis, portal hypertension, splenomegaly, ascites, edema, decompensated chronic liver disease
Acute liver failure	Severe coagulopathy with or without early encephalopathy, Coombs-negative intravascular hemolysis, very high bilirubin, renal failure; aminotransferases may be disproportionately low
Neurologic	Basal ganglia movement disorder: dysarthria, dysphagia, drooling, dystonia, rigidity/parkinsonism, ataxia, gait disturbance, dysgraphia, choreiform movements, and classic *wing-beating* tremor
Psychiatric	Declining school or work performance, personality change, irritability, poor impulse control, depression, anxiety, emotional lability, compulsive or antisocial behavior; may precede neurologic signs
Ocular	**Kayser-Fleischer ring**: golden-brown/greenish-brown copper deposition in Descemet membrane, detected best by slit lamp; **sunflower cataract** may occur
Extrahepatic	Coombs-negative hemolytic anemia, renal Fanconi syndrome, renal tubular acidosis, nephrolithiasis, aminoaciduria, phosphaturia, osteoporosis/rickets, osteoarthritis, amenorrhea, infertility, hypoparathyroidism, rarely cardiomyopathy/arrhythmias

- Hepatic presentation is more common in younger patients; neuropsychiatric presentation usually appears in adolescents and young adults, but overlap is common and some degree of liver disease is usually present.
- Kayser-Fleischer rings are present in most patients with neurologic disease but may be absent in hepatic-only or asymptomatic disease; absence of the ring never excludes Wilson's disease.
- Wilson's disease should be excluded in any young patient with unexplained hepatitis, splenomegaly with hypersplenism, portal hypertension, Coombs-negative hemolysis, movement disorder, or new psychiatric illness.

Diagnostic approach

Test	Typical finding / interpretation
Serum ceruloplasmin	Low; <14 mg/dL supports diagnosis and <10 mg/dL is strongly suggestive, but normal values occur because ceruloplasmin is an acute-phase reactant; low levels are not specific

Test	Typical finding / interpretation
Serum copper	Total serum copper is often low because ceruloplasmin-bound copper is low; **non-ceruloplasmin copper** is increased, but calculated values are assay-dependent
24-hour urinary copper	>40 mcg/day requires further evaluation; usually >100 mcg/day in symptomatic disease. Use complete, contamination-free collection with creatinine check
Penicillamine challenge	A marked increase in urinary copper after penicillamine supports the diagnosis; in the standard provocative test, very high 24-hour copper excretion is diagnostic but sensitivity is imperfect
Hepatic copper	>250 mcg/g dry liver is diagnostic in the correct setting; 20-50 mcg/g is normal. Sampling error occurs in cirrhosis because copper distribution is uneven
Slit-lamp examination	Detects Kayser-Fleischer rings and sunflower cataract; repeat if suspicion remains high
MRI brain	May show basal ganglia, brainstem, or cerebellar involvement, even early in neurologic disease
ATP7B molecular testing	Confirms diagnosis when clinical and biochemical tests are equivocal; also enables family screening

- Diagnosis is usually by a **composite** of clinical features, copper studies, slit-lamp findings, and genetics; the **Leipzig scoring system** is a useful structured framework.
- Liver biopsy may show steatosis, acute or chronic hepatitis, autoimmune hepatitis-like interface activity, macronodular cirrhosis, and characteristic mitochondrial injury; copper stain may be negative early because copper is diffusely cytosolic.
- Important limitations: ceruloplasmin may be low in malnutrition, nephrotic syndrome, malabsorption, and other chronic liver diseases; hepatic copper may be high in chronic cholestasis and MDR3-related disease.

Wilsonian acute liver failure

- Suspect Wilsonian acute liver failure in a child or young adult with jaundice, severe coagulopathy, hemolysis, kidney injury, and unexpectedly modest transaminase elevation.
- Classic clues are **Coombs-negative intravascular hemolysis**, very high bilirubin, normal or low alkaline phosphatase, and urinary copper that is markedly elevated.
- In adults, two simple biochemical ratios are useful screening clues: **alkaline phosphatase : total bilirubin <4** and **AST : ALT >2.2**.
- Serum ceruloplasmin is often not diagnostically reliable in acute liver failure.
- These patients respond poorly to chelation alone; manage in a transplant-capable ICU, treat complications of acute liver failure, and use plasma exchange, albumin dialysis, or MARS as a bridge when available.
- **Urgent liver transplantation** is indicated for Wilsonian acute liver failure and for decompensated cirrhosis unresponsive to medical therapy.

Treatment

Modality	Dose / role	Key cautions
Dietary copper restriction	Avoid shellfish, organ meats, nuts, mushrooms, soy-based products, chocolate; assess high-copper water when relevant	Useful adjunct only; never sufficient as sole therapy
D-penicillamine	0.75-2 g/day in divided doses, taken 1 hour before or 2 hours after food; add pyridoxine supplementation	Rash, fever, GI intolerance, proteinuria, nephrotoxicity, leukopenia, thrombocytopenia, aplastic anemia, autoimmune syndromes, elastosis perforans serpiginosa; may worsen neurologic disease initially
Trientine hydrochloride	250-500 mg three times daily, or about 1-1.5 g/day initially in divided doses; effective first-line or alternative chelator	Fewer adverse effects; monitor for gastritis, iron deficiency, and rare marrow suppression
Zinc acetate / gluconate	50 mg elemental zinc three times daily, taken away from meals; induces enterocyte metallothionein and blocks copper absorption	Slow onset; best for presymptomatic patients, pregnancy, neurologic disease, or maintenance after decoppering; gastritis and adherence problems are common
Combination therapy	Chelator plus zinc may be used short term in severe hepatic/neurologic disease	Separate doses by at least 4-5 hours to avoid mutual neutralization
Tetrathiomolybdate	Investigational copper-binding therapy, mainly explored for neurologic disease	Watch for bone marrow suppression, hepatotoxicity, and copper deficiency
Liver transplantation	Acute liver failure or decompensated cirrhosis not responding to drug therapy	Not generally recommended for isolated intractable neuropsychiatric disease

- Treatment is **lifelong**. Stopping chelator or zinc therapy can cause neurologic relapse or rapidly progressive hepatic decompensation.
- In pregnancy, treatment must continue; chelator dose is usually reduced, while zinc can often be continued. Untreated disease increases miscarriage and relapse risk; breastfeeding is generally avoided with anticopper drugs.

Monitoring, family screening and prognosis

- Monitor response and toxicity with symptoms, adherence review, liver biochemical tests, CBC, renal function, urinalysis, and 24-hour urinary copper.
- Therapeutic targets: with chelators, 24-hour urinary copper is typically maintained around **200-500 mcg/day**; with zinc, urinary copper should fall to about **30-75 mcg/day**. Undetectable urinary copper suggests overtreatment.
- Serum non-ceruloplasmin copper can guide chelator dose reduction once it is in the normal range, approximately **50-150 mcg/L**.
- With zinc, adherence can be checked by urinary zinc excretion or serum zinc; rising aminotransferases after previous control often indicates nonadherence.

- Screen all **first-degree relatives**, especially siblings, using liver biochemical tests, serum ceruloplasmin, copper studies, slit-lamp examination, and ATP7B variant testing if the familial variants are known.
- Prognosis is excellent when diagnosed before hepatic or neurologic injury and treated consistently. Cirrhosis at diagnosis reduces long-term survival, and severe neurologic disease may not fully reverse.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Copper metabolism in Wilson's disease**: dietary copper absorption in small intestine -> portal transport to liver -> normal ATP7B-mediated ceruloplasmin formation and biliary excretion -> ATP7B defect -> hepatic copper accumulation -> spillover to brain, cornea, kidney, RBCs.
- **Kayser-Fleischer ring slit-lamp diagram**: cornea, limbus, Descemet membrane, superior and inferior early copper crescents, circumferential brown-green ring; add labels for sunflower cataract if drawn.

Clinical / Diagnostic significance

- Wilson's disease is a mandatory differential for **young-onset hepatitis, cirrhosis, acute liver failure, movement disorder, psychiatric decline, Coombs-negative hemolysis, and unexplained splenomegaly**.
- A normal ceruloplasmin or absent Kayser-Fleischer ring does not rule it out; combine urinary copper, slit-lamp examination, hepatic copper, and genetics.
- In acute liver failure, low/normal alkaline phosphatase with massive bilirubin and hemolysis is a life-saving clue because early transplant referral is decisive.
- Distinguish Wilson-related fatty liver from MASLD by copper studies, especially basal 24-hour urinary copper.
- Family screening prevents irreversible disease because presymptomatic patients treated early usually have the best outcome.

High-yield exam pointers

- Write the triad: **liver disease + neuropsychiatric disease + Kayser-Fleischer ring**, but state that the full triad is uncommon.
- Gene: **ATP7B**, chromosome 13, autosomal recessive, defective biliary copper excretion.
- Diagnostic numbers: ceruloplasmin <14 mg/dL supports diagnosis; 24-hour urinary copper >40 mcg/day needs evaluation and usually >100 mcg/day in disease; hepatic copper >250 mcg/g dry liver is diagnostic.
- Kayser-Fleischer ring is copper in **Descemet membrane**, best seen by slit lamp.
- Wilsonian acute liver failure: **Coombs-negative hemolysis**, low/normal ALP, very high bilirubin, **ALP:bilirubin <4**, **AST:ALT >2.2**, urgent transplant.
- Main drugs: **D-penicillamine**, **trientine**, and **zinc**; treatment is lifelong and adherence is central.

- D-penicillamine can worsen neurologic disease initially and can cause renal, marrow, skin, and autoimmune toxicity.
- Screen all first-degree relatives; use ATP7B mutation testing when the familial variants are known.

SOURCE & COVERAGE

Harrison 22e — "Wilson's Disease"; Sleisenger & Fordtran's GI & Liver 11e — "Wilson Disease"; CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders".

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Zollinger-Ellison syndrome

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Zollinger-Ellison syndrome (ZES)* is the clinical triad of **gastric acid hypersecretion, severe/refractory peptic ulcer disease, and a non–β-cell gastrin-secreting neuroendocrine tumour (gastrinoma)**. Unregulated gastrin release from a usually well-differentiated NET of the duodenum or pancreas drives parietal-cell stimulation and hyperplasia, producing peptic ulceration in atypical sites, reflux disease and secretory diarrhoea. It accounts for <1% of peptic ulcer disease; ~80% of cases are sporadic and ~20–25% occur as part of **multiple endocrine neoplasia type 1 (MEN 1)**.

Etiology, Epidemiology & Pathology

- **Incidence:** rare — ~0.5–3 per million population per year; estimated in 0.1–1% of patients presenting with PUD. Slight female preponderance; most diagnosed between **30–65 years**. Diagnosis is typically delayed **4–7 years** after symptom onset (widespread PPI use both masks symptoms and confounds gastrin testing).
- **Two forms:**
  - **Sporadic (~80%):** usually solitary, more often pancreatic, potentially curable by resection.
  - **MEN 1–associated (~20–25%):** autosomal dominant, caused by inactivating mutations of the **MEN1 tumour-suppressor gene on chromosome 11q13** encoding **menin**; tumours are typically **small, multiple and duodenal**; presents earlier and runs a more indolent course.
- **Tumour location — the *gastrinoma triangle* (triangle of Passaro):** bounded by (1) confluence of the **cystic and common bile ducts** superiorly, (2) junction of the **2nd and 3rd parts of the duodenum** inferiorly, and (3) junction of the **neck and body of the pancreas** medially. 60–90% of gastrinomas lie within it.
- **Distribution:** the **duodenum is now the commonest primary site** (≈60–100%; mostly 1st/2nd part) — duodenal tumours are small (>90% <1 cm), slow-growing and less likely to metastasise; pancreatic tumours are larger and more aggressive. Other sites: lymph nodes (a primary node gastrinoma can be curable), stomach, ovary, liver, bone.
- **Malignant potential: 60–90% are malignant** (defined by local invasion/metastasis); **25–50% have nodal or hepatic metastases at presentation**. Histology is well-differentiated (NET grade 1–2), staining for **chromogranin A and neuron-specific enolase**.

Pathophysiology

- **Autonomous hypergastrinemia** is the central driver. Gastrin acts on **CCK-2/gastrin receptors on parietal cells** and stimulates **histamine release from ECL cells**, markedly increasing acid output.
- Gastrin is also **trophic** — chronic hypergastrinemia expands parietal-cell mass and ECL-cell hyperplasia (predisposing to **type 2 gastric carcinoids**, especially in MEN 1/ZES).
- The massive acid load produces: **peptic ulcer diathesis**, **erosive oesophagitis/GERD**, and **diarrhoea** — the last via direct mucosal injury, volume overload of the small bowel, and acid **inactivation of pancreatic lipase/precipitation of bile salts** causing maldigestion and steatorrhoea.

Clinical Features

- **Peptic ulcer (>90%):** abdominal pain is the commonest presenting symptom; classically ulcers that are **multiple, in unusual locations (distal duodenum/jejunum), refractory to therapy, recurrent, complicated (bleed/perforation/obstruction), or H. pylori- and NSAID-negative**. Isolated gastric ulcers do *not* occur.
- **Diarrhoea (up to 70%):** may precede or occur independently of ulcers; **classically abates with nasogastric aspiration or PPI** (an important clinical clue).
- **GERD / oesophageal disease (up to two-thirds):** from mild oesophagitis to stricture and Barrett's mucosa.
- **MEN 1 clues:** younger age at presentation, **nephrolithiasis/renal colic**, hypercalcaemia, and personal/family history of parathyroid, pituitary or pancreatic islet tumours. In MEN 1: hyperparathyroidism 80–90%, pancreatic NETs 40–80%, pituitary tumours 30–60%. Hypercalcaemia of hyperparathyroidism aggravates acid secretion — parathyroidectomy lowers gastrin/acid output.

Diagnosis — Biochemical Confirmation

Diagnosis requires demonstration of **inappropriate gastric acid hypersecretion in the presence of hypergastrinemia**. **PPIs must be stopped (≥7 days, covered by an H2-blocker stopped 24 h before testing)** as they elevate gastrin and can cause false positives — but stop with caution, monitoring for acid-peptic complications.

Test	Finding diagnostic of ZES	Comment
Fasting serum gastrin (FSG)	>150–200 pg/mL (normal <150); present in 97–99%	>10× normal (>1000 pg/mL) with low pH is highly suggestive
Gastric pH / BAO	pH <2–3; **BAO >15 mEq/h** (>5 mEq/h if prior gastric surgery)	BAO >15 with hypergastrinemia is near-pathognomonic
BAO/MAO ratio	>0.6	Limited — pentagastrin no longer available
Secretin stimulation test	**Rise in gastrin ≥120 pg/mL within 15 min** of IV secretin (2 U/kg)	Most useful provocative test; sensitivity & specificity >90%

Test	Finding diagnostic of ZES	Comment
Calcium infusion	Rise in gastrin	Largely obsolete (cumbersome, less sensitive)

- **Practical rule (CMDT):** gastrin **>1000 pg/mL + gastric pH <2 establishes the diagnosis**; for intermediate gastrin (150–1000 pg/mL) with acid, perform the **secretin test**.
- **Exclude other causes of hypergastrinemia** — these give a **negative secretin test**: PPI/H2-blocker use, **atrophic gastritis / pernicious anaemia / achlorhydria** (commonest cause), H. pylori, retained gastric antrum, gastric outlet obstruction, renal failure, G-cell hyperplasia.
- Always screen for **MEN 1**: serum **calcium/PTH, prolactin, and pancreatic polypeptide** (± LH-FSH, GH).

Tumour Localization & Staging

- Once biochemically confirmed, localise the tumour and exclude metastases.

Modality	Primary tumour sensitivity	Hepatic metastasis
CT / MRI	low for small lesions	88–100%
EUS	28–86% (best for pancreas; poor for duodenum)	N/A
OctreoScan (^{111}In-pentetreotide)	55–77%	90–100%
^{68}Ga-DOTATATE PET-CT	**>90% (investigation of choice)**	>90%
Selective arterial secretin injection (SASI)	55–78%	—

- **^{68}Ga-DOTATATE PET/CT** (exploits SSTR2 expression) is the **functional imaging study of choice**, superior to OctreoScan. ^{18}F-FDG PET is used as a prognostic marker.
- **WHO grading of the NET (prognostic):** G1 <2 mitoses/10 HPF & Ki-67 <3%; G2 2–20 mitoses or Ki-67 3–20%; G3 >20 mitoses or Ki-67 >20% (poorly differentiated = neuroendocrine carcinoma).

Treatment / Management

- **Control of acid hypersecretion (first priority): high-dose PPIs are the treatment of choice** — omeprazole/lansoprazole/rabeprazole/esomeprazole, initial **60 mg/day (CMDT: 40–120 mg/day) in divided doses**, titrated to **BAO <10 mEq/h** (<5 mEq/h if prior acid-reducing surgery). PPIs have made **total gastrectomy obsolete**.
- **Curative surgery (sporadic, non-metastatic disease):** exploratory laparotomy with **duodenotomy, intraoperative palpation and ultrasound**; immediate cure in ~33–40%, with 10-year disease-free rates up to 95%. **Lymph-node metastasis does not adversely affect prognosis.**
- **MEN 1/ZES:** surgery is **generally deferred** — tumours are multifocal, <5% are disease-free at 5 years, and the course is indolent; manage hyperparathyroidism (parathyroidectomy reduces gastrin/acid).

- **Metastatic disease:** somatostatin analogues (**octreotide LAR, lanreotide**); **peptide receptor radionuclide therapy (PRRT)** with radiolabelled somatostatin analogues; **temozolomide + capecitabine** (≈70% response); targeted agents — **sunitinib (VEGFR), everolimus (mTOR)**; cytotoxics (streptozotocin/5-FU/doxorubicin); hepatic-artery embolization, RFA, debulking.
- **Prognosis:** overall 5-/10-year survival 62–75% / 47–53%; complete resection or negative laparotomy >90% at 10 years; **hepatic metastases <20% at 5 years**. Poor prognostic markers: pancreatic primary >2–3 cm, gastrin >10,000 pg/mL, poor differentiation/high Ki-67, liver/bone metastases, Cushing's syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **The gastrinoma triangle (triangle of Passaro):** draw the liver/porta hepatis, gallbladder with cystic duct, common bile duct, duodenal C-loop (mark 2nd–3rd part junction) and pancreas (head/neck/body). **Labels:** *Confluence of cystic + common bile ducts (superior apex)*, *Junction of 2nd & 3rd parts of duodenum (inferior apex)*, *Junction of neck & body of pancreas (medial apex)*, *Gastrinoma triangle*.
- **Diagnostic algorithm flow box:** *Clinical suspicion → Fasting serum gastrin → if >1000 pg/mL + pH <2 = ZES; if 150–1000 pg/mL → Secretin test (≥120 pg/mL rise = positive) + BAO → Localize with ^{68}Ga-DOTATATE PET-CT/EUS → Resectable vs Metastatic.*

Clinical / Diagnostic significance

- Suspect ZES in any patient with **multiple, distal, recurrent or complicated ulcers, ulcers with diarrhoea, severe/refractory GERD, H. pylori-negative/NSAID-negative PUD, or prominent gastric folds**.
- **Diarrhoea relieved by NG aspiration or PPI** is a strong pointer; **hypercalcaemia or family history** mandates MEN 1 screening.
- A **fasting gastrin done while on a PPI** is the commonest diagnostic pitfall — interpret cautiously and confirm off therapy.
- Early diagnosis matters: it allows curative resection before hepatic spread, the strongest determinant of survival.

High-yield exam pointers

- ZES = **gastrinoma + acid hypersecretion + refractory PUD**; <1% of all PUD.
- **Duodenum is the commonest primary site**; 60–90% lie in the **gastrinoma triangle of Passaro**.
- **~80% sporadic, ~20–25% MEN 1** (MEN1 gene, 11q13, menin); MEN 1 → parathyroid > pancreas > pituitary.
- **Fasting gastrin >1000 pg/mL + gastric pH <2 is diagnostic**; **secretin test = ≥120 pg/mL rise in 15 min** (sens/spec >90%).
- **BAO >15 mEq/h** with hypergastrinemia is near-pathognomonic.
- **Commonest cause of hypergastrinemia overall = achlorhydria/atrophic gastritis (PPI use)**, not gastrinoma — gives a *negative* secretin test.
- **^{68}Ga-DOTATATE PET-CT** is the localization investigation of choice.

- **High-dose PPI** controls symptoms (titrate BAO <10 mEq/h); **resection cures sporadic disease**; surgery usually avoided in MEN 1.
- Most important survival predictor = **hepatic metastasis**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Peptic Ulcer Disease and Related Disorders" (Zollinger-Ellison Syndrome section) and "Gastrointestinal Neuroendocrine Tumors."
- **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — "Neuroendocrine Tumors" (gastrinoma/ZES: clinical features, diagnostic algorithm, secretin test, gastrinoma triangle, WHO grading) and "Peptic Ulcer Disease."
- **CMDT 2026** — "Gastrointestinal Disorders: Zollinger-Ellison Syndrome (Gastrinoma)" for current diagnostic thresholds, ^{68}Ga-PET imaging, and management/PPI dosing.

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