General Medicine

MBBS Recap: high-yield notes for revision

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Revision notes for the MD/MS entrance, arranged by the topics of our General Medicine questions. Each section sets out what an examiner asks; a wrong answer links to its section. Where the classic textbook answer and current practice differ, the **exam answer** comes first, then **current practice** with its source and year.

Cardiology

Pulse and neck veins

Pulse	Feature	Think of
Pulsus parvus et tardus	small, slow rise, late peak	fixed aortic stenosis
Collapsing (water-hammer, Corrigan)	abrupt rise, abrupt fall, wide pulse pressure	severe aortic regurgitation, PDA, high-output states
Bisferiens	two systolic peaks	AR (alone or with AS), HOCM
Pulsus alternans	strong and weak beats alternate, regular rhythm	severe LV failure
Dicrotic	systolic plus diastolic peak	dilated cardiomyopathy, low output with low resistance (sepsis)
Pulsus paradoxus	inspiratory fall in systolic BP over 10 mmHg	tamponade, severe asthma/ COPD, constriction (less often)
Jerky	brisk then abrupt halt	HOCM

- **Kussmaul sign** (JVP rises, or fails to fall, on inspiration): **constrictive pericarditis**, restrictive cardiomyopathy, right ventricular infarction, severe tricuspid disease. It is usually **absent in tamponade**.
- JVP waves: a = atrial contraction; c = tricuspid bulging into the atrium; x descent = atrial relaxation and descent of the base; **v = atrial filling against a closed tricuspid valve** (giant, systolic v waves in tricuspid regurgitation); y descent = tricuspid opening. **Cannon a waves**: AV dissociation (complete heart block, VT); regular cannon waves in junctional rhythm; **absent a: atrial fibrillation**; giant a: tricuspid stenosis, pulmonary hypertension, pulmonary stenosis; steep x and y (M or W pattern): constriction; **x present, y absent: tamponade**.
- Wide pulse pressure in chronic AR: **large stroke volume plus diastolic back-leak**, so systolic rises and diastolic falls. Signs named for it: Corrigan (carotid), de Musset (head nodding), Quincke (nail-bed pulsation), Traube (pistol shot femorals), Duroziez (femoral to-and-fro murmur), Hill (popliteal systolic over brachial by more than 60 mmHg in severe AR).
- The old bedside rule (radial pulse felt means systolic about 80 mmHg, femoral 70, carotid 60) is still asked, but it **overestimates** the pressure and is not relied on now.

Murmurs and valve disease

- **Aortic stenosis:** ejection systolic murmur to the carotids, slow-rising pulse, soft or single S2 (paradoxical splitting when severe), S4; **angina, syncope, dyspnoea**, in order of worsening prognosis. Severe: **peak velocity 4 m/s or more, mean gradient 40 mmHg or more, valve area 1.0 cm^2 or less** (ACC/AHA 2020). Causes: degenerative calcific in the elderly (commonest in the West), **bicuspid valve** in younger adults, rheumatic (with mitral disease) in Nepal and South Asia. Symptomatic severe AS needs valve replacement; **TAVI** is preferred in the elderly (ESC 2021: 75 or more; ESC/EACTS 2025 lowered this to 70), surgery in the younger.
- **Aortic regurgitation:** early diastolic decrescendo murmur at the left sternal edge, louder sitting forward in expiration. **Austin Flint** = functional mid-diastolic apical rumble from the jet hitting the anterior mitral leaflet. **Graham Steell** = early diastolic murmur of pulmonary regurgitation in pulmonary hypertension (classically in mitral stenosis). **Carey Coombs** = short mid-diastolic apical murmur of acute rheumatic mitral valvulitis.
- **Mitral stenosis:** almost always rheumatic; loud S1, **opening snap**, low-pitched mid-diastolic rumble with presystolic accentuation (lost in AF); **the shorter the A2-to-snap gap, the more severe**. Severe: valve area **1.5 cm^2 or less** (ACC/AHA 2020). Echo: diastolic doming of the anterior leaflet, the **"hockey-stick" leaflet**, and a fish-mouth orifice. Treatment: **percutaneous balloon mitral commissurotomy** if the valve is pliable (Wilkins score 8 or less) and there is no left atrial thrombus or more than mild MR; otherwise surgery.
- In **pure mitral stenosis the left ventricle is normal in size** (it is underfilled; LV dysfunction is not a feature), while the **left atrium enlarges** (atrial fibrillation, thrombus, Ortner syndrome of hoarseness from the recurrent laryngeal nerve) and pulmonary hypertension then loads the right ventricle. **Haemoptysis** (from rupture of bronchial veins, or pulmonary oedema) is a classic complication.
- **Mitral regurgitation:** pansystolic apical murmur radiating to the axilla, soft S1, S3. Commonest cause in the West is degenerative (prolapse); in Nepal and in young people, rheumatic. Acute severe MR (papillary muscle rupture, endocarditis) causes flash pulmonary oedema with a short or soft murmur.
- **Mitral valve prolapse:** mid-systolic click then late systolic murmur; **standing and Valsalva move the click earlier** (smaller ventricle), squatting delays it. Myxomatous degeneration; associated with Marfan and Ehlers–Danlos. It is the **commonest cause of primary MR referred for surgery in high-income countries**; repair is preferred to replacement.
- Other: VSD = pansystolic at the left sternal edge; PDA = continuous machinery murmur below the left clavicle; **ASD = wide, fixed splitting of S2** with a pulmonary flow murmur; HOCM = ejection murmur at the left sternal edge, no carotid radiation.

- Dynamic rules: right-sided murmurs louder on inspiration (Carvallo sign for TR); **handgrip (raised afterload) louder for regurgitant murmurs, softer for AS and HOCM**; **HOCM and MVP louder on standing and Valsalva**, softer on squatting; AS softer on Valsalva.
- Chest X-ray shapes: **water-bottle (flask) heart = pericardial effusion** with clear lung fields; boot-shaped = tetralogy of Fallot; **figure of 3 and rib notching = coarctation**; egg on a string = transposition; snowman (figure of 8) = supracardiac TAPVC; straightened left border and double right-heart shadow = mitral stenosis (left atrial enlargement, splayed carina).

Hypertension

Category	ACC/AHA 2017 (kept in 2025)	ESC 2024
Normal / non-elevated	under 120 and under 80	under 120/70
Elevated	120–129 and under 80	120–139 / 70–89
Stage 1 hypertension	**130–139 or 80–89**	(hypertension starts at 140/90)
Stage 2 hypertension	**140 or more, or 90 or more**	140/90 or more

- When systolic and diastolic fall in different categories, **the higher category applies** (155/70 is stage 2). JNC 7 (2003) still appears in exams: stage 1 140–159/90–99, stage 2 160/100 or more, prehypertension 120–139/80–89.
- **Targets:** ACC/AHA 2017 and 2025: under 130/80 for most adults; **ESC 2024: systolic 120–129** if tolerated. The **SPRINT trial** (2015) showed benefit from a systolic target under 120 in high-risk non-diabetic adults. JNC 8 (2014) allowed under 150/90 at 60 or older; this is now superseded.
- **First-line classes:** thiazide or thiazide-like diuretic (chlorthalidone, indapamide), ACE inhibitor or ARB, calcium channel blocker. **Stage 2 or BP well above target: start with two drugs, preferably as one pill** (ACC/AHA 2025, ESC 2024). ACE inhibitor or ARB for diabetes with albuminuria and CKD; beta-blocker only for a specific reason (angina, HF, AF rate). **Resistant hypertension** (uncontrolled on three drugs including a diuretic): add **spironolactone** (PATHWAY-2).
- **In pregnancy:** labetalol, nifedipine, methyldopa; **ACE inhibitors and ARBs contraindicated**.
- **Hypertensive emergency** (severe BP with acute organ damage: encephalopathy, dissection, pulmonary oedema, eclampsia): IV labetalol, nicardipine or nitroprusside; lower mean pressure by **no more than 25% in the first hour**, except in aortic dissection (systolic under 120 within 20 minutes) and acute ischaemic stroke before thrombolysis (under 185/110).
- **Secondary causes:** in the young, think renal parenchymal disease, renal artery stenosis (fibromuscular dysplasia in young women, atherosclerosis in older), primary aldosteronism (the commonest endocrine cause), phaeochromocytoma, Cushing, coarctation, obstructive sleep apnoea.

Ischaemic heart disease

- **Troponin I/T:** myocardium-specific; rises 3–4 h, peaks 24–48 h, stays up 7–10 days (troponin T up to 14). Myoglobin is earliest (1–2 h) but non-specific. **CK-MB returns to normal in 2–3 days, so it detects reinfarction.** Current practice: **high-sensitivity troponin with a 0/1-hour or 0/2-hour rule-in and rule-out** (ESC 2023). The **Fourth Universal Definition of MI (2018)** needs a rise or fall of troponin above the 99th centile with clinical evidence of ischaemia; type 1 = plaque rupture, **type 2 = supply-demand mismatch** (anaemia, tachyarrhythmia, hypotension).
- ECG evolution: hyperacute T, then ST elevation, Q waves (hours), T inversion; **new LBBB alone is no longer a STEMI equivalent** (AHA 2013), but ESC 2023 sends any bundle branch block with ongoing ischaemic symptoms for primary PCI; Sgarbossa criteria help. Territories: V1–V4 = LAD (septal and anterior); I, aVL, V5–V6 = circumflex or diagonal (lateral); **II, III, aVF = inferior (RCA in about 80–90%)**; ST depression V1–V3 with tall R = posterior (confirm with V7–V9); **ST elevation in V4R = RV infarct**.
- **STEMI reperfusion: primary PCI if it can be done within 120 minutes** (AHA: of first medical contact; ESC 2023: of the STEMI diagnosis); otherwise **fibrinolysis within 12 hours of symptom onset**, then transfer for angiography 2–24 h later (rescue PCI if ST resolution is under 50% at 60–90 minutes). Time targets: **AHA 2013: door-to-needle within 30 minutes**; **ESC 2023: needle within 10 minutes of the STEMI diagnosis**. With fibrinolysis the P2Y12 inhibitor is **clopidogrel**; with primary PCI, prasugrel or ticagrelor. Fibrinolysis is for STEMI only, never NSTEMI or unstable angina. Tenecteplase is the preferred fibrinolytic (single bolus). Absolute contraindications: any previous intracranial haemorrhage, ischaemic stroke within 6 months (3 months in AHA), known intracranial neoplasm or AVM, active bleeding, suspected aortic dissection.
- After MI, for all: aspirin plus a P2Y12 inhibitor for 12 months, high-intensity statin (**LDL target under 55 mg/dL, 1.4 mmol/L, ESC 2019**), beta-blocker (now mainly if EF reduced: REDUCE-AMI 2024), ACE inhibitor if EF 40% or less, diabetes or hypertension.
- **Inferior MI with RV involvement:** hypotension with clear lungs and raised JVP; preload-dependent: **avoid nitrates and diuretics**, give IV fluids; bradycardia and AV block are common (RCA supplies the AV node in most).
- **Prinzmetal (vasospastic) angina:** transient ST elevation at rest, often early morning; **calcium channel blockers and nitrates**; avoid non-selective beta-blockers. Unstable angina and NSTEMI show ST depression or T inversion; NSTEMI managed with antiplatelets, anticoagulant, and invasive angiography within 24 h if high risk (GRACE score over 140).
- **Fibrinolysis is not given in NSTEMI or unstable angina:** there is no mortality benefit and more bleeding, because the culprit thrombus is usually platelet-rich and non-occlusive. Treatment is aspirin plus a P2Y12 inhibitor, anticoagulation (fondaparinux or enoxaparin) and an invasive strategy timed by risk (ESC 2023: immediate for refractory pain or instability, within 24 hours for high risk).
- **Nitrates in angina:** glyceryl trinitrate releases **nitric oxide, raising cGMP and relaxing vascular smooth muscle, chiefly in veins**: venodilatation lowers venous return (preload) and ventricular wall tension, so **myocardial oxygen demand falls**; it also dilates the large coronary arteries and relieves spasm, but a fixed atheromatous plaque does not dilate. Sublingual GTN works in 1–3 minutes (headache, flushing, hypotension, reflex tachycardia). Tolerance needs a nitrate-free interval. **Contraindicated with phosphodiesterase-5 inhibitors (sildenafil within 24 h, tadalafil within 48 h), severe aortic stenosis, hypertrophic obstructive cardiomyopathy, RV**

infarction and hypotension. Nitrates relieve symptoms but do not improve survival.

- Complications by time: **VF and arrhythmias in the first 24–48 h** (commonest cause of early death); **papillary muscle rupture 2–7 days** (posteromedial muscle, single RCA supply, inferior MI), **septal rupture 3–5 days** (new pansystolic murmur, step-up in oxygen saturation in the RV), **free wall rupture 5–14 days** (tamponade, electromechanical dissociation); true ventricular aneurysm weeks later (persistent ST elevation); **Dressler syndrome** 2–10 weeks (autoimmune pericarditis; aspirin or NSAID, colchicine). **Accelerated idioventricular rhythm is the commonest reperfusion arrhythmia** and needs no treatment.
- **Histology of an infarct (Robbins):** nothing visible in the first 4 hours (wavy fibres at most); **coagulative necrosis from 4–12 hours, with neutrophils arriving at 12–24 hours and dense at 1–3 days**; macrophages removing debris at 3–7 days; **granulation tissue at 7–14 days**; a **collagen scar by about 2 months**.
- **Chronic coronary syndrome (stable angina):** beta-blocker or calcium channel blocker for symptoms, plus aspirin and statin for prognosis. Exam answer: exercise treadmill test first, **coronary angiography the gold standard**. Current practice: **CT coronary angiography first** for most patients with intermediate pre-test probability (NICE 2016, ESC 2024), functional imaging as the alternative. CABG for left main or triple-vessel disease (especially with diabetes or reduced EF), PCI for single- or two-vessel disease.

Heart failure

- **By ejection fraction (ESC 2021):** HFrEF 40% or less, **HFmrEF 41–49%**, HFpEF 50% or more (with evidence of raised filling pressure). **Natriuretic peptides** rule it out: non-acute **NT-proBNP under 125 pg/mL** or BNP under 35; acute NT-proBNP under 300 or BNP under 100. Obesity lowers them; renal failure, AF and age raise them.
- **HFrEF mortality-reducing drugs, the "four pillars" (ESC 2021, AHA/ACC/HFSA 2022): ACE inhibitor or ARNI** (sacubitril-valsartan, preferred), **beta-blocker** (carvedilol, bisoprolol, metoprolol succinate, nebivolol), **mineralocorticoid antagonist** (spironolactone, eplerenone), **SGLT2 inhibitor** (dapagliflozin, empagliflozin). Start all early, at low dose (STRONG-HF 2022). Add-ons: ivabradine (sinus rate 70 or more), hydralazine with isosorbide dinitrate, vericiguat, IV iron for iron deficiency. **Digoxin reduces admissions only; loop diuretics relieve congestion only**; amlodipine is neutral; non-dihydropyridine calcium blockers (verapamil, diltiazem) worsen HFrEF.
- **HFmrEF and HFpEF: SGLT2 inhibitors are the first proven therapy** (ESC 2023 focused update, class I, from EMPEROR-Preserved and DELIVER), with diuretics for congestion and control of BP and AF; finerenone reduced events in FINEARTS-HF (2024).
- **Devices:** ICD for EF 35% or less despite 3 months of treatment; **CRT for EF 35% or less with LBBB and QRS 150 ms or more**.
- NYHA I–IV by symptoms (IV = symptoms at rest). ACC/AHA stages A–D by structure (A at risk, B structural disease without symptoms, C symptomatic, D refractory).
- **Acute pulmonary oedema:** sit up, oxygen if SpO_2 under 90%, **IV loop diuretic (furosemide: venodilatation within minutes, then diuresis; a saline bolus, beta-blocker or verapamil would worsen it)**, nitrates if BP allows, non-invasive ventilation; routine morphine is no longer advised.

Arrhythmias and the ECG

- **WPW:** accessory pathway (**bundle of Kent**); short PR, delta wave, wide QRS. Orthodromic AVRT is commonest. **In pre-excited AF avoid AV-nodal blockers** (adenosine, verapamil, diltiazem, digoxin, beta-blockers), which speed conduction down the pathway and risk VF; give procainamide or ibutilide, or cardiovert; **definitive treatment is catheter ablation**. James fibres = Lown–Ganong–Levine (short PR, no delta wave).
- **PSVT (AVNRT commonest):** vagal manoeuvres (modified Valsalva with leg raise), then **IV adenosine** (6, then 12 mg); verapamil if adenosine is contraindicated (asthma); synchronised cardioversion if unstable; ablation for recurrence.
- **Carotid sinus massage** (one side at a time for 5–10 seconds, after excluding a carotid bruit or recent stroke) raises vagal tone, slows AV nodal conduction and can terminate AVNRT or AVRT; in atrial flutter or fibrillation it only slows the ventricular rate for a moment and shows the atrial activity. Adenosine is the next step.
- **Atrial fibrillation:** rate control with beta-blocker or diltiazem (digoxin in HF or sedentary people); rhythm control (early, EAST-AFNET 4, 2020) with cardioversion, amiodarone or flecainide (no structural disease), or **pulmonary vein isolation**. Stroke risk: **CHA_2DS_2-VASc** (anticoagulate at 2 or more in men, 3 or more in women); **ESC 2024 uses CHA_2DS_2-VA, dropping sex**: anticoagulate at 2 or more, consider at 1. **DOACs preferred to warfarin**, except in **moderate-to-severe rheumatic mitral stenosis or a mechanical valve: warfarin** (INVICTUS 2022 showed rivaroxaban inferior in rheumatic AF). HAS-BLED estimates bleeding risk but is not a reason to withhold anticoagulation.
- **Heart block:** first degree PR over 200 ms; **Mobitz I (Wenckebach)**: progressive PR lengthening, AV node, benign; **Mobitz II**: dropped beats with fixed PR, infranodal, **needs a pacemaker**; complete block: AV dissociation, cannon waves, pacemaker. Atropine first for symptomatic bradycardia, then pacing or adrenaline infusion.
- **ECG of electrolytes and drugs:** hyperkalaemia peaked T, flat P, wide QRS, sine wave; hypokalaemia flat T, ST depression, **U waves**; **hypercalcaemia short QT**, hypocalcaemia long QT; **digoxin effect: down-sloping ST depression, the "reverse tick" or "hockey-stick" (Salvador Dalí moustache)**, which is not toxicity; digoxin toxicity: any arrhythmia, classically atrial tachycardia with block and bidirectional VT (worse with hypokalaemia; antidote digoxin-specific Fab). Long QT: macrolides, fluoroquinolones, antipsychotics, methadone, ondansetron; **torsades: IV magnesium**. **Brugada**: coved ST elevation in V1–V2, SCN5A, sudden death in young men, ICD.
- **Cardiac arrest (AHA 2020, ERC 2021):** compressions 100–120/min, depth 5–6 cm, 30:2 without an airway; shockable rhythm (VF, pulseless VT): shock, then **adrenaline 1 mg** every 3–5 minutes (AHA: after the second shock; ERC: after the third) and **amiodarone 300 mg after the third shock**, 150 mg after the fifth; non-shockable (asystole, PEA): adrenaline as soon as possible. Reversible causes: 4 Hs (hypoxia, hypovolaemia, hypo/hyperkalaemia, hypothermia), 4 Ts (tension pneumothorax, tamponade, toxins, thrombosis).
- **Pulseless VT is treated exactly as VF: unsynchronised defibrillation at once.** Synchronised cardioversion (the shock

timed to the R wave, so it avoids the vulnerable T wave) is for VT or SVT *with a pulse* and instability.

Rheumatic fever and endocarditis

- **Mechanism:** molecular mimicry between group A streptococcal **M protein** and cardiac myosin and valve glycoproteins (**type II hypersensitivity**), 2–4 weeks after pharyngitis (not skin infection); the organism is not in the lesion. The **Aschoff body** (fibrinoid necrosis with Anitschkow caterpillar cells and Aschoff giant cells) is the lesion; pancarditis, with the **mitral valve the commonest valve** (mitral more than aortic; tricuspid and pulmonary rarely).
- **Revised Jones criteria (AHA 2015): major** = carditis (clinical or subclinical on echo), arthritis, Sydenham chorea, erythema marginatum, subcutaneous nodules. In low-risk populations arthritis means polyarthritis; in **moderate-to-high-risk populations (Nepal) monoarthritis or polyarthralgia counts**. **Minor** = fever (38.5 °C low-risk, 38 °C high-risk), arthralgia, raised ESR (60 or 30 mm/h) or CRP (3 mg/dL), prolonged PR. Diagnosis: **2 major, or 1 major plus 2 minor, with evidence of preceding streptococcal infection** (raised or rising ASO or anti-DNase B, positive culture or rapid antigen); chorea alone suffices.
- **Secondary prophylaxis: benzathine penicillin G 1.2 million units IM every 4 weeks** (every 3 weeks in high-risk settings): without carditis, 5 years or to age 21; carditis without residual valve disease, 10 years or to 21; **carditis with residual valve disease, 10 years or to age 40, sometimes lifelong** (whichever is longer; AHA 2009, WHO 2024 RHD guideline similar). Primary prevention: treat streptococcal pharyngitis with penicillin for 10 days.
- **Endocarditis diagnosis:** modified Duke criteria, now the **2023 Duke–ISCVID criteria** (adds PET-CT and cardiac CT as imaging evidence and more organisms as "typical"). Major: typical organism in two separate blood cultures (or Coxiella phase I IgG over 1:800), imaging evidence of vegetation, abscess or new valvular regurgitation. Definite = 2 major, 1 major plus 3 minor, or 5 minor. **Minor criteria:** predisposing heart condition or injection drug use, fever 38 °C or more, **vascular phenomena** (major emboli, mycotic aneurysm, Janeway lesions), **immunological phenomena** (Osler nodes, Roth spots, glomerulonephritis, rheumatoid factor), positive cultures short of major criteria. Take three sets of blood cultures before antibiotics; TOE more sensitive than TTE.
- **Organisms:** classic answer **viridans streptococci for subacute native-valve disease** (damaged valve, after dental work; still common with rheumatic disease in Nepal); in high-income countries **Staphylococcus aureus is now the commonest overall**. **S. aureus in people who inject drugs (tricuspid valve, septic pulmonary emboli)** and healthcare-associated disease. **Early prosthetic valve (under 1 year): coagulase-negative staphylococci.** *Streptococcus gallolyticus* (bovis): colon cancer, so colonoscopy. Culture-negative: prior antibiotics, HACEK, Coxiella, Bartonella. Signs: **Janeway lesions (painless, septic emboli)**, **Osler nodes (painful, immune)**, Roth spots, splinter haemorrhages, splenomegaly, microscopic haematuria. **Libman–Sacks (lupus, both valve surfaces) and marantic (malignancy) vegetations are sterile.**
- **Prosthetic valve endocarditis:** coagulase-negative staphylococci (*S. epidermidis*) are typical because they stick to prosthetic material and form a **biofilm** that resists host defences and antibiotics; early disease (within a year of surgery, most in the first 2 months; ESC 2023) comes from perioperative contamination, later disease resembles native-valve endocarditis in its organisms. Staphylococcal prosthetic disease is treated with a beta-lactam (or vancomycin) plus **rifampicin** (started once the bloodstream is clear) and gentamicin, and needs surgery more often.
- Treatment: prolonged IV bactericidal antibiotics (4–6 weeks); surgery for heart failure, uncontrolled infection or abscess, or large vegetations with embolism. Current practice: **partial oral step-down in stable left-sided disease** (POET trial, ESC 2023). Prophylaxis (amoxicillin 2 g before dental procedures) only for the highest-risk: prosthetic valve, previous endocarditis, certain congenital heart disease (ESC 2023, AHA 2021).

Pericardium, myocardium, aorta, shock

- **Acute pericarditis:** pleuritic chest pain eased by sitting forward, friction rub, **widespread concave ST elevation with PR depression**; NSAID or aspirin plus **colchicine for 3 months** (reduces recurrence, ESC 2015). In Nepal, a pericardial effusion is often tuberculous.
- **Tamponade: Beck's triad (hypotension, raised JVP, muffled sounds)**, pulsus paradoxus, **electrical alternans**, small ECG voltages; echo shows diastolic collapse of the right atrium and ventricle; treat by **pericardiocentesis**. **Constriction:** pericardial knock, **Kussmaul sign**, steep y descent, pericardial calcification; **TB is the usual cause in Nepal and South Asia** (post-viral, post-surgical and radiation in the West); pericardiectomy.
- **Cardiomyopathies: HOCM** = autosomal dominant sarcomere mutation (**MYH7, MYBPC3**), asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, sudden death in young athletes; avoid dehydration, vasodilators and digoxin; beta-blockers or verapamil, **mavacamten** (cardiac myosin inhibitor, 2022), septal reduction, ICD if high risk. Dilated: commonest cardiomyopathy; alcohol, peripartum, Chagas, doxorubicin, TTN. Restrictive: amyloid (tafamidis for transthyretin type), sarcoid, haemochromatosis.
- **Aortic dissection:** tearing pain to the back, **pulse or BP difference between arms over 20 mmHg**, new AR murmur, widened mediastinum; hypertension and Marfan are the risks. **CT angiography** (TOE if unstable). **Stanford A (ascending) needs emergency surgery; B is medical** (IV beta-blocker first, heart rate under 60, systolic 100–120) unless complicated (malperfusion, rupture), when **TEVAR** is used.
- **Abdominal aortic aneurysm:** repair electively at **5.5 cm in men, 5.0 cm in women** (ESVS 2024), growth over 1 cm a year, or symptoms; **EVAR** is now commonest. **Ruptured AAA: an unstable patient goes straight to theatre without imaging**; permissive hypotension on the way; CT angiography only if stable.
- **Shock profiles: cardiogenic = low output, high SVR, high wedge pressure (cold and wet)**; hypovolaemic = low output, high SVR, low wedge; distributive (septic, anaphylactic) = high output, low SVR, low or normal wedge; obstructive (tamponade, massive PE, tension pneumothorax) = low output, high SVR, high right-sided pressures. Norepinephrine is the first-line vasopressor in cardiogenic and septic shock.
- **Anaphylaxis** (distributive shock; Resuscitation Council UK 2021, WAO 2020): stridor, wheeze, urticaria and hypotension within minutes of exposure. **Give intramuscular adrenaline 0.5 mg (0.5 mL of 1 in 1,000) into the anterolateral thigh at once**, repeated after 5 minutes if there is no response; lie flat with legs raised, oxygen, IV crystalloid. Antihistamines and

hydrocortisone are second-line and do not treat shock or the airway; serum tryptase supports the diagnosis; discharge with an adrenaline auto-injector.

- The Cushing reflex is in Neurology.

Respiratory medicine

Pneumonia

- **Streptococcus pneumoniae** is the commonest bacterial cause of community-acquired pneumonia (no organism is found in most cases; viruses are frequent). Atypicals (Mycoplasma, Chlamydophila, Legionella) in young adults: dry cough, patchy shadows, **cold agglutinins and haemolysis with Mycoplasma**; **Legionella**: hyponatraemia, diarrhoea, confusion, urinary antigen. Haemophilus and Moraxella in COPD; **Klebsiella in alcoholics and diabetics (currant-jelly sputum, upper-lobe cavitation, bulging fissure)**; **Staphylococcus aureus after influenza (pneumatoceles, cavities)**; Pseudomonas in bronchiectasis, cystic fibrosis and ventilated patients; aspiration in alcoholics: anaerobes, right lower lobe (posterior segment of upper lobe if supine).
- **HIV with CD4 below 200/µL: Pneumocystis jirovecii** with bilateral ground-glass opacities, exertional desaturation, raised LDH, often normal early film; silver stain or PCR of induced sputum or BAL; **high-dose cotrimoxazole for 21 days**, with **prednisolone if PaO_2 under 70 mmHg**; cotrimoxazole also prevents it.
- **CURB-65** (confusion; **urea over 7 mmol/L**; **respiratory rate 30 or more**; **systolic BP under 90 or diastolic 60 or less**; age 65 or more): 0–1 home, 2 hospital (short stay or supervised), **3 or more severe, consider ICU**. CRB-65 drops urea for use in the community.
- Empirical treatment: amoxicillin for mild CAP (doxycycline or a macrolide if allergic); amoxicillin-clavulanate or a third-generation cephalosporin plus a macrolide for severe disease. Hospital-acquired pneumonia (48 h or more after admission): cover Gram-negatives and Pseudomonas.

Tuberculosis

- **New drug-susceptible TB: 2HRZE then 4HR**, daily, with fixed-dose combinations by weight band (WHO; **Nepal's National TB Programme** for all new cases, pulmonary and extrapulmonary, as its 2024 DR-TB guideline restates). **Severe extrapulmonary TB** (meningitis, bone and joint, miliary): **Nepal NTP 2019 (as presented in the programme's training material): 2HRZE then 7HRE, extendable**; WHO: TB meningitis and osteoarticular TB 2HRZE then 10HR (12 months), with **corticosteroids for TB meningitis and pericarditis**. Nepal dropped the streptomycin-containing Category II retreatment regimen in 2019: every previously treated patient is tested for drug resistance (Xpert) first.
- **Shorter regimens (WHO 2022): 4 months of HPMZ (2HPZM/2HPM: isoniazid, rifapentine, moxifloxacin, pyrazinamide) for age 12 or more** with drug-susceptible pulmonary TB; **4 months (2HRZ(E)/2HR) for children and adolescents (3 months–16 years) with non-severe TB**.
- **Isoniazid-resistant, rifampicin-sensitive TB: 6 months of REZ plus levofloxacin** (WHO 2018; Nepal DR-TB guideline 2024: 6(H)REZ-Lfx).
- **Drug-resistant TB definitions (WHO 2021, used by Nepal): MDR = resistant to isoniazid and rifampicin**; **pre-XDR = rifampicin-resistant plus a fluoroquinolone**; **XDR = pre-XDR plus bedaquiline or linezolid** (the old definition used injectables). **Xpert MTB/RIF (Ultra)** is the initial test and detects rifampicin resistance (rpoB); isoniazid resistance by katG (high level) or inhA (low level, ethionamide cross-resistance).
- **MDR/RR-TB treatment: 6 months of BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin)** for age 14 or more (WHO 2022; **Nepal's preferred regimen, DR-TB guideline 2024**), BPaL if fluoroquinolone-resistant; 9-month all-oral regimens for children under 14 and in pregnancy; WHO 2025 added a second 6-month regimen, **BDLLfxC** (bedaquiline, delamanid, linezolid, levofloxacin, clofazimine). Injectable-based long regimens are obsolete. Linezolid is the most toxic (myelosuppression, neuropathy, optic neuropathy); bedaquiline prolongs QT.
- **Drug mechanisms and effects:** isoniazid blocks mycolic acid synthesis (katG activates it); rifampicin inhibits DNA-dependent RNA polymerase; pyrazinamide works in acid pH inside macrophages; ethambutol inhibits arabinosyl transferase. **Ethambutol = retrobulbar optic neuritis, red–green colour loss** (check acuity and colour vision); **isoniazid = peripheral neuropathy (slow acetylators), hepatitis, drug-induced lupus, sideroblastic anaemia**, so **pyridoxine** in at-risk patients (isoniazid depletes pyridoxine and inhibits pyridoxal kinase); **rifampicin = orange secretions, strong CYP and P-glycoprotein induction** (contraceptive, warfarin, antiretroviral failure), flu-like syndrome with intermittent use, thrombocytopenia; **pyrazinamide = hyperuricaemia and arthralgia, the most hepatotoxic**. Streptomycin = ototoxicity and nephrotoxicity, **contraindicated in pregnancy** (the first-line oral drugs are safe in pregnancy).
- **Activity:** isoniazid kills rapidly dividing bacilli fastest (early bactericidal); **rifampicin and pyrazinamide have the best sterilising action**; **ethambutol is the only bacteriostatic first-line drug**. Safest in liver disease: ethambutol (with streptomycin, levofloxacin); safest in renal disease: rifampicin (and isoniazid).
- **Drug-induced hepatitis:** stop all drugs if **ALT over 3 times normal with symptoms or jaundice, or over 5 times without**; reintroduce one at a time once ALT is under twice normal.
- **Tuberculin (Mantoux) test:** 0.1 mL PPD intradermally, read at **48–72 h**, induration (not redness) measured across the forearm. **Nepal's TB Preventive Treatment Protocol (NTCC 2024): induration under 10 mm negative, over 10 mm positive** (it does not say how to read exactly 10 mm; WHO and standard texts count 10 mm or more as positive). Lower cut-offs belong to WHO and CDC: **5 mm or more in HIV, recent close contacts, immunosuppression (TNF inhibitors, transplant) and fibrotic changes**; CDC's 15 mm applies only to people with no risk factor in a low-incidence country. A positive test shows **infection, not disease**. False positive: BCG, non-tuberculous mycobacteria. False negative: HIV, malnutrition, steroids, miliary TB, measles, sarcoidosis, very young or old. **Interferon-gamma release assays and the new TB antigen skin tests (Cy-Tb, ESAT-6/CFP-10; WHO 2022) are not affected by BCG**; none separates latent from active TB.
- **TB preventive treatment (Nepal 2024, following WHO): 3HP (weekly rifapentine plus isoniazid for 12 doses) first choice from age 2**, with or without HIV; **3HR** for HIV-negative people if HP is unavailable; **6H** for people with HIV if HP is unavailable. Active TB must be excluded first; people with HIV get TPT whatever their test result.

- Other TB facts asked: commonest site of extrapulmonary TB is lymph node (cervical); **haemoptysis in TB comes mainly from the bronchial arteries** (Rasmussen aneurysm of a pulmonary artery in a cavity is the classic massive bleed); Ghon focus = subpleural lower part of upper lobe or upper part of lower lobe, Ghon complex adds the hilar node; Assmann focus = adult reinfection lesion below the clavicle; Simon focus = apical seeding.

Obstructive disease: COPD and asthma

- **Sputum in asthma: Charcot–Leyden crystals come from eosinophils** (the crystal protein is galectin-10, once called eosinophil lysophospholipase); **Curschmann spirals** are mucus casts of small airways; Creola bodies are clumps of shed epithelium.
- **COPD (GOLD 2025, updated by GOLD 2026):** diagnosis by **post-bronchodilator FEV_1/FVC under 0.7**; severity grades GOLD 1–4 by FEV_1 (80% or more, 50–79, 30–49, under 30% predicted); groups **A, B and E** (the old C and D were merged in 2023; E was 2 or more moderate exacerbations or 1 leading to admission in a year, and **GOLD 2026 lowered it to 1 or more moderate or severe exacerbation**) by symptoms (mMRC 2 or more, or CAT 10 or more) and exacerbations. Initial therapy: A = a bronchodilator; **B = LABA plus LAMA**; **E = LABA plus LAMA, adding ICS if blood eosinophils are 300/µL or more**. ICS alone is never used in COPD; ICS raises pneumonia risk. Add-ons for continued exacerbations: roflumilast (chronic bronchitis), azithromycin, and **dupilumab (GOLD 2025) or mepolizumab (GOLD 2026) when eosinophils are 300/µL or more despite triple therapy**. **Only smoking cessation, long-term oxygen in chronic hypoxaemia, and (in selected patients) triple inhaled therapy, NIV and lung volume reduction reduce mortality.**
- **Long-term oxygen therapy:** PaO_2 55 mmHg (7.3 kPa) or less, or SpO_2 88% or less; or PaO_2 55–60 with cor pulmonale, oedema or polycythaemia (haematocrit over 55%); for at least 15 h a day.
- **COPD exacerbation: controlled oxygen to SpO_2 88–92%**, nebulised bronchodilators, **prednisolone 40 mg for 5 days**, antibiotics if sputum is purulent; **NIV (BiPAP) for respiratory acidosis: pH under 7.35 with $PaCO_2$ over 45 mmHg** (6 kPa). High-flow oxygen worsens hypercapnia chiefly by **abolishing hypoxic pulmonary vasoconstriction (worse V/Q mismatch)** plus the Haldane effect; loss of hypoxic drive is a minor part.
- **Smoking:** pack-years = cigarettes a day ÷ 20 × years; **smoking index = cigarettes a day × years** (over 300 heavy). Alpha-1 antitrypsin deficiency: panacinar, lower-lobe emphysema in young non-smokers or light smokers, with liver disease (PiZZ).
- **Asthma (GINA 2024): SABA alone is no longer recommended** for adults and adolescents. **Track 1 (preferred): as-needed low-dose ICS-formoterol** at steps 1–2, then **maintenance-and-reliever therapy (MART)** with ICS-formoterol at steps 3–5; Track 2: SABA reliever with regular ICS. Step 5: add LAMA (tiotropium), refer for phenotyping and biologics (**omalizumab** anti-IgE; **mepolizumab, reslizumab, benralizumab** anti-IL-5/5R; **dupilumab** anti-IL-4Rα; **tezepelumab** anti-TSLP). Montelukast is a preventer (neuropsychiatric warning); cromoglicate rarely used. Exam answer for a single "drug of choice" in an acute attack remains inhaled salbutamol; for long-term control, ICS.
- **Acute asthma severity (BTS/SIGN 2019, kept in BTS/NICE/SIGN 2024): acute severe** = peak flow 33–50% of best, cannot complete sentences, respiratory rate 25 or more, pulse 110 or more; **life-threatening** = **peak flow under 33%, SpO_2 under 92%**, PaO_2 under 8 kPa, **normal $PaCO_2$**, silent chest, cyanosis, exhaustion, hypotension, arrhythmia, confusion; **near-fatal = raised $PaCO_2$** (needs ICU). GINA calls it severe at SpO_2 under 90% or peak flow 50% or less, speaking in words, agitation.
- **Acute severe asthma treatment: oxygen to SpO_2 93–95% in adults (94–98% in children)**, repeated or continuous **nebulised salbutamol with ipratropium**, **systemic corticosteroid early** (prednisolone 40–50 mg or IV hydrocortisone), then **IV magnesium sulphate** (2 g over 20 minutes) if not responding; IV aminophylline only on specialist advice; ICU for intubation. No sedatives. Montelukast and cromoglicate have no role in the acute attack.

Lung function and respiratory failure

- Spirometry: obstruction = FEV_1/FVC under 0.7 (or below the lower limit of normal); restriction = low FVC and TLC with a normal or high ratio.
- **Emphysema: low FEV_1/FVC, high TLC and RV, low DLCO.** Asthma: obstructive, reversible (FEV_1 rise of 12% and 200 mL after bronchodilator), **normal or raised DLCO**; chronic bronchitis: normal or slightly low DLCO.
- **Restriction:** interstitial lung disease (low DLCO); **neuromuscular weakness (Guillain–Barré, myasthenia) and chest-wall disease: low FVC with a normal or high FEV_1/FVC ratio and normal DLCO** (normal KCO); obesity. **Raised DLCO**: alveolar haemorrhage (Goodpasture, GPA), polycythaemia, asthma, left-to-right shunt. In Guillain–Barré, **vital capacity under 20 mL/kg** (or a fall over 30%) signals impending failure and the need to intubate (20-30-40 rule: VC under 20 mL/kg, maximal inspiratory pressure weaker than −30, maximal expiratory under 40 cmH_2O).
- **Respiratory failure: type 1 = PaO_2 under 60 mmHg with low or normal $PaCO_2$** (pneumonia, pulmonary oedema, ARDS, PE); **type 2 = $PaCO_2$ over 50 mmHg** (COPD, neuromuscular disease, opioids, chest-wall disease).
- **ARDS:** Berlin 2012: acute (within a week), bilateral opacities not explained by heart failure, **PaO_2/FiO_2 300 or less on PEEP 5 or more** (mild 201–300, moderate 101–200, severe 100 or less); the **2023 global definition** also accepts SpO_2/FiO_2, high-flow oxygen and ultrasound. Treatment: **low tidal volume (6 mL/kg predicted body weight), plateau pressure under 30 cmH_2O**, PEEP, **prone positioning for 12–16 h a day in moderate-severe ARDS**, conservative fluids.
- **Breathing patterns:** Cheyne–Stokes (crescendo-decrescendo with apnoea: heart failure, stroke, opioids, raised ICP); **Kussmaul (deep, rapid: metabolic acidosis, DKA)**; Biot (irregular with apnoea: pontine and medullary lesions). **Tachypnoea is a raised rate** (over 20/min in adults); hyperpnoea a raised depth.

Pleura, embolism, interstitial disease, cancer

- **Light's criteria** (exudate if any one): **fluid:serum protein over 0.5**; fluid:serum LDH over 0.6; **fluid LDH over two-thirds of the upper normal serum LDH**. Transudate: heart failure (commonest effusion overall), cirrhosis, nephrotic syndrome, hypoalbuminaemia. Exudate: pneumonia (parapneumonic), TB, malignancy, PE. **Low pleural glucose**: empyema, **rheumatoid** (very low), TB, malignancy; **pleural fluid pH under 7.2 in a parapneumonic effusion means chest drain**;

adenosine deaminase over 40 U/L supports TB (lymphocytic effusion); high amylase: pancreatitis, oesophageal rupture; chylous: triglyceride over 110 mg/dL.

- Minimum fluid visible: **about 200 mL on a PA chest film** (blunted costophrenic angle), about 50 mL on a lateral film, about 5–20 mL on ultrasound (most sensitive at the bedside), CT also detects small amounts.
- **Pneumothorax (BTS 2023):** primary, small and few symptoms: observe or aspirate; ambulatory devices; chest drain if large or secondary; **tension pneumothorax: immediate needle decompression (second intercostal space midclavicular line; ATLS 10th edition (2018) prefers the fourth or fifth space between the anterior and mid-axillary lines in adults)** then chest drain.
- **Pulmonary embolism:** commonest symptom dyspnoea, commonest sign tachypnoea, **commonest ECG finding sinus tachycardia** (S1Q3T3 is classic but uncommon); Wells score, then **D-dimer if PE is unlikely** (age-adjusted cut-off over 50), **CT pulmonary angiography** the investigation of choice (V/Q scan in pregnancy or renal failure); **DOAC (apixaban, rivaroxaban) first-line**; **systemic thrombolysis for high-risk (massive) PE with hypotension**; LMWH in pregnancy and cancer (or DOAC in cancer). Westermark sign (oligaemia), Hampton hump (wedge infarct), Palla sign.
- **HRCT signs: tram-track and signet-ring signs = bronchiectasis** (bronchus wider than its artery); **honeycombing with traction bronchiectasis, subpleural basal = usual interstitial pneumonia (IPF)**; galaxy sign and perilymphatic nodules = sarcoid; crazy paving = pulmonary alveolar proteinosis; halo sign = invasive aspergillosis; tree-in-bud = endobronchial spread (TB, infection); mosaic attenuation = small airways disease.
- **Bronchiectasis:** commonest cause after childhood infection (TB and measles in Nepal); cystic fibrosis (CFTR, upper lobes), Kartagener (dynein, situs inversus), ABPA (central bronchiectasis); chest physiotherapy, treat exacerbations, long-term macrolide if frequent.
- **Cystic fibrosis:** autosomal recessive, **CFTR on chromosome 7 (ΔF508 commonest)**; chronic productive cough with *Pseudomonas aeruginosa* and *S. aureus* infection, **upper-zone bronchiectasis, pancreatic insufficiency with steatorrhoea and failure to thrive, meconium ileus, nasal polyps, male infertility** (absent vas deferens). **Diagnosis: sweat chloride over 60 mmol/L on two occasions** (30–59 intermediate), then CFTR genotype; the newborn screen is immunoreactive trypsinogen. CFTR modulators (elexacaftor–tezacaftor–ivacaftor) have changed prognosis. Primary ciliary dyskinesia (Kartagener) is diagnosed by nasal nitric oxide and ciliary study, not sweat chloride.
- **Idiopathic pulmonary fibrosis:** older men, smokers, dry cough, clubbing, **fine end-inspiratory "Velcro" crackles**, UIP pattern; **antifibrotics pirfenidone or nintedanib** slow FVC decline; **steroids are harmful** (PANTHER 2012). **Sarcoidosis:** bilateral hilar lymphadenopathy, **lupus pernio, erythema nodosum (Löfgren syndrome with arthritis and fever: good prognosis)**, uveitis, hypercalcaemia (macrophage 1-alpha-hydroxylase), raised ACE, **non-caseating granulomas**; steroids if symptomatic or organ-threatening.
- **Sarcoid syndromes: Löfgren** = bilateral hilar lymphadenopathy, erythema nodosum, ankle arthritis and fever (usually women under 40; remits); **Heerfordt syndrome (uveoparotid fever)** = fever, parotid enlargement, anterior uveitis and facial nerve palsy.
- **Lung cancer: adenocarcinoma is the commonest type overall, in non-smokers and in women** (peripheral; **EGFR, ALK, ROS1, KRAS G12C** mutations; **TTF-1, napsin A**); **squamous**: central, cavitation, **PTHrP hypercalcaemia**; **small cell**: central, smokers, **SIADH, ectopic ACTH, Lambert–Eaton**, early spread, chemotherapy rather than surgery. **Pancoast tumour**: shoulder pain, **Horner syndrome**, C8–T1 wasting. Current practice: **test for driver mutations and PD-L1 before treating advanced NSCLC**: osimertinib for EGFR (also adjuvant, ADAURA), alectinib for ALK, pembrolizumab or other immunotherapy for PD-L1 50% or more; **low-dose CT screening** for heavy smokers aged 50–80 (USPSTF 2021).
- **Pneumoconioses: silicosis**: upper-zone nodules, **eggshell calcification of hilar nodes**, raised risk of **tuberculosis** (and lung cancer); **coal worker's pneumoconiosis**: upper-zone nodules, progressive massive fibrosis; **asbestosis**: **lower-zone** fibrosis, **calcified pleural plaques** (a marker of exposure, not of disease), asbestos bodies, and a raised risk of **bronchial carcinoma** (the commonest asbestos cancer, multiplied by smoking) and **mesothelioma**; **Caplan syndrome** = rheumatoid nodules with pneumoconiosis; berylliosis resembles sarcoidosis.
- **Malignant pleural mesothelioma:** asbestos exposure 20–40 years earlier; chest pain and breathlessness, a unilateral effusion with nodular or circumferential pleural thickening. Fluid cytology is often negative, so **pleural biopsy, thoracoscopic or CT-guided, is the diagnostic test** (calretinin, WT1 positive; BAP1 loss); prognosis poor; nivolumab with ipilimumab for unresectable disease (CheckMate 743, 2021).
- **Obstructive sleep apnoea:** snoring, daytime sleepiness (Epworth), resistant hypertension; polysomnography (AHI 5 or more abnormal, 30 or more severe); **CPAP**.
- Sleep apnoea is **confirmed by overnight polysomnography** (home sleep testing is accepted for uncomplicated adults with a high pre-test probability); the Epworth scale and STOP-BANG only screen, and the multiple sleep latency test is for narcolepsy.

Gastroenterology and hepatology

Hepatitis B and other viral hepatitides

- Marker sequence: HBsAg first (**chronic if present over 6 months**), then HBeAg, IgM anti-HBc, anti-HBe, and anti-HBs last. **Window period: HBsAg gone, anti-HBs not yet present, IgM anti-HBc the only marker. Vaccination gives anti-HBs alone**; past infection gives anti-HBs plus IgG anti-HBc; isolated anti-HBc may be occult infection. **HBeAg means active replication and high infectivity**; HBeAg-negative disease with high DNA is a **precore or core-promoter mutant**. HBV DNA is the best measure of replication.

	HBsAg	Anti-HBs	Anti-HBc	HBeAg
Acute infection	+	–	IgM	+
Window period	–	–	**IgM**	–
Chronic, replicating	+	–	IgG	+ (or – with high DNA)
Recovered	–	+	IgG	–
Vaccinated	–	**+**	–	–

- **Viruses:** HBV is a DNA virus (partly double-stranded, reverse transcriptase); A, C, D, E are RNA. **A and E are faecal–oral**; E causes **fulminant hepatitis in pregnancy (mortality up to**

20–25%, third trimester) and water-borne epidemics (Kathmandu valley outbreaks); E can become chronic only in the immunosuppressed (genotype 3, transplant recipients). D needs HBsAg (co-infection or superinfection; superinfection is worse).

- **Chronicity: HCV is the virus most likely to become chronic** (about 55–85% of infections), but **HBV is the commonest cause of chronic viral hepatitis worldwide** (about 250 million carriers against about 50 million with HCV; WHO 2024). Chronicity of HBV depends on age: about 90% after perinatal infection, 30% in early childhood, under 5% in adults.
- **Treatment (current):** HBV: **tenofovir (TDF or TAF) or entecavir**, long term; **WHO 2024 widened eligibility** (significant fibrosis, or HBV DNA over 2,000 IU/mL with raised ALT, or co-morbidities, family history of HCC); **tenofovir in pregnancy from the second trimester when HBV DNA is 200,000 IU/mL or more** (or HBeAg-positive) to prevent transmission; interferon for selected young patients. **HCV: pan-genotypic direct-acting antivirals for 12 weeks** (sofosbuvir-velpatasvir; sofosbuvir-daclatasvir; glecaprevir-pibrentasvir 8 weeks), cure (sustained virological response) over 95%; interferon and ribavirin are obsolete.
- **Needlestick, vaccinated health worker with anti-HBs 10 mIU/mL or more: no treatment.** Non-responder or unvaccinated, source positive: **HBIG plus vaccine** (non-responder after two series: HBIG twice). Antivirals are not used as HBV post-exposure prophylaxis (unlike HIV). **Newborn of an HBsAg-positive mother: HBIG plus vaccine within 12 hours** (birth-dose vaccine within 24 h for all babies, WHO).
- Pathology: ground-glass hepatocytes = chronic HBV (HBsAg in the ER); Councilman (acidophil) bodies = apoptosis in acute viral hepatitis; **Mallory–Denk bodies = alcohol** (also Wilson, PBC, NASH); lymphoid aggregates and steatosis = HCV. Extrahepatic: **polyarteritis nodosa and membranous nephropathy with HBV; mixed cryoglobulinaemia, MPGN, porphyria cutanea tarda and lichen planus with HCV**.

Cirrhosis and its complications

- **SAAG 1.1 g/dL or more = portal hypertension** (cirrhosis, heart failure, Budd–Chiari); in cardiac ascites the protein is also high (over 2.5 g/dL), in cirrhosis low. **Low SAAG: TB peritonitis, peritoneal malignancy, pancreatic ascites, nephrotic syndrome.** TB peritonitis: lymphocytic, high ADA.
- **Spontaneous bacterial peritonitis: ascitic neutrophils 250/mm^3 or more**; E. coli and Klebsiella commonest; **cefotaxime or ceftriaxone plus albumin (1.5 g/kg on day 1, 1 g/kg on day 3)** to prevent renal failure. **Any cirrhotic with ascites who is admitted, or has fever, pain, encephalopathy or renal deterioration, gets a diagnostic paracentesis.** Prophylaxis with norfloxacin or ciprofloxacin after an episode or with low ascitic protein. Large-volume paracentesis: 8 g albumin per litre removed over 5 L.
- **Hepatic encephalopathy (West Haven grades 1–4; asterixis):** precipitants: GI bleed, infection, constipation, hypokalaemia, sedatives, diuretics. **Lactulose first line** (acidifies the colon, traps ammonia as ammonium, cathartic); **rifaximin added after a recurrence**; **no protein restriction** (1.2–1.5 g/kg/day). Neomycin and metronidazole are poorly tolerated.
- **Variceal bleed (Baveno VII, 2022):** resuscitate; **restrictive transfusion (threshold Hb 7, target 7–9 g/dL)**; **vasoactive drug (terlipressin, octreotide or somatostatin) plus antibiotic (ceftriaxone 1 g daily, up to 7 days) before endoscopy**; **endoscopic band ligation within 12 hours**; **pre-emptive TIPS within 72 h for Child–Pugh C 10–13, or B over 7 with active bleeding**; balloon tamponade (Sengstaken–Blakemore) or oesophageal stent as a bridge. Gastric varices: cyanoacrylate glue. **Prevention: non-selective beta-blocker (carvedilol preferred in Baveno VII, propranolol) or band ligation; after a bleed, both.** Baveno VII also uses liver stiffness 25 kPa or more to diagnose clinically significant portal hypertension.
- **Extrahepatic portal vein obstruction (EHPVO)**, a leading cause of variceal bleeding in children in Asia (neonatal umbilical sepsis, catheterisation): **splenomegaly and variceal bleeding with a normal-sized liver, preserved liver function and no ascites** (except after a bleed or transfusion), a portal cavernoma on Doppler, and hypersplenism. Treatment: band ligation, beta-blockers, shunt surgery (meso-Rex) when feasible. Cirrhosis, Budd–Chiari and congenital hepatic fibrosis show liver dysfunction, ascites or a nodular liver.
- **Hepatorenal syndrome (now HRS-AKI):** functional renal failure in cirrhosis with ascites, urine sodium very low, no response to 2 days of diuretic withdrawal and albumin; **terlipressin with albumin** (noradrenaline in ICU); liver transplant is definitive.
- **Scores:** Child–Pugh (**bilirubin, albumin, INR, ascites, encephalopathy**; A 5–6, B 7–9, C 10–15); **MELD (bilirubin, INR, creatinine; MELD-Na adds sodium; MELD 3.0 adds sex and albumin)** for transplant priority.
- **Alcohol: AST:ALT over 2**, both usually under 300, because alcohol depletes pyridoxal phosphate (more needed for ALT) and injures mitochondria (mitochondrial AST); **raised GGT and MCV**. **Alcoholic hepatitis: Maddrey discriminant function 32 or more (or MELD over 20) = severe: prednisolone 40 mg for 28 days** (STOPAH 2015 showed only short-term benefit); **Lille score at day 7** stops non-responders. Viral hepatitis and MASLD: ALT over AST.
- **MASLD** (2023 renaming of NAFLD: steatosis with at least one cardiometabolic risk factor; MASH replaces NASH): commonest liver disease worldwide; FIB-4 then elastography; weight loss of 7–10%; **resmetirom (2024) and semaglutide (2025) approved for non-cirrhotic MASH with fibrosis**.
- **Hepatocellular carcinoma:** surveillance in cirrhosis and in selected HBV carriers **by ultrasound with or without AFP every 6 months**; diagnosis without biopsy on multiphase CT or MRI: **arterial-phase hyperenhancement with portal or delayed washout** (LI-RADS); BCLC staging; resection, ablation, transplant (**Milan criteria: one lesion 5 cm or less, or up to three 3 cm or less**), TACE; first-line systemic: **atezolizumab plus bevacizumab** (IMbrave150) or durvalumab-tremelimumab; sorafenib was the old standard.

Cholestatic, metabolic and other liver disease

- **Primary biliary cholangitis:** middle-aged women, itch and fatigue first, raised ALP and GGT, **antimitochondrial antibody (M2, over 90%)**, normal biliary imaging, raised IgM; associated with Sjögren, thyroid disease; **ursodeoxycholic acid** first line; for inadequate response, **obeticholic acid or now the PPAR agonists elafibranor and seladelpar (2024)** or bezafibrate. **Primary sclerosing cholangitis:** young men, **ulcerative colitis (about 70%)**, p-ANCA, **beaded ducts on MRCP**, onion-skin periductal fibrosis, **cholangiocarcinoma risk**; no proven drug; transplant.

- **Autoimmune hepatitis:** young women, raised IgG, ANA and anti-smooth-muscle (type 1) or anti-LKM1 (type 2, children); interface hepatitis; prednisolone plus azathioprine.
- **Amoebic liver abscess:** young adult men, alcohol, usually **solitary, right lobe** (portal streaming from the caecum and ascending colon via the superior mesenteric vein), **anchovy-sauce pus** (trophozoites at the wall); serology; **metronidazole for 7–10 days, then a luminal agent (diloxanide furoate or paromomycin)**; **aspirate if over 5 cm, left lobe (risk of pericardial rupture), no response in 3–5 days, or uncertain diagnosis**. Pyogenic abscess: older, often multiple, biliary source (E. coli, Klebsiella; hypervirulent Klebsiella in diabetics in Asia), drainage and antibiotics. Hydatid cyst: water-lily sign, albendazole with PAIR or surgery.
- **Wilson disease:** autosomal recessive, **ATP7B, chromosome 13**; **low caeruloplasmin, high 24-h urinary copper**, **Kayser–Fleischer rings** (Descemet membrane; nearly always present with neurological disease), sunflower cataract; hepatic, neurological (lentiform nucleus) and psychiatric disease, Coombs-negative haemolysis; **penicillamine or trientine, zinc for maintenance**; transplant for fulminant disease. **Haemochromatosis: HFE (C282Y), chromosome 6**, high transferrin saturation (over 45%, the earliest marker) and ferritin; bronze diabetes, arthropathy (second and third MCP), cardiomyopathy, HCC; **venesection**.
- **Hereditary jaundice: Gilbert** (reduced UGT1A1, mild unconjugated rise with fasting or illness, benign); **Crigler–Najjar I** (absent UGT1A1, kernicterus, no response to phenobarbital) and **II** (responds to phenobarbital); **Dubin–Johnson** (conjugated, MRP2 defect, **black liver**, gallbladder not seen on oral cholecystography) and Rotor (conjugated, no pigment, gallbladder seen); both benign.

Stomach, pancreas and bowel

- **Helicobacter pylori:** gram-negative, urease, antral gastritis, duodenal ulcer (about 90%), gastric ulcer, **gastric adenocarcinoma and MALT lymphoma** (WHO class I carcinogen). Treatment (**ACG 2024, Maastricht VI 2022**): **bismuth quadruple therapy (PPI, bismuth, tetracycline, metronidazole) for 14 days** first line where clarithromycin resistance is common (as in South Asia); vonoprazan-based dual or triple therapy is an option; **clarithromycin triple therapy only where resistance is under 15%** or proven susceptible. **Test of cure: urea breath test or stool antigen, at least 4 weeks after antibiotics and 2 weeks off PPI**; serology stays positive and cannot confirm cure; rapid urease test needs endoscopy.
- **Upper GI bleeding:** commonest cause peptic ulcer (varices in cirrhosis); **Glasgow–Blatchford score 0–1 can be managed as an outpatient**; Rockall after endoscopy; **endoscopy within 24 h**; Forrest classification (Ia spurting, Ib oozing, IIa visible vessel: treat endoscopically); **high-dose PPI after endoscopic therapy**; restrictive transfusion (Hb 7, or 8 with cardiovascular disease); tranexamic acid does not help (HALT-IT 2020).
- **Autoimmune atrophic gastritis (pernicious anaemia):** body and fundus, **achlorhydria, high gastrin** (loss of acid feedback on antral G cells), anti-parietal cell and anti-intrinsic factor antibodies, B12 deficiency, **gastric carcinoid (ECL-cell) and adenocarcinoma risk**. **Zollinger–Ellison:** gastrin high with **high acid**, multiple and distal ulcers, diarrhoea, MEN1; secretin stimulation test.
- **Acute pancreatitis:** gallstones and alcohol commonest; also hypertriglyceridaemia (over 1,000 mg/dL), hypercalcaemia, post-ERCP, drugs, scorpion sting. **Diagnosis (revised Atlanta 2012): two of three: typical pain, lipase or amylase 3 times normal or more, imaging.** Severity: mild (no organ failure), moderately severe (transient organ failure under 48 h or local complications), **severe = organ failure over 48 h**; BISAP, Ranson, CRP over 150 mg/L at 48 h. Treatment: **moderate goal-directed Ringer's lactate** (aggressive fluids caused overload, WATERFALL 2022), **early oral or enteral feeding**, analgesia, **no prophylactic antibiotics**; ERCP within 24 h only with cholangitis; **cholecystectomy in the same admission for mild gallstone pancreatitis**; infected necrosis (gas on CT): antibiotics (carbapenem) and a **step-up approach**, endoscopic drainage delayed beyond 4 weeks (walled-off necrosis). Signs: **Cullen (periumbilical) and Grey Turner (flank) bruising**.
- **Lipase versus amylase: serum lipase is preferred**: it rises within 4–8 hours, peaks at about 24 hours and stays raised for **8–14 days**, and it is more specific; amylase returns to normal within 3–5 days and also rises in salivary gland disease, macroamylasaemia, perforated ulcer and ectopic pregnancy. A level over 3 times the upper limit counts. **Why fluid comes first:** inflammation leaks fluid into the retroperitoneum (third spacing), so intravascular volume and pancreatic perfusion fall, favouring necrosis and organ failure. The exam answer is early aggressive hydration; **current practice (WATERFALL, NEJM 2022; ACG 2024)** is **moderate goal-directed Ringer's lactate** (about 1.5 mL/kg/h after a 10 mL/kg bolus if hypovolaemic), because aggressive fluid caused more overload with no better outcome. ALP and GGT rise instead in biliary obstruction.
- **Achalasia:** loss of the **inhibitory (nitric oxide and VIP) ganglion cells of the myenteric plexus**, so the lower oesophageal sphincter (LES) does not relax and the body has no peristalsis. Dysphagia to **solids and liquids from the start**, regurgitation of undigested food, weight loss, nocturnal cough; **barium swallow: dilated oesophagus tapering to a "bird's beak"**. Endoscopy first to exclude cancer at the junction (pseudoachalasia). **Oesophageal manometry confirms it: incomplete LES relaxation (raised integrated relaxation pressure) with absent peristalsis**; the Chicago classification (v4.0, 2021) divides it into types I–III (type III has spastic contractions). Treatment: **pneumatic dilatation, laparoscopic Heller myotomy with partial fundoplication, or peroral endoscopic myotomy (POEM)**, which is preferred for type III; botulinum toxin only for the unfit (ACG 2020). Cancer risk is raised (squamous). Chagas disease causes a secondary form. **Diffuse oesophageal spasm** shows simultaneous contractions with normal LES relaxation (corkscrew oesophagus); **scleroderma** shows a weak LES and absent peristalsis, with reflux.
- **Hypercontractile (jackhammer) oesophagus and distal oesophageal spasm:** episodic chest pain and dysphagia. Exam answer: **nutcracker oesophagus**, high-amplitude peristalsis (mean distal amplitude over 180 mmHg) with normal LES relaxation. Current practice: the Chicago classification dropped "nutcracker" in v3.0 (2015); its severe form is the **hypercontractile (jackhammer) oesophagus** of v4.0 (2021: distal contractile integral over 8,000 mmHg·s·cm in at least 20% of swallows); **distal oesophageal spasm** has premature contractions in at least 20%. Treatment: PPI, calcium channel blockers or nitrates, peppermint oil; POEM if refractory.

- **Chronic pancreatitis:** alcohol commonest (tropical pancreatitis with calculi in South Asia), calcification on CT, **faecal elastase low**, diabetes, steatorrhoea; enzyme replacement.
- **Inflammatory bowel disease: Crohn disease**: any site (terminal ileum commonest), skip lesions, **transmural**, cobblestones, **non-caseating granulomas**, fistulas and strictures, **smoking worsens it**, ASCA positive. **Ulcerative colitis**: **rectum upward, continuous, mucosal**, crypt abscesses, pseudopolyps, lead-pipe colon, **p-ANCA**, PSC, **smoking protects**; toxic megacolon (transverse colon over 6 cm). Treatment: 5-ASA (mesalazine) for mild-moderate UC; steroids for flares (never maintenance); thiopurines; **biologics: anti-TNF (infliximab, adalimumab), vedolizumab (gut-selective), ustekinumab and risankizumab (IL-12/23, IL-23)**; JAK inhibitors (tofacitinib, upadacitinib); **acute severe UC (Truelove–Witts): IV steroids, rescue infliximab or ciclosporin at day 3, colectomy**. **Intestinal TB** (caseating granulomas, **transverse ulcers**, ileocaecal, patulous valve, necrotic nodes, ascites) is the main differential in Nepal; if unsure, a trial of anti-TB treatment comes before steroids or anti-TNF.
- **Coeliac disease:** HLA-DQ2/DQ8; **anti-tissue transglutaminase IgA with total IgA** (IgA deficiency gives a false negative), on a gluten diet; **duodenal biopsy: villous atrophy, crypt hyperplasia, intraepithelial lymphocytes (Marsh)**; dermatitis herpetiformis, iron deficiency, osteoporosis, T-cell lymphoma; lifelong gluten-free diet.
- **Malabsorption tests: 72-h faecal fat over 7 g/day = steatorrhoea**; D-xylose absorption normal in pancreatic insufficiency and abnormal in mucosal disease; faecal elastase low in pancreatic insufficiency; hydrogen breath test for lactose intolerance and bacterial overgrowth; Schilling test is obsolete.
- **Diarrhoea: secretory (cholera, VIPoma, carcinoid): stool osmotic gap under 50 mOsm/kg, persists on fasting**; **osmotic (lactose intolerance, laxatives): gap over 100 (often quoted 125), stops on fasting**. **IBS (Rome IV): recurrent pain at least 1 day a week for 3 months, linked to defecation or a change in stool frequency or form**; alarm features (age over 50, bleeding, weight loss, anaemia, nocturnal symptoms) need investigation.
- **Colorectal cancer:** right-sided = anaemia, left-sided = obstruction and altered habit; **FIT** testing and colonoscopy screening from 45 (USPSTF 2021); CEA for follow-up, not diagnosis; Lynch (mismatch repair, MSI-high, responds to immunotherapy) and FAP (APC).

Nephrology and acid-base

Acute kidney injury

- **KDIGO 2012 definition:** creatinine rise of **0.3 mg/dL or more within 48 h**, or to **1.5 times baseline or more within 7 days**, or **urine output under 0.5 mL/kg/h for 6 h**. Stages: 1 = 1.5–1.9 times or a 0.3 rise, or under 0.5 mL/kg/h for 6–12 h; 2 = 2.0–2.9 times, or under 0.5 for 12 h or more; **3 = 3 times, or creatinine 4.0 mg/dL or more, or dialysis started, or under 0.3 mL/kg/h for 24 h or anuria for 12 h**.
- **Prerenal vs acute tubular necrosis:**

	Prerenal	Acute tubular necrosis
FENa	**under 1%**	**over 2%**
FEUrea (useful on diuretics)	under 35%	over 50%
Urine osmolality (mOsm/kg)	over 500	under 350
Urine sodium (mmol/L)	under 20	over 40
BUN:creatinine	over 20	under 15
Sediment	bland, hyaline casts	**muddy-brown granular casts**

- FENa under 1% also occurs in early obstruction, contrast nephropathy, rhabdomyolysis (pigment) and acute glomerulonephritis, so a low value is not specific for prerenal failure.
- **Casts: red cell casts = glomerular bleeding (glomerulonephritis, vasculitis)**, with dysmorphic red cells and acanthocytes; **white cell casts = pyelonephritis or interstitial nephritis**; urinary eosinophils suggest allergic interstitial nephritis (poor sensitivity); **waxy and broad casts = advanced CKD**; fatty casts and oval fat bodies (Maltese cross) = nephrotic syndrome; hyaline casts = normal or prerenal.
- **ACE inhibitors and ARBs dilate the efferent arteriole** (removing angiotensin II's efferent constriction), lowering glomerular pressure; in **bilateral renal artery stenosis** (or stenosis of a single kidney, volume depletion, heart failure) GFR falls and creatinine rises sharply; a rise up to 30% after starting is accepted. **NSAIDs block the prostaglandins that dilate the afferent arteriole**: avoid in CKD and with ACE inhibitors and diuretics (the "triple whammy").
- Causes to remember: rhabdomyolysis (CK over 5,000, haem-positive dipstick without red cells, aggressive fluids), contrast (risk only with low eGFR; hydration), aminoglycosides (non-oliguric, after 5–7 days), tumour lysis, myeloma, **snakebite (Russell's viper) and falciparum malaria** in South Asia.
- **Urgent dialysis (AEIOU):** refractory **acidosis**, **electrolytes (hyperkalaemia)**, **intoxication** with dialysable toxins (methanol, ethylene glycol, lithium, salicylate), **overload** (pulmonary oedema), **uraemia** (pericarditis, encephalopathy, bleeding). Starting dialysis early has no benefit over a watchful strategy (STARRT-AKI 2020). **Cimino–Brescia fistula: radial artery to cephalic vein** at the wrist, the preferred access, mature in 6–8 weeks.

Chronic kidney disease

- **KDIGO 2024: CKD = reduced eGFR under 60 or markers of damage (albuminuria, sediment, imaging, biopsy) for over 3 months**. Staged by **cause, GFR (G1 90 or more, G2 60–89, G3a 45–59, G3b 30–44, G4 15–29, G5 under 15) and albuminuria (A1 urine albumin:creatinine under 30 mg/g, A2 30–300, A3 over 300)**. eGFR by the **race-free CKD-EPI 2021** equation; cystatin C where creatinine misleads (muscle mass).
- Commonest causes worldwide: **diabetes, then hypertension**, then glomerulonephritis; CKD of unknown cause affects farm workers in hot countries.
- **Slowing progression (KDIGO 2024, ADA 2025):** BP control; **ACE inhibitor or ARB at maximum tolerated dose when albuminuric**; **SGLT2 inhibitor at eGFR 20 or more with urine ACR 200 mg/g or more, or with heart failure, with or without diabetes, and for all with type 2 diabetes and CKD at eGFR 20 or more** (suggested also at eGFR 20–45 with lower ACR; DAPA-CKD, EMPA-KIDNEY); **finerenone** (non-steroidal MRA)

for type 2 diabetes with albuminuria; **GLP-1 agonist semaglutide** in type 2 diabetes (FLOW 2024); statin; avoid nephrotoxins.

- **Complications: anaemia of CKD** (low erythropoietin; correct iron first, then ESA, **target Hb 10–11.5 g/dL, not normal**, since higher targets raised stroke and death; HIF prolyl hydroxylase inhibitors such as daprodustat are new); **CKD-mineral bone disorder**: high phosphate, low calcium and calcitriol, **secondary hyperparathyroidism**, renal osteodystrophy (osteitis fibrosa, adynamic bone), vascular calcification; **phosphate binders, calcitriol or analogues, cinacalcet**; metabolic acidosis (bicarbonate if under 18–22); hyperkalaemia (patiromer, sodium zirconium cyclosilicate). Uraemic pericarditis needs dialysis.
- **ADPKD: PKD1 (chromosome 16, about 85%, more severe) or PKD2 (chromosome 4)**; flank pain, haematuria, hypertension, stones, infection; **hepatic cysts are the commonest extrarenal feature**; **berry aneurysms** (screen if family history of SAH), MVP, diverticula; **tolvaptan slows growth** of the kidneys. **ARPKD:** PKHD1 (fibrocystin), infancy, **congenital hepatic fibrosis**.

Glomerular disease

Disease	Light microscopy, IF and EM	Clue
Post-streptococcal GN	hypercellular glomeruli, **lumpy-bumpy granular IgG and C3, subepithelial humps**	**1–3 weeks after pharyngitis, 3–6 weeks after skin infection**; low C3 recovering in 6–8 weeks; children recover, adults less often
IgA nephropathy (commonest GN worldwide)	**mesangial IgA** with C3	haematuria 1–3 days after a mucosal infection (synpharyngitic); IgA vasculitis is its systemic form
Anti-GBM (Goodpasture)	crescents, **linear IgG**	lung haemorrhage with RPGN; plasma exchange, steroids, cyclophosphamide
Membranous	thick GBM, **granular IgG, subepithelial spikes and domes (silver stain)**	**commonest primary nephrotic syndrome in white adults**; **anti-PLA2R in about 70% of primary disease**; secondary: HBV, SLE (class V), malignancy, NSAIDs, gold, penicillamine; rituximab first line (KDIGO 2021)
Minimal change	normal on LM, negative IF, **foot-process effacement**	**commonest nephrotic syndrome in children**; selective proteinuria; steroid-sensitive; NSAIDs, Hodgkin lymphoma
FSGS	segmental sclerosis, foot-process effacement	**commonest primary nephrotic syndrome in adults in the US** (especially of African descent, APOL1); **collapsing variant in HIV**, heroin, obesity, reflux
MPGN	**tram-track (split) GBM**	low C3; **hepatitis C** (cryoglobulins), SLE; C3 glomerulopathy (C3 nephritic factor, dense deposits)
Pauci-immune crescentic	crescents, little or no immune deposit	**ANCA vasculitis** (RPGN type III)
Alport	**basket-weave GBM**	**COL4A5, X-linked**: haematuria, **sensorineural deafness, anterior lenticonus**
Thin basement membrane	thin GBM	benign familial haematuria

- **Nephritic syndrome:** haematuria with red cell casts, hypertension, oedema, oliguria, modest proteinuria. **Low complement**: post-infectious GN, MPGN and C3 glomerulopathy, lupus nephritis, cryoglobulinaemia, shunt nephritis, endocarditis; **normal complement**: IgA nephropathy, anti-GBM, ANCA vasculitis. **RPGN types**: I anti-GBM (linear), II immune complex (granular), III pauci-immune (ANCA).
- **Nephrotic syndrome: proteinuria over 3.5 g/day** (over 40 mg/m^2/h in children), hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria. **Thrombosis risk mainly from urinary loss of antithrombin III**, with raised fibrinogen and factors and platelet hyperaggregability; **renal vein thrombosis is classic (most in membranous)**. Infection from IgG loss (pneumococcal peritonitis in children); vitamin D-binding protein and thyroxine-binding globulin lost.
- **Lupus nephritis:** ISN/RPS classes I–VI; **class IV (diffuse proliferative) commonest and most severe**, wire loops; class V membranous. Treatment: mycophenolate or low-dose cyclophosphamide with steroids, plus **belimumab or voclosporin** (KDIGO 2024, EULAR 2023); hydroxychloroquine for all.
- **Diabetic nephropathy:** earliest change GBM thickening and hyperfiltration; **Kimmelstiel–Wilson nodules** (nodular glomerulosclerosis) are pathognomonic; first clinical sign is moderately increased albuminuria (A2, 30–300 mg/g); **hyaline arteriolosclerosis of both afferent and efferent arterioles**.

Urinary stones and renal colic

- **Renal colic:** sudden severe loin-to-groin pain with restlessness (unlike peritonitis, the patient cannot lie still), haematuria, vomiting. **Imaging of choice: non-contrast (low-dose) CT of the kidneys, ureters and bladder**: it finds almost all stones including radiolucent uric acid stones, gives size and position, and shows hydronephrosis or another diagnosis (EAU 2024); **ultrasound first in pregnancy and children** (and as a quick bedside test); a plain film misses small and radiolucent stones; the intravenous urogram is obsolete.
- **Treatment: NSAID (diclofenac) is the best analgesic**; most stones under 5 mm pass; **tamsulosin (medical expulsive therapy)** is used for distal ureteric stones over 5 mm. **Obstruction with infection is an emergency: decompress (stent or nephrostomy)**. Intervention: shock-wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy for renal stones over 2 cm.
- **Stone types: calcium stones commonest (about 80%, mostly calcium oxalate)**; **uric acid is radiolucent** (acid urine, gout); **struvite (magnesium ammonium phosphate) from urease-producing Proteus, forming staghorn calculi**; cystine (hexagonal crystals, autosomal recessive, nitroprusside test). Prevention: fluids to over 2.5 L of urine a day; thiazide for hypercalciuria; potassium citrate for hypocitraturia and uric acid stones.
- **Sterile pyuria** (white cells in urine with a negative routine culture): **genitourinary tuberculosis** first (three early-morning urines for AFB or Xpert; "beaded" ureter, thimble bladder, autonephrectomy), then partly treated UTI, chlamydial

urethritis, stones, interstitial nephritis, analgesic nephropathy, Kawasaki disease and catheters.

Acid-base

1. Look at the pH (acidosis or alkalosis), then which of PCO_2 or HCO_3^- moves in the direction that explains it.
2. Compensation never overshoots to normal pH; if the compensating variable moves the wrong way, or more or less than expected, think of a mixed disorder.
3. **Metabolic acidosis: Winter formula, expected $PaCO_2$ = 1.5 × HCO_3^- + 8 (± 2).** HCO_3^- 9 gives about 21.5; a measured 21 is appropriate compensation (so a child with diarrhoea and pH 7.28, $PaCO_2$ 21, HCO_3^- 9 has a simple metabolic acidosis). A shortcut: expected $PaCO_2$ is about the last two digits of the pH.
4. **Metabolic alkalosis:** expected $PaCO_2$ rises about **0.7 mmHg per 1 mmol/L rise in HCO_3^-** (to about 55 at most). **Vomiting: pH raised, HCO_3^- raised, $PaCO_2$ raised as compensation, urine chloride under 20 (saline-responsive)**, hypokalaemia; **saline with potassium corrects it**. Saline-resistant (urine chloride over 20): hyperaldosteronism, Cushing, Bartter, Gitelman, current diuretic use.
5. **Respiratory disorders:** acute acidosis HCO_3^- rises 1 per 10 mmHg rise in $PaCO_2$, chronic 3.5–4; acute alkalosis HCO_3^- falls 2 per 10 mmHg fall, chronic 4–5.
6. **Anion gap = Na^+ – (Cl^- + HCO_3^-); normal 8–12** (about 3 times the albumin in g/dL); **correct for low albumin: add 2.5 for each 1 g/dL fall below 4. High gap (MUDPILES; GOLDMARK is the newer list):** methanol, uraemia, DKA (and alcoholic and starvation ketoacidosis), paraldehyde/propylene glycol, isoniazid/iron, lactate, ethylene glycol, salicylates; **5-oxoproline (chronic paracetamol)** and D-lactate in GOLDMARK. A raised **osmolar gap (over 10)** with a high anion gap points to toxic alcohols. **Normal gap (hyperchloraemic): diarrhoea, renal tubular acidosis, acetazolamide, ureterosigmoidostomy, large volumes of saline. Urine anion gap (Na + K – Cl) is negative in diarrhoea (high ammonium excretion) and positive in distal RTA. Delta ratio** (rise in gap ÷ fall in bicarbonate): under 1 adds a normal-gap acidosis, over 2 adds a metabolic alkalosis.
7. Salicylate poisoning: **mixed respiratory alkalosis and high-gap metabolic acidosis** in adults; urinary alkalinisation, dialysis if severe.

- **Mineral-acid (hyperchloraemic) acidosis causes hyperkalaemia because H^+ enters cells and K^+ leaves**; organic acidoses (lactic, keto) shift potassium much less. Hypokalaemia goes with alkalosis, except in RTA types 1 and 2 and diarrhoea.

Renal tubular acidosis

Type	Defect	Potassium	Urine pH	Notes
1 distal	H^+ secretion (α-intercalated cell)	**low**	**over 5.5**	**nephrocalcinosis, calcium phosphate stones**, rickets/osteomalacia; Sjögren, SLE, amphotericin B, lithium; potassium citrate or bicarbonate (small dose)
2 proximal	HCO_3^- reabsorption	low	under 5.5 once the filtered load falls	**Fanconi syndrome** (glycosuria with normal blood glucose, phosphaturia, aminoaciduria, uricosuria); myeloma, **tenofovir**, ifosfamide, Wilson, cystinosis, outdated tetracycline; large alkali doses
4	**hypoaldosteronism or resistance**	**high**	under 5.5	**diabetic nephropathy (hyporeninaemic hypoaldosteronism)**; ACE inhibitors, ARBs, spironolactone, **trimethoprim**, heparin, calcineurin inhibitors; hyperkalaemia suppresses ammonium production; fludrocortisone, potassium restriction, loop diuretic

Electrolytes

- **Hyperkalaemia with ECG changes (peaked T, lost P, wide QRS, sine wave): IV calcium gluconate (10 mL of 10%) first** (stabilises the myocardial membrane within minutes; **does not lower potassium**; repeat if the ECG persists), then **shift: insulin with glucose and nebulised salbutamol**, then **remove: loop diuretic, potassium binders (sodium zirconium cyclosilicate, patiromer; calcium resonium is slow), dialysis**. Sodium bicarbonate only if acidotic. Exclude pseudohyperkalaemia (haemolysed sample, high platelets or white cells).
- **Hypokalaemia:** flat T, U waves, ST depression, weakness, ileus, polyuria (nephrogenic DI), arrhythmia with digoxin; replace orally, IV no faster than 10–20 mmol/h on a ward; **correct magnesium too**, or potassium will not rise.
- **Inherited tubular disorders: Bartter** (**NKCC2** in the thick ascending limb, or ROMK, ClC-Kb, barttin; like taking a loop diuretic; **hypercalciuria**, nephrocalcinosis, onset in infancy; the barttin type has **deafness**); **Gitelman** (**NCC** in the distal tubule; like a thiazide; **low urine calcium, low magnesium**, milder, adolescence or adulthood); **Liddle** (**ENaC gain of function**: hypertension, hypokalaemia, alkalosis, **low renin and low aldosterone**; **amiloride or triamterene**, not spironolactone); **Gordon** (pseudohypoaldosteronism type 2, WNK1/WNK4, NCC overactivity: hypertension, **hyperkalaemia**, acidosis; **thiazides**). Apparent mineralocorticoid excess (11β-HSD2 deficiency, liquorice): like Liddle, but responds to spironolactone.
- **Hyponatraemia:** assess serum osmolality, volume status and urine osmolality and sodium (see Endocrinology for SIADH). **Severe symptoms (seizures, coma): 150 mL of 3% saline over 20 minutes, repeated up to twice, aiming for a 5 mmol/L rise** (European 2014); **chronic hyponatraemia: correct no faster than 10 mmol/L in 24 h (8 in high-risk patients: alcohol, malnutrition, hypokalaemia, liver disease)** to avoid **osmotic demyelination** (central pontine myelinolysis: quadriparesis, dysarthria, locked-in, days later). Pseudohyponatraemia: hyperlipidaemia, paraproteinaemia; hyperglycaemia lowers sodium by about 1.6–2.4 mmol/L per 100 mg/dL of glucose.
- **Hypercalcaemia:** see Endocrinology. **Hypocalcaemia:** perioral tingling, **Trousseau sign (carpopedal spasm within 3 minutes of a cuff inflated above systolic pressure; more**

sensitive) and **Chvostek sign (facial twitch on tapping the facial nerve)**, long QT; IV calcium gluconate; check magnesium.

Endocrinology

Diabetes

- **ADA diagnostic criteria: fasting plasma glucose 126 mg/dL (7.0 mmol/L) or more**; **2-h glucose 200 or more on a 75 g OGTT**; **HbA1c 6.5% or more** (standardised assay); or **random glucose 200 or more with classic symptoms**. Without symptoms, two abnormal results (same or different tests) are needed. **Prediabetes: fasting 100–125 (impaired fasting glucose; WHO uses 110–125), 2-h 140–199 (impaired glucose tolerance), HbA1c 5.7–6.4%**. HbA1c is unreliable in haemoglobinopathies, anaemia, recent transfusion, pregnancy and CKD: use glucose or fructosamine (2–3 week average).
- **Screening (ADA 2025):** everyone from 35, earlier if overweight (**BMI 25 or more; 23 or more in Asian people**) with a risk factor.
- **Type 2 treatment (ADA 2025):** lifestyle and **metformin** for most (avoid at **eGFR under 30**, reduce at 30–45; lactic acidosis, B12 deficiency); **independently of HbA1c and metformin, an SGLT2 inhibitor or a GLP-1 receptor agonist with proven benefit for those with atherosclerotic disease, heart failure (SGLT2) or CKD**; for weight, semaglutide or **tirzepatide (dual GIP/GLP-1 agonist)**. Target **HbA1c under 7%** for most (less strict in the frail elderly). **SGLT2 inhibitors:** genital mycotic infections, **euglycaemic DKA** (stop before surgery), volume depletion, Fournier gangrene (rare); benefit heart and kidney. **GLP-1 agonists:** nausea, weight loss, gallstones, pancreatitis caution, **contraindicated with personal or family history of medullary thyroid carcinoma or MEN2**. Sulfonylureas: hypoglycaemia, weight gain; pioglitazone: fluid retention, heart failure, fractures; DPP-4 inhibitors: weight-neutral, saxagliptin raised HF admissions.
- **Type 1:** autoimmune (anti-GAD65, IA-2, ZnT8, insulin antibodies), low C-peptide; basal-bolus insulin or pumps; **teplizumab (anti-CD3, 2022) delays onset in stage 2 disease**. LADA in adults: slow, antibody-positive. MODY: autosomal dominant, HNF1A (sensitive to sulfonylureas), glucokinase (mild, no treatment).
- **DKA:** exam answer (ADA 2009): **glucose over 250 mg/dL, pH under 7.3, bicarbonate under 18, ketonaemia, raised anion gap**; **first step rapid isotonic saline** (1 L in the first hour), then **fixed-rate IV insulin 0.1 unit/kg/h once potassium is 3.3 mmol/L or more**, potassium added when it is under 5.2 (with urine output); dextrose when glucose falls to 200–250; **bicarbonate only if pH under 6.9**. Current practice (**ADA/EASD/JBDS/AACE/DTS consensus 2024**): **glucose 200 or more or known diabetes; β-hydroxybutyrate 3.0 mmol/L or more** (or urine ketones 2+); pH under 7.3 or bicarbonate under 18; the anion gap is no longer a first-line criterion; **balanced crystalloids suggested** over saline; **delay insulin if potassium is under 3.5**; bicarbonate only if pH under 7.0. Resolution: ketones under 0.6, pH 7.3 or more, bicarbonate 18 or more. **Cerebral oedema** is the dreaded complication in children (too rapid fluid or osmolality change). Hypokalaemia is the commonest dangerous electrolyte problem during treatment.
- **Hyperosmolar hyperglycaemic state (2024 consensus):** glucose 600 or more, effective osmolality over 300 (total over 320), no significant ketonaemia, pH 7.3 or more; older type 2 patients, high mortality, thrombosis; fluids first, insulin only once glucose stops falling with fluids.
- **Hypoglycaemia (ADA):** level 1 under 70 mg/dL, **level 2 under 54**, level 3 severe (needs help); glucose 15–20 g orally, IV dextrose or **glucagon** (intranasal glucagon now available). **Somogyi effect**: morning hyperglycaemia after night hypoglycaemia (reduce the evening insulin; continuous glucose monitoring shows it is uncommon). **Dawn phenomenon**: early-morning rise from growth hormone and cortisol (increase or move the evening basal insulin).
- **Insulinoma: Whipple triad** (symptoms of hypoglycaemia, low glucose, relief with glucose); **72-hour fast: raised insulin, C-peptide and proinsulin with low glucose**, negative sulfonylurea screen. Exogenous insulin: high insulin, **low C-peptide**. Sulfonylurea: high insulin and C-peptide, drug detected.
- **Complications:** retinopathy (annual screen), **nephropathy (urine albumin:creatinine yearly**; once albuminuric, the **maximum tolerated ACE inhibitor or ARB plus an SGLT2 inhibitor** whatever the HbA1c, finerenone if albuminuria persists, KDIGO 2022 and 2024, ADA 2025; details under Nephrology), neuropathy (**distal symmetric sensory, stocking-glove, commonest**; mononeuritis such as CN III with pupil sparing; autonomic; diabetic amyotrophy), foot ulcer (monofilament test). Diabetes in pregnancy is in Obstetrics.

Thyroid

- **Graves disease: TSH-receptor stimulating antibodies (TRAb)**; diffuse goitre with a bruit, **ophthalmopathy** (smoking worsens it; teprotumumab, an IGF-1R antibody, 2020), **pretibial myxoedema**, acropachy; **diffuse high uptake** on scan. Toxic multinodular goitre: older, patchy uptake; **toxic adenoma: single hot nodule**; **subacute (de Quervain) thyroiditis: painful gland after a viral illness, high ESR, low uptake** (NSAIDs, steroids, beta-blocker); painless and postpartum thyroiditis: low uptake, no pain.
- **Antithyroid drugs: carbimazole or methimazole first line** (agranulocytosis: stop and check a count with sore throat or fever; cholestatic hepatitis); **propylthiouracil in the first trimester** (methimazole embryopathy: **aplasia cutis, choanal and oesophageal atresia**), switching to methimazole afterwards because of PTU's **hepatocellular hepatotoxicity** (ATA 2016 hyperthyroidism, ATA 2017 pregnancy). PTU also blocks peripheral T4 to T3 conversion. **Radioiodine contraindicated in pregnancy and breastfeeding** (avoid pregnancy for 6 months after); it worsens eye disease (steroid cover). Beta-blocker for symptoms.
- **Wolff–Chaikoff effect:** a large iodine load **inhibits organification (thyroid peroxidase)** and transiently suppresses hormone synthesis; normal glands escape in days; **Jod–Basedow** is the opposite, iodine-induced hyperthyroidism in nodular glands or iodine deficiency. **Amiodarone** can cause either (type 1 thyrotoxicosis from iodine; type 2 destructive thyroiditis, steroids).
- **Thyroid storm** (Burch–Wartofsky score): **propranolol, PTU (preferred in storm: besides blocking thyroid peroxidase it inhibits type 1 deiodinase, so it lowers T3 within hours; or methimazole), then iodine (Lugol, at least 1 hour after the thionamide), hydrocortisone**, cooling, treat the precipitant. **Myxoedema coma:** IV levothyroxine (with or without T3) **plus hydrocortisone**, warming, ventilation.

- **Hypothyroidism:** commonest cause worldwide **iodine deficiency**; in iodine-sufficient areas **Hashimoto thyroiditis** (anti-TPO, Hürthle cells, lymphoid follicles, thyroid lymphoma risk); **TSH is the best single test** (raised in primary, low or inappropriately normal in central disease, where free T4 guides treatment); levothyroxine, start low in the elderly and in heart disease. Subclinical: raised TSH, normal T4; treat if TSH over 10 or in pregnancy.
- **Hypothyroidism in pregnancy:** needs rise early, by about 20–30%, so a woman on levothyroxine who becomes pregnant should **increase the dose at once (about two extra tablets a week, or 20–30%) and have TSH checked every 4 weeks** until mid-pregnancy, aiming for the lower half of the trimester range, under 2.5 mIU/L if no local range exists (ATA 2017); return to the earlier dose after delivery. Untreated overt disease raises miscarriage and pre-eclampsia and impairs fetal neurodevelopment; take levothyroxine apart from iron and calcium.
- **Endemic goitre:** from **iodine deficiency**: low iodine intake lowers hormone output, TSH rises and the gland enlarges to trap more iodide. The **Himalayan and sub-Himalayan belts are classic**, because glaciation, heavy rain and flooding leach iodine from soil and water, so locally grown food has little. Goitrogens in food (cassava, cabbage) play a minor part. Severe deficiency in pregnancy causes **endemic cretinism** (neurological or myxoedematous), miscarriage and stillbirth. Control is by **universal salt iodisation**; WHO advises 150 µg iodine daily for adults and 250 µg in pregnancy and lactation. WHO grading: 0 none, 1 palpable, 2 visible.
- **Pendred syndrome:** autosomal recessive; defect of **pendrin (SLC26A4, an iodide–chloride transporter)**: goitre with **sensorineural deafness**, enlarged vestibular aqueducts and a **positive perchlorate discharge test** (an organification defect); usually euthyroid. **Riedel thyroiditis:** a hard, woody, fixed, painless goitre (IgG4-related fibrosis) that mimics anaplastic carcinoma.
- **Thyroid nodules and cancer:** TSH first, ultrasound (TIRADS), **fine-needle aspiration (Bethesda)**. **Papillary** commonest (about 80%), radiation, **Orphan Annie nuclei, psammoma bodies**, lymphatic spread, **BRAF V600E, RET/PTC**; **follicular**: diagnosed by capsular or vascular invasion (not FNA), **haematogenous** spread (bone, lung), RAS; **medullary**: parafollicular C cells, **calcitonin**, amyloid, **RET**, MEN2 (prophylactic thyroidectomy in carriers); **anaplastic**: elderly, rapid, poor. Targeted therapy for advanced disease (BRAF, RET inhibitors selpercatinib).

Adrenal

- **Cushing syndrome:** commonest cause overall is **exogenous glucocorticoid**; **commonest endogenous cause is a pituitary ACTH adenoma (Cushing disease), about 70%. Screen (Endocrine Society 2008, 2021 consensus): overnight 1 mg dexamethasone suppression (cortisol over 1.8 µg/dL fails), 24-hour urinary free cortisol, or late-night salivary cortisol**; confirm with a second test. Then **plasma ACTH**: **low = adrenal source** (adrenal CT); **high = pituitary or ectopic**, separated by **high-dose (8 mg) dexamethasone suppression (suppresses in pituitary disease)**, CRH stimulation and **bilateral inferior petrosal sinus sampling (the gold standard)**, with pituitary MRI. Ectopic ACTH (small cell lung cancer, carcinoid): very high ACTH, hypokalaemic alkalosis, pigmentation, little cushingoid appearance. Treatment: **transsphenoidal surgery**; drugs: metyrapone, ketoconazole, osilodrostat, pasireotide. **Nelson syndrome** (enlarging pituitary tumour, pigmentation) follows bilateral adrenalectomy.
- **Primary adrenal insufficiency (Addison): autoimmune commonest worldwide (21-hydroxylase antibodies), TB commonest in developing countries** (enlarged, calcified glands); others HIV, fungal (histoplasmosis), haemorrhage, metastases, adrenoleukodystrophy. Low cortisol and aldosterone; **raised ACTH and POMC-derived α-MSH acting on melanocortin (MC1) receptors, so hyperpigmentation** (buccal mucosa, palmar creases, scars); **hyponatraemia (the commonest electrolyte change), hyperkalaemia, mild hyperchloraemic acidosis**, hypoglycaemia, eosinophilia, postural hypotension. Diagnosis: low morning cortisol with high ACTH, **cosyntropin (short Synacthen, 250 µg) test: cortisol fails to rise above about 18 µg/dL (500 nmol/L)**. Replacement: hydrocortisone (15–25 mg/day in divided doses) plus **fludrocortisone**; **sick-day rules** (double the dose with fever, injection when vomiting). **Adrenal crisis: IV hydrocortisone 100 mg at once, then 200 mg/day, with IV saline and dextrose**; do not wait for results. **Secondary (pituitary) insufficiency: low ACTH, no pigmentation, no hyperkalaemia** (aldosterone is driven by renin–angiotensin and potassium), though hyponatraemia (from cortisol lack and ADH) and hypoglycaemia may occur; commonest cause stopping long-term steroids. **Waterhouse–Friderichsen syndrome**: bilateral adrenal haemorrhage in **meningococcal** septicaemia.
- **Primary aldosteronism:** hypertension (often resistant) with hypokalaemia (only in about a third), alkalosis, low renin. Exam answer: **Conn adenoma** commonest cause; current data: **bilateral adrenal hyperplasia is now commoner (about 60%)** as screening finds milder cases. **Screen with plasma aldosterone:renin ratio**; **confirm with saline infusion, oral salt loading, captopril or fludrocortisone suppression**; CT, then **adrenal vein sampling** to lateralise; **adenoma: laparoscopic adrenalectomy; hyperplasia: spironolactone or eplerenone** (Endocrine Society 2016). Glucocorticoid-remediable aldosteronism: dexamethasone.
- **Phaeochromocytoma:** episodic headache, sweating, palpitations, hypertension; **plasma free metanephrines (most sensitive) or 24-hour urinary fractionated metanephrines**; urinary VMA is older and less sensitive; CT or MRI (bright on T2), MIBG or ^{68}**Ga-DOTATATE PET**. **Alpha-blockade first (phenoxybenzamine or doxazosin) for 10–14 days, with high salt and fluids, then a beta-blocker**, then surgery. The classic **"rule of 10s"** (10% bilateral, extra-adrenal, malignant, familial, in children) is outdated: **up to 40% carry a germline mutation** (SDHx, VHL, RET, NF1), so all should have genetic testing (Endocrine Society 2014). Associations: **MEN2A and 2B, VHL, NF1**, SDH paraganglioma syndromes.
- **Carcinoid tumours and carcinoid syndrome:** commonest site now the small bowel (ileum), then the appendix (older texts put the appendix first). The syndrome appears when **liver metastases** let serotonin reach the systemic circulation: **flushing, secretory diarrhoea, bronchospasm, right-sided valve lesions** (tricuspid regurgitation, pulmonary stenosis) and a pellagra-like dermatitis (tryptophan is diverted to serotonin). Diagnosis: **24-hour urinary 5-HIAA** (or plasma chromogranin A; DOTATATE PET to localise); symptoms are treated with **octreotide or lanreotide**. Vanillylmandelic acid and metanephrines belong to phaeochromocytoma.

- **Congenital adrenal hyperplasia: 21-hydroxylase deficiency commonest (over 90%)**: **raised 17-hydroxyprogesterone**, virilisation of girls, salt-wasting crisis in boys at 1–3 weeks; **11β-hydroxylase deficiency: virilisation with hypertension** (raised 11-deoxycorticosterone) and hypokalaemia; 17α-hydroxylase deficiency: hypertension with sexual infantilism. Glucocorticoid and mineralocorticoid replacement.
- **Adrenal incidentaloma:** test all for cortisol excess (1 mg dexamethasone test) and metanephrines, and aldosterone:renin ratio if hypertensive; over 4 cm or suspicious imaging (density over 10 HU) suggests resection.

Calcium, pituitary and MEN

- **Primary hyperparathyroidism: high calcium, low phosphate, high or inappropriately normal PTH**, raised urine calcium; **single adenoma about 85%**, hyperplasia (MEN), carcinoma rare; stones, bones (osteitis fibrosa cystica, **salt-and-pepper skull, subperiosteal resorption of the radial side of the middle phalanges**, brown tumours), abdominal groans, psychic moans; sestamibi scan localises; parathyroidectomy if symptomatic, calcium over 1 mg/dL above normal, osteoporosis, stones, eGFR under 60, age under 50. **Familial hypocalciuric hypercalcaemia** (CaSR): low urine calcium, no surgery. **Secondary (CKD, vitamin D deficiency): low or normal calcium, high phosphate in CKD, high PTH. Tertiary: high calcium and very high PTH after long secondary stimulation** (autonomous). **Malignancy: high calcium with suppressed PTH** (PTHrP from squamous cancers, bone metastases, myeloma, calcitriol in lymphoma); sarcoidosis also suppresses PTH.
- **Hypoparathyroidism and its look-alike: hypoparathyroidism** (post-thyroidectomy commonest) gives low calcium, **high phosphate and low PTH**. **Pseudohypoparathyroidism type 1a** (GNAS mutation, end-organ resistance to PTH, maternal inheritance) gives low calcium, **high phosphate and high PTH**, with **Albright hereditary osteodystrophy: round face, short stature, short fourth and fifth metacarpals, subcutaneous calcification, obesity**, and resistance to other hormones (TSH). **Pseudopseudohypoparathyroidism** has the same appearance with normal calcium (paternal inheritance). Signs: Chvostek, Trousseau, long QT.
- **Severe hypercalcaemia treatment: IV saline first**, then **IV bisphosphonate (zoledronate)**; calcitonin for a quick but short effect; denosumab if bisphosphonates are contraindicated; steroids for sarcoid, lymphoma and vitamin D toxicity; dialysis if renal failure.
- **SIADH: hyponatraemia, low serum osmolality (under 275), urine osmolality over 100 mOsm/kg (inappropriately concentrated), urine sodium over 40 mmol/L in classic teaching (over 30 in the European 2014 guideline), euvolaemia**, normal thyroid, adrenal and renal function, no diuretics. Causes: small cell lung cancer, CNS disease, pneumonia, drugs (**carbamazepine, SSRIs, cyclophosphamide, vincristine, chlorpropamide**), pain, nausea. Treatment: **fluid restriction first**; then **tolvaptan** (vasopressin V2 antagonist; liver injury warning), **oral urea** (European 2014), salt tablets with loop diuretic; demeclocycline (classic exam answer, now little used); **hypertonic saline for severe symptoms**.
- **Diabetes insipidus**, renamed in 2022 **arginine vasopressin deficiency (central) and AVP resistance (nephrogenic)**: polyuria with dilute urine (osmolality under 300), high-normal sodium. **Water deprivation test**, then **desmopressin**: urine concentrates in central DI, not in nephrogenic; **hypertonic-saline-stimulated copeptin is now more accurate** (copeptin over 21.4 pmol/L unstimulated = nephrogenic). Central: head injury, surgery, tumours (craniopharyngioma), **Langerhans cell histiocytosis**, sarcoid; desmopressin. Nephrogenic: **lithium** (commonest drug), hypercalcaemia, hypokalaemia, X-linked V2 receptor mutation; thiazides, amiloride for lithium.
- **Pituitary: prolactinoma is the commonest functioning adenoma**; galactorrhoea, amenorrhoea, low libido; drug causes (antipsychotics, metoclopramide); **cabergoline first line** even for large tumours (bromocriptine in pregnancy). **Acromegaly: IGF-1 to screen, failure of GH suppression on an oral glucose load (under 1 µg/L) to confirm**; transsphenoidal surgery, then somatostatin analogues (octreotide), pegvisomant (GH receptor antagonist); deaths from heart disease. **Sheehan syndrome**: postpartum pituitary necrosis, first sign failure of lactation. Pituitary apoplexy: sudden headache, visual loss, ophthalmoplegia, hydrocortisone. Bitemporal hemianopia from chiasmal compression.
- **Causes of hyperprolactinaemia:** physiological (pregnancy, lactation, stress, sleep, nipple stimulation); **drugs** (dopamine antagonists: antipsychotics, metoclopramide, domperidone; also methyldopa, verapamil, oestrogens); **primary hypothyroidism** (raised TRH stimulates lactotrophs, and the thyrotroph hyperplasia can mimic a macroadenoma that shrinks with levothyroxine); chronic renal failure; cirrhosis; polycystic ovary syndrome; and **stalk compression** by a non-functioning mass (usually under about 2,000 mIU/L, 100 ng/mL), whereas a level over about 200 ng/mL suggests a macroprolactinoma. Men present with hypogonadism and gynaecomastia, less often galactorrhoea.
- **Sheehan syndrome in detail:** the pituitary enlarges in pregnancy (lactotroph hyperplasia) without a matching rise in blood supply, so **severe postpartum haemorrhage with hypotension infarcts the anterior gland**. **Failure of lactation (prolactin deficiency) and no return of periods** come first, then loss of pubic and axillary hair, fatigue, hypothyroidism and hypocortisolism (hypoglycaemia, hypotension). Diagnosis: low prolactin, gonadotrophins, TSH and ACTH with an empty or small sella on MRI. **Replace hydrocortisone before levothyroxine.** Diabetes insipidus is rare because the posterior lobe is usually spared.
- **Osteoporosis: DEXA T-score –2.5 or less** (osteopenia –1 to –2.5); Z-score for the young; FRAX for fracture risk; vitamin D and calcium, **bisphosphonate first line** (alendronate weekly, zoledronate yearly; osteonecrosis of the jaw, atypical femoral fracture), denosumab, teriparatide or romosozumab for severe disease.

MEN syndrome	Gene	Features
MEN1 (Wermer)	MEN1 (menin), chromosome 11	**parathyroid hyperplasia (commonest, about 95%), pancreatic and duodenal neuroendocrine tumours (gastrinoma, insulinoma), pituitary adenoma**
MEN2A (Sipple)	**RET**	**medullary thyroid carcinoma (nearly all)**, phaeochromocytoma, parathyroid hyperplasia
MEN2B	**RET** (M918T)	medullary thyroid carcinoma (early, aggressive), phaeochromocytoma, **mucosal neuromas, marfanoid habitus**, no hyperparathyroidism

Neurology

Stroke and vascular syndromes

- **Wallenberg (lateral medullary) syndrome: posterior inferior cerebellar artery (PICA), the exam answer**, though occlusion of the **vertebral artery** is actually the commoner cause; ipsilateral facial pain and temperature loss (spinal trigeminal nucleus), **Horner syndrome**, cerebellar ataxia, **dysphagia and hoarseness (nucleus ambiguus)**, vertigo, nystagmus, hiccups; **contralateral body pain and temperature loss**; no limb weakness. **Medial medullary (Dejerine):** anterior spinal or vertebral artery; contralateral hemiplegia and dorsal-column loss, **tongue deviates toward the lesion**. **AICA:** lateral pons, with **facial palsy and deafness**. **Weber:** midbrain (PCA branches), **ipsilateral CN III palsy with contralateral hemiplegia**; Benedikt adds tremor (red nucleus); Millard–Gubler: pons, CN VI and VII with contralateral hemiplegia.
- **Why brainstem lesions cross:** corticospinal fibres in the cerebral peduncle and pons lie above their decussation at the medullary pyramids, so a lesion above the medulla weakens the **opposite** limbs, while the cranial nerve nucleus or fascicle on the same side gives the **ipsilateral** palsy (a crossed syndrome, as in Weber's).
- **Locked-in syndrome: basilar artery occlusion, ventral pons;** quadriplegia and loss of speech with preserved consciousness, vertical eye movements and blinking (the midbrain is spared). **Top of the basilar**: visual, oculomotor and behavioural deficits. MCA: contralateral face and arm weakness, aphasia (dominant) or neglect (non-dominant); ACA: contralateral leg; PCA: contralateral homonymous hemianopia with macular sparing.
- **Acute ischaemic stroke: non-contrast CT first to exclude haemorrhage**; an early MCA infarct is often invisible on CT but shows on diffusion-weighted MRI (hyperdense MCA sign = clot). **IV thrombolysis within 4.5 hours** of last known well if **BP under 185/110** (kept under 180/105 for 24 h after) and no contraindication: **alteplase 0.9 mg/kg** (10% bolus, rest over 1 h) or **tenecteplase 0.25 mg/kg single bolus**, now an equal or preferred option (AcT 2022; ESO 2023, AHA). **Mechanical thrombectomy for large-vessel occlusion (ICA, M1)** within 6 h, and **6–24 h with favourable perfusion imaging** (DAWN, DEFUSE-3); large-core infarcts benefit too (SELECT2, ANGEL-ASPECT 2023). **Aspirin 160–325 mg within 24–48 h for those not thrombolysed; after thrombolysis, antiplatelets are delayed 24 h** (AHA/ASA 2019). **Minor stroke (NIHSS 3 or less) or high-risk TIA: aspirin plus clopidogrel for 21 days** (CHANCE, POINT). Full-dose heparin does not improve outcome. **Do not lower BP in the first days** unless over 220/120 (or for thrombolysis).
- **Secondary prevention:** statin, BP control, antiplatelet; **AF: DOAC** (start about day 1–3 for minor and 6–14 for large strokes; early start is safe, ELAN 2023); **carotid endarterectomy for symptomatic stenosis 70–99% (50–69% in selected men), ideally within 2 weeks**. **TIA** is now defined by tissue (no infarct on imaging); $ABCD^2$ is no longer used alone to triage (NICE 2019: everyone seen within 24 h).
- **Subarachnoid haemorrhage:** thunderclap headache, worst ever, neck stiffness; **ruptured berry aneurysm in about 85%** (ADPKD, coarctation, Ehlers–Danlos), **commonest site the anterior communicating artery**; posterior communicating aneurysm gives a **painful pupil-involving CN III palsy**. **Non-contrast CT within 6 hours is almost 100% sensitive**; **lumbar puncture at 12 h or later for xanthochromia** if CT is negative; **CT angiography** (or DSA) finds the aneurysm. **Nimodipine 60 mg 4-hourly for 21 days reduces delayed cerebral ischaemia from vasospasm (days 4–14)**; **rebleeding** (highest in the first 24 h) is prevented by **endovascular coiling (preferred where feasible, ISAT 2002) or clipping**. Hyponatraemia (cerebral salt wasting or SIADH) and hydrocephalus are complications. Grades: Hunt–Hess, WFNS; Fisher scale for spasm risk.
- **Hypertensive intracerebral haemorrhage:** commonest site the **putamen** (lenticulostriate arteries; Charcot–Bouchard microaneurysms), then thalamus, pons, cerebellum; **lobar haemorrhage in the elderly suggests amyloid angiopathy**. Lower systolic BP to about 140 (INTERACT); reverse anticoagulation (prothrombin complex concentrate, idarucizumab for dabigatran, andexanet for factor Xa inhibitors); **cerebellar haemorrhage over 3 cm or with hydrocephalus needs surgery**.
- **Cushing reflex (raised ICP): hypertension, bradycardia, irregular breathing.** The opposite of shock. Papilloedema, sixth nerve palsy (false localising), and the uncal herniation picture (ipsilateral fixed dilated pupil, then contralateral hemiparesis) are the other signs. Treat with head elevation, osmotherapy (mannitol or hypertonic saline), brief hyperventilation as a bridge.
- **Venous sinus thrombosis:** headache, seizures, papilloedema, haemorrhagic infarcts; pregnancy and puerperium, the pill, dehydration; **empty delta sign** on contrast CT; MR venography; **anticoagulate even if haemorrhagic**.

Aphasia, cortex and cranial nerves

- **Broca:** non-fluent, comprehension intact, repetition poor, patient aware (dominant **inferior frontal gyrus, areas 44–45**; superior MCA division), often with right arm and face weakness. **Wernicke: fluent, empty speech with paraphasias, poor comprehension and repetition, unaware** (posterior **superior temporal gyrus, area 22**; inferior MCA division), often with a superior quadrantanopia. **Conduction:** fluent, comprehension intact, **poor repetition** (arcuate fasciculus or supramarginal gyrus). **Global:** all lost. **Transcortical** aphasias: **repetition preserved** (watershed infarcts). Anomic aphasia: word-finding only.
- **Gerstmann syndrome** (dominant angular gyrus): acalculia, agraphia, finger agnosia, left-right confusion. Non-dominant parietal: neglect, dressing apraxia. Frontal: disinhibition, primitive reflexes. Bilateral medial temporal (hippocampus): amnesia; **Klüver–Bucy (amygdala): hyperorality, hypersexuality**.
- **Facial palsy: UMN lesion spares the forehead** (bilateral cortical supply); **LMN (Bell) palsy involves the whole half of the face**, with hyperacusis and taste loss if proximal; **prednisolone within 72 h** improves recovery (antivirals add little); protect the eye. **Ramsay Hunt syndrome**: VZV in the geniculate ganglion, vesicles in the ear, worse prognosis, steroids plus aciclovir.
- **Reflex roots:** biceps C5–6, supinator C5–6, triceps C7 (C6–7), knee L3–4, **ankle S1**, plantar L5–S1; superficial abdominal T8–T12, cremasteric L1–L2, anal S2–S4. **Muscle power (MRC): 0 none, 1 flicker, 2 movement with gravity eliminated, 3 against gravity, 4 against some resistance, 5 normal.**
- **UMN lesion:** spasticity (clasp-knife), brisk reflexes, clonus, **extensor plantar (Babinski)**, no wasting. **LMN:** flaccid,

wasting, **fasciculation**, absent reflexes. Extrapyramidal: rigidity (lead-pipe, cogwheel with tremor), bradykinesia, normal reflexes and plantars.

- **Pupils:** the light reflex runs retina, optic nerve, pretectal nucleus, Edinger–Westphal nucleus, then the third nerve. **Argyll Robertson pupil: small, irregular, accommodates but does not react to light (light–near dissociation)**, from a pretectal lesion; the **classic cause is neurosyphilis (tabes dorsalis)**, and diabetic autonomic neuropathy can mimic it (pseudo-Argyll Robertson). **Horner syndrome**: small pupil that still reacts, with ptosis and anhidrosis. **Holmes–Adie**: large, tonic, slowly reacting pupil with absent knee jerks in young women. **Third-nerve compression** (posterior communicating aneurysm): dilated fixed pupil. **Relative afferent pupillary defect**: optic neuritis (multiple sclerosis). Neurosyphilis is treated with IV benzylpenicillin 18–24 million units a day for 10–14 days.

Neuromuscular and spinal disease

- **Guillain–Barré syndrome:** ascending symmetrical flaccid weakness, **areflexia**, back pain, autonomic instability, 1–4 weeks after **Campylobacter jejuni** (worst prognosis, axonal), CMV, EBV, Zika or vaccination; **CSF raised protein with a normal cell count (albuminocytological dissociation: usually under 10 cells/μL; under 50 by the Brighton criteria), often only after the first week**; nerve conduction: demyelination (AIDP, commonest in the West) or axonal forms (**AMAN, anti-GM1**, commoner in Asia). **IVIG (0.4 g/kg for 5 days) or plasma exchange**, equally effective; **steroids do not help**; monitor **vital capacity (intubate if under 20 mL/kg or falling quickly)**, swallowing and autonomic function. **Miller Fisher variant: ophthalmoplegia, ataxia, areflexia, anti-GQ1b.** CIDP: over 8 weeks, responds to steroids.
- **Myasthenia gravis: postsynaptic acetylcholine-receptor antibodies (about 85%)**, or anti-MuSK (bulbar, women, poor response to pyridostigmine) or anti-LRP4; **fatigable** ptosis, diplopia, bulbar and proximal weakness, **no reflex or sensory change**; **decremental response on repetitive stimulation**, **single-fibre EMG most sensitive**; ice-pack test at the bedside (the edrophonium test is obsolete); CT chest for **thymoma (about 10–15%)**; **thymic hyperplasia in most**. Treatment: **pyridostigmine** for symptoms, steroids and azathioprine, **thymectomy for AChR-positive generalised disease under 65 (MGTX 2016)**; crisis: IVIG or plasma exchange, ventilation; newer: complement inhibitors (eculizumab, zilucoplan) and **FcRn blockers (efgartigimod)**. Avoid aminoglycosides, fluoroquinolones, magnesium, beta-blockers.
- **Lambert–Eaton: antibodies to presynaptic voltage-gated calcium channels**, proximal leg weakness, autonomic symptoms (dry mouth), **reduced reflexes that return after exercise**, **strength improves with sustained effort; incremental response at high-frequency stimulation (over 100%)**; **small cell lung cancer in about half**; 3,4-diaminopyridine (amifampridine).
- **Tetanus:** tetanospasmin travels retrogradely to the cord and **cleaves synaptobrevin, blocking release of glycine and GABA** from inhibitory interneurons; **botulinum toxin cleaves SNARE proteins at the neuromuscular junction, blocking acetylcholine release (descending flaccid paralysis)**. Tetanus: **trismus (first sign), risus sardonicus, opisthotonus, reflex spasms**, autonomic storm, clear consciousness; **human tetanus immunoglobulin, metronidazole, wound debridement, benzodiazepines, magnesium, ventilation**, then a full vaccine course (the disease does not confer immunity). Neonatal tetanus: cord infection.
- **Spinal cord syndromes: Brown-Séquard (hemisection): ipsilateral motor and proprioceptive loss, contralateral pain and temperature loss** a segment or two below. **Anterior cord (anterior spinal artery)**: motor and pain loss, dorsal columns spared. **Central cord (hyperextension in cervical spondylosis, syringomyelia)**: arms worse than legs; **syringomyelia: cape-like dissociated loss of pain and temperature, wasting of hand muscles**, with Chiari I. **Subacute combined degeneration (B12)**: dorsal columns and corticospinal tracts (absent ankle jerks with extensor plantars). Tabes dorsalis: dorsal columns, Argyll Robertson pupils. **Cauda equina** (saddle anaesthesia, urinary retention, LMN legs): emergency MRI and decompression; conus medullaris: mixed signs.
- **Motor neuron disease (ALS): both UMN and LMN signs**, no sensory or sphincter loss, eye movements spared; SOD1, C9orf72; **riluzole** (and edaravone; tofersen for SOD1, 2023); NIV improves survival.
- **Duchenne muscular dystrophy:** X-linked recessive, **dystrophin gene (Xp21) deletion or frameshift**; onset at 2–5 years with delayed walking, frequent falls, **Gowers sign** and **calf pseudohypertrophy**; **serum CK 10–100 times normal from birth** (the first test); wheelchair by about 12; **cardiomyopathy and respiratory failure** cause death; diagnosis by dystrophin gene analysis (or biopsy with absent dystrophin); corticosteroids prolong walking. **Becker** is milder with partial dystrophin. **Spinal muscular atrophy:** SMN1 deletion, a floppy infant with tongue fasciculation; nusinersen, risdiplam and gene therapy change the course.

Movement, dementia and demyelination

- **Parkinson disease:** loss of dopaminergic neurons in the **substantia nigra pars compacta**, **Lewy bodies (α-synuclein)**; asymmetric **rest tremor (pill-rolling, 4–6 Hz), rigidity, bradykinesia (essential), postural instability (late)**; anosmia, REM sleep behaviour disorder and constipation precede it. **Levodopa with carbidopa** (peripheral decarboxylase inhibitor) is the most effective; dopamine agonists (pramipexole, ropinirole: impulse control disorders), MAO-B inhibitors (rasagiline), COMT inhibitors (entacapone), amantadine for dyskinesia; **deep brain stimulation (subthalamic nucleus)** for motor fluctuations. **Drug-induced parkinsonism** (antipsychotics, metoclopramide): symmetrical, stop the drug. Parkinson-plus: **PSP (vertical gaze palsy, early falls, midbrain "hummingbird" sign)**, MSA (autonomic failure, "hot cross bun" pons), Lewy body dementia (fluctuation, hallucinations, antipsychotic sensitivity).
- **Huntington disease:** autosomal dominant **CAG repeat (HTT, chromosome 4), anticipation (paternal)**; **caudate atrophy** (box-shaped frontal horns); chorea, psychiatric change, dementia; tetrabenazine. **Hemiballismus: contralateral subthalamic nucleus.** Wilson disease: lentiform nucleus (putamen), wing-beating tremor. **Essential tremor**: postural, bilateral, improves with alcohol; propranolol or primidone.
- **Where lesions cause which movement disorder: hemiballismus = contralateral subthalamic nucleus** (small infarct, often in diabetic elderly; haloperidol or tetrabenazine); **chorea = caudate and putamen** (Huntington); **athetosis and dystonia = striatum and globus pallidus**; **parkinsonism =**

substantia nigra pars compacta; **Wilson disease = putamen and lenticular nuclei**.

- **Alzheimer disease:** commonest dementia; extracellular **amyloid-β plaques** and intracellular **tau neurofibrillary tangles**, loss of cholinergic neurons in the **nucleus basalis of Meynert**; early memory loss, hippocampal atrophy; APOE ε4 risk, APP, presenilin 1 and 2 in early-onset; **cholinesterase inhibitors (donepezil, rivastigmine, galantamine), memantine**; **anti-amyloid antibodies lecanemab (2023) and donanemab (2024)** for early disease with confirmed amyloid (ARIA: brain oedema and microbleeds). Vascular dementia: stepwise; frontotemporal: early behaviour or language change, Pick bodies. **Normal-pressure hydrocephalus: gait apraxia, urinary incontinence, dementia ("wet, wobbly, wacky")**, large ventricles; shunt.
- **Prion disease (CJD):** rapidly progressive dementia with **myoclonus**, ataxia; **EEG periodic sharp-wave complexes** (sporadic); **MRI diffusion: cortical ribboning and caudate-putamen hyperintensity**; **CSF RT-QuIC is the most specific test** (14-3-3 and tau less specific). **Variant CJD** (bovine spongiform encephalopathy, younger patients, psychiatric onset): **pulvinar sign and the "hockey-stick" sign** (hyperintense pulvinar and dorsomedial thalamus on MRI), tonsil biopsy positive. Kuru: cerebellar, New Guinea.
- **Multiple sclerosis:** young women, relapsing-remitting; **optic neuritis** (painful, central scotoma, relative afferent pupillary defect), **internuclear ophthalmoplegia** (bilateral in the young), **Lhermitte sign**, **Uhthoff phenomenon** (worse with heat), transverse myelitis, sensory symptoms. **McDonald criteria (2017)**: dissemination in space and time on clinical or MRI grounds (periventricular, cortical or juxtacortical, infratentorial, spinal), **CSF oligoclonal bands can substitute for dissemination in time**; the **2024 revision (Lancet Neurology 2025)** adds the **optic nerve as a fifth region**, accepts CSF kappa free light chains in place of oligoclonal bands, and uses the central vein sign and paramagnetic rim lesions as supportive markers. MRI: **Dawson fingers** (perivenular, perpendicular to the ventricles). Relapse: IV methylprednisolone; disease-modifying drugs: interferon-β, glatiramer, dimethyl fumarate, fingolimod, **ocrelizumab (anti-CD20; also for primary progressive)**, natalizumab (PML risk). **NMO spectrum disorder**: **aquaporin-4 antibody**, longitudinally extensive myelitis (3 or more segments), severe optic neuritis, area postrema vomiting; MS drugs can worsen it; eculizumab, inebilizumab, satralizumab. MOG antibody disease is separate.
- **Tuberous sclerosis:** autosomal dominant, **TSC1 (hamartin, chromosome 9) or TSC2 (tuberin, chromosome 16)**, overactive mTOR; **hypopigmented ash-leaf macules (earliest skin sign, Wood lamp)**, shagreen patch, **facial angiofibromas (adenoma sebaceum)**, periungual (Koenen) fibromas, confetti lesions; **cardiac rhabdomyomas (fetal, often regress)**, renal angiomyolipomas, lymphangioleiomyomatosis, retinal hamartomas; cortical tubers, **calcified subependymal nodules, subependymal giant cell astrocytoma** at the foramen of Monro; **seizures (commonest presentation), infantile spasms (vigabatrin first line in tuberous sclerosis)**, intellectual disability, autism; **mTOR inhibitors (everolimus, sirolimus)** shrink SEGA and angiomyolipoma and help seizures.
- **Other neurocutaneous syndromes: neurofibromatosis 1** (NF1, chromosome 17, neurofibromin): 6 or more café-au-lait spots, axillary freckling, **Lisch nodules**, neurofibromas, optic glioma, phaeochromocytoma; selumetinib for plexiform neurofibromas; **NF2** (chromosome 22, merlin): **bilateral vestibular schwannomas**, meningiomas. **Sturge–Weber**: facial port-wine stain (ophthalmic division), leptomeningeal angioma, **"tram-track" gyriform calcification**, glaucoma, seizures, GNAQ. **Von Hippel–Lindau** (chromosome 3): **cerebellar and retinal haemangioblastomas**, clear cell renal carcinoma, phaeochromocytoma, polycythaemia; belzutifan (2021).

Epilepsy, infection and headache

- **Absence seizures alone: ethosuximide** (T-type calcium channels in the thalamus; **3 Hz spike-and-wave**, provoked by hyperventilation); **valproate** if generalised tonic-clonic seizures coexist; lamotrigine the alternative. **Carbamazepine, phenytoin, oxcarbazepine, gabapentin and vigabatrin can worsen absence and myoclonic seizures. Juvenile myoclonic epilepsy**: morning jerks, valproate (levetiracetam or lamotrigine in women). **Generalised tonic-clonic: valproate in men** (**avoid in women of childbearing potential**: neural tube defects, lower IQ, autism; MHRA 2024 also restricts new use under 55 in men), **lamotrigine or levetiracetam** in women. **Focal: lamotrigine or levetiracetam first line (NICE 2022, SANAD II)**, carbamazepine the classic answer. **Infantile spasms (West syndrome: spasms, hypsarrhythmia, regression): ACTH or prednisolone; vigabatrin in tuberous sclerosis.** In pregnancy: lamotrigine or levetiracetam with **folic acid 5 mg**.
- **Status epilepticus** (5 minutes or more, or repeated seizures without recovery): **benzodiazepine first: IV lorazepam (or diazepam), or IM midazolam (RAMPART) or buccal midazolam without IV access**; second line at 10–20 min: **levetiracetam, fosphenytoin or valproate, equally effective (ESETT 2019)**; refractory: anaesthesia (midazolam, propofol, thiopental) in ICU. Check glucose and give thiamine first if alcohol is suspected.
- **Bacterial meningitis:** if lumbar puncture will be delayed (imaging needed for papilloedema, focal signs, reduced consciousness, immunosuppression, new seizures), **take blood cultures, give ceftriaxone (plus vancomycin where pneumococcal resistance occurs) and dexamethasone immediately**, dexamethasone with or before the first antibiotic dose (benefit mainly in pneumococcal disease); **add ampicillin for Listeria over 50 years, in pregnancy, alcoholism, immunosuppression and neonates**. Commonest organisms: neonates **group B streptococcus, E. coli, Listeria**; children and adults **Streptococcus pneumoniae** (the commonest adult cause) and **Neisseria meningitidis** (petechial rash; close contacts get ciprofloxacin or rifampicin prophylaxis).

CSF	Cells	Protein	Glucose (CSF:blood)	Other
Bacterial	**neutrophils**, hundreds to thousands	high	**low (under 0.4)**	Gram stain, culture, raised lactate
Tuberculous	**lymphocytes** (neutrophils early), 100–500	**very high**, cobweb clot	**low**	**basal exudates, hydrocephalus, infarcts; Xpert Ultra**; 12 months of treatment with dexamethasone

CSF	Cells	Protein	Glucose (CSF:blood)	Other
Viral	lymphocytes	normal or slightly high	normal	PCR (enterovirus, HSV)
Fungal (Crypto-coccus)	lymphocytes	high	low	**India ink, CSF cryptococcal antigen (most sensitive)**, high opening pressure

- **HSV encephalitis:** fever, confusion, behaviour change, seizures, **temporal lobe** involvement on MRI, periodic lateralised discharges on EEG, CSF HSV PCR; **IV aciclovir at once, do not wait for results**. **Japanese encephalitis** (Culex, pigs, paddy fields; endemic in Nepal's Terai, monsoon season): thalamic and basal ganglia lesions, parkinsonian features; prevented by vaccine (**Nepal's schedule gives one dose at 12 months**, MoHP). **Cryptococcal meningitis in HIV (WHO 2022): single high-dose liposomal amphotericin B (10 mg/kg) with 14 days of flucytosine and fluconazole**, therapeutic lumbar punctures for high pressure; delay ART 4–6 weeks.
- **Neurocysticercosis: commonest cause of acquired epilepsy in endemic countries (including Nepal)**; Taenia solium eggs (faecal–oral, not pork); **cyst with an eccentric scolex ("hole with a dot")**, ring-enhancing lesions, calcified dots; **albendazole (with praziquantel for multiple cysts) plus steroids** for viable cysts, antiepileptic drugs; no antiparasitic drug for calcified lesions or with untreated raised ICP (IDSA 2017).
- **Headache: migraine**: unilateral throbbing with nausea and photophobia, aura in a third; acute: NSAID or **triptan** (avoid in vascular disease), antiemetic; **prophylaxis: propranolol, topiramate (teratogenic), amitriptyline, candesartan; CGRP monoclonal antibodies (erenumab, fremanezumab) and gepants (rimegepant)** for refractory cases. **Cluster**: men, short (15–180 minutes) orbital attacks with lacrimation and rhinorrhoea, nightly in bouts; **acute: 100% oxygen at 12–15 L/min by non-rebreather mask, or subcutaneous sumatriptan**; prophylaxis **verapamil**. **Tension-type**: band-like, bilateral, simple analgesics. **Trigeminal neuralgia: carbamazepine**. **Idiopathic intracranial hypertension**: obese young women, papilloedema, sixth nerve palsy, normal imaging, high opening pressure; weight loss, **acetazolamide**, optic nerve sheath fenestration if vision fails. **Medication-overuse headache**: stop the analgesic. Giant cell arteritis is in Rheumatology.

Haematology

Anaemia

- **WHO thresholds:** Hb under 13 g/dL in men, under 12 in non-pregnant women, **under 11 in pregnancy** (WHO 2024 refines pregnancy to under 11 in the first and third trimesters, under 10.5 in the second), under 11 in children 6–59 months. **Iron deficiency is the commonest anaemia worldwide and in Nepal** (diet, hookworm, menstrual and pregnancy losses); **in adult men and postmenopausal women in high-income countries, think of GI blood loss** (colonoscopy and endoscopy).
- **Iron profile:**

	Serum iron	Ferritin	TIBC (trans-ferrin)	Saturation
Iron deficiency	low	**low**	**high**	low
Chronic disease (hepcidin)	low	**normal or high**	**low**	low or normal
Sideroblastic / iron overload	high	high	normal or low	high
Thalassaemia trait	normal	normal	normal	normal

- **Ferritin is the best single test for iron deficiency** (under 15 µg/L diagnostic; under 30 in most guidelines; up to 100 with inflammation); it is an acute-phase protein. Treat with **oral iron once daily or on alternate days** (hepcidin rises after a dose); IV iron (ferric carboxymaltose, derisomaltose) when oral fails, in late pregnancy, CKD and heart failure. Reticulocytes rise in 5–10 days.
- **Mentzer index (MCV ÷ RBC in millions): over 13 favours iron deficiency, under 13 thalassaemia trait.** Example: MCV 68, RBC 5.4, index 12.6, normal RDW = **beta-thalassaemia trait**, confirmed by **HbA_2 over 3.5% (typically 4–6%)** on electrophoresis or HPLC; iron deficiency lowers HbA_2 and can mask it. **RDW is raised in iron deficiency and normal in trait.** Microcytic causes: iron deficiency, thalassaemia, chronic disease, **sideroblastic (ring sideroblasts on Prussian blue; ALAS2, alcohol, isoniazid, lead, copper deficiency)**, **lead (basophilic stippling)**.
- **Megaloblastic anaemia:** B12 or folate deficiency; **hypersegmented neutrophils (5 or more lobes) and macro-ovalocytes** are the earliest smear signs; pancytopenia, raised LDH and bilirubin (ineffective erythropoiesis). **Methylmalonic acid rises only in B12 deficiency (methylmalonyl-CoA mutase needs B12; linked to the neurological damage); homocysteine rises in both; FIGLU in folate deficiency. Never treat B12 deficiency with folate alone** (neurological worsening). Causes of B12 deficiency: **pernicious anaemia** (anti-intrinsic factor, more specific; anti-parietal cell, more sensitive; high gastrin), strict vegetarian diet (common in South Asia), terminal ileal resection or Crohn, **metformin and PPIs**, Diphyllobothrium latum. Folate: diet, pregnancy, haemolysis, alcohol, methotrexate, phenytoin, trimethoprim. Treat B12 by IM hydroxocobalamin (high-dose oral works too). **Non-megaloblastic macrocytosis**: alcohol, liver disease, hypothyroidism, reticulocytosis, myelodysplasia, hydroxyurea and zidovudine.
- **Haemolytic anaemia:** raised reticulocytes, unconjugated bilirubin and LDH, **low haptoglobin**; **direct Coombs (DAT)** separates immune causes: **warm (IgG; SLE, CLL, methyldopa; steroids, rituximab)** and **cold (IgM; Mycoplasma, EBV, lymphoma; avoid cold)**. **Hereditary spherocytosis**: autosomal dominant, spectrin or ankyrin, spherocytes, raised MCHC, splenomegaly, gallstones, **EMA binding test** (osmotic fragility older), splenectomy for severe disease. **G6PD deficiency**: X-linked, **bite cells and Heinz bodies**, haemolysis after **primaquine, dapsone, sulfonamides, nitrofurantoin, fava beans**, infection; enzyme assay is falsely normal during an episode (test at 3 months). **PNH**: PIGA mutation, loss of **CD55 and CD59 (flow cytometry)**, haemolysis with dark morning urine, **thrombosis at unusual sites (Budd–Chiari)**, pancytopenia; **eculizumab or ravulizumab** (complement C5), iptacopan.
- **Sickle cell disease:** HbS (**β-globin position 6, glutamate to valine**, chromosome 11), autosomal recessive; vaso-occlusive crises, acute chest syndrome (commonest cause of death in

adults), stroke, **functional asplenia with Howell–Jolly bodies** (encapsulated organism infection, so penicillin and vaccines), **Salmonella osteomyelitis** (the classic answer; S. aureus is also common), **parvovirus B19 aplastic crisis**, splenic sequestration in children; **Hydroxyurea** (raises HbF) for all with frequent crises; transfusion; **gene therapies exagamglogene (Casgevy, CRISPR) and lovotibeglogene (2023)**; crizanlizumab; **voxelotor was withdrawn in 2024**. Diagnosis by electrophoresis or HPLC.

- **Howell–Jolly bodies** (nuclear remnants) mean **hyposplenism**: after splenectomy, sickle cell disease, coeliac disease. Other smear clues: pencil cells (iron deficiency), target cells (thalassaemia, liver disease, HbC), schistocytes (microangiopathy, mechanical valves), teardrop cells (myelofibrosis), spur cells (liver disease), rouleaux (myeloma), Pappenheimer bodies (siderocytes).
- **Thalassaemia: major (homozygous β)**: presents at 6–12 months as HbF falls, **HbF predominant**, hepatosplenomegaly, **hair-on-end skull and chipmunk facies** (marrow expansion); regular transfusion with **iron chelation (deferasirox oral, deferoxamine, deferiprone: agranulocytosis)**; HSCT curative; luspatercept reduces transfusion need; gene therapy (betibeglogene). **α-thalassaemia**: one deletion silent, two trait, **three HbH disease (β4 tetramers)**, **four Hb Bart's (γ4) hydrops fetalis**.
- **Aplastic anaemia:** pancytopenia with **hypocellular (fatty) marrow and no splenomegaly**; idiopathic (autoimmune T-cell), drugs (chloramphenicol, carbamazepine), hepatitis, PNH; **HSCT in the young with a matched sibling; otherwise ATG with ciclosporin plus eltrombopag** (RACE 2022).

Leukaemias and myeloid neoplasms

Disease	Clues
ALL	commonest childhood cancer (peak 2–5 years); lymphoblasts with scant cytoplasm; **PAS positive (block), TdT positive, CD10 (CALLA) positive in common B-ALL; myeloperoxidase negative**; CNS and testicular sanctuary sites; **good prognosis: t(12;21) ETV6-RUNX1, hyperdiploidy**; **poor: t(9;22) BCR-ABL (more in adults), t(4;11) KMT2A in infants**; Ph-positive ALL gets a TKI; **blinatumomab and CAR-T cells** for relapse
AML	adults; abundant cytoplasm; **Auer rods**, **MPO and Sudan black positive**; FLT3, NPM1, IDH mutations guide treatment (**midostaurin** for FLT3, ivosidenib or enasidenib for IDH); **venetoclax with azacitidine for the unfit elderly**; **APL (M3): t(15;17) PML-RARA, faggot cells, DIC; ATRA with arsenic trioxide (no chemotherapy in low-risk disease)**, start ATRA on suspicion; differentiation syndrome; **M4/M5 (monocytic): gum infiltration, non-specific esterase positive**; M7 in Down syndrome
CML	**t(9;22) BCR-ABL1 (Philadelphia chromosome)**, massive splenomegaly, raised neutrophils at all stages of maturity, **basophilia**, **low leukocyte alkaline phosphatase**; **imatinib first line** (dasatinib, nilotinib, bosutinib; ponatinib for T315I; asciminib); chronic, accelerated, blast phase
CLL	commonest leukaemia in the elderly in the West; **smudge cells, CD5 and CD23 positive, weak CD20 and surface Ig**; autoimmune haemolysis, hypogammaglobulinaemia, **Richter transformation** to DLBCL; Rai and Binet stages; **BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) and venetoclax with obinutuzumab** have replaced FCR; treat only when active
Hairy cell	middle-aged men, **pancytopenia, massive splenomegaly, no lymphadenopathy, dry tap**; **TRAP positive** (classic), **CD11c, CD25, CD103, annexin A1; BRAF V600E**; **cladribine**
Polycythaemia vera	**JAK2 V617F (about 95%)**, low erythropoietin, raised Hb (over 16.5 men, 16 women), **aquagenic pruritus**, erythromelalgia, thrombosis; **venesection to haematocrit under 45% and aspirin**; hydroxyurea or ruxolitinib if high risk
Essential thrombocythaemia	platelets over 450,000; **JAK2, CALR or MPL**; aspirin, hydroxyurea
Primary myelofibrosis	**teardrop cells, leucoerythroblastic film, dry tap, massive spleen**; **ruxolitinib** (JAK inhibitor), HSCT

- **Tumour lysis syndrome:** after starting treatment of bulky, fast-growing tumours (Burkitt, ALL); **high potassium, phosphate and urate, low calcium**; acute kidney injury and arrhythmias; **prevention: hydration with allopurinol, or rasburicase** for high risk (rasburicase contraindicated in G6PD deficiency).
- **Cytochemistry:** MPO and Sudan black = myeloid; PAS (block) and TdT = lymphoid; **non-specific esterase (inhibited by fluoride) = monocytic**; TRAP = hairy cell.
- **Myelodysplastic syndromes:** elderly, cytopenias with dysplasia, ringed sideroblasts; **del(5q) responds to lenalidomide**; luspatercept for anaemia; azacitidine.

Lymphomas, myeloma and histiocytosis

- **Hodgkin lymphoma: Reed–Sternberg cells (owl's eye) CD15 and CD30 positive, CD45 and CD20 negative**; bimodal age, **contiguous spread**, B symptoms (fever, **weight loss over 10% in 6 months**, drenching night sweats), **alcohol-induced pain**, Pel–Ebstein fever, EBV in mixed cellularity. **Nodular sclerosis is the commonest subtype in high-income countries** (young women, mediastinal mass, lacunar cells); **mixed cellularity is relatively commoner in children and in developing countries**; lymphocyte-depleted has the worst prognosis. **Nodular lymphocyte-predominant: CD20 positive, CD15 and CD30 negative** ("popcorn" cells). Staging: **PET-CT, Lugano 2014 (from Ann Arbor)**; **ABVD**; newer: **brentuximab vedotin (anti-CD30)** with AVD, and **nivolumab** (PD-1) with AVD (S1826, 2024) in advanced disease; radiotherapy for early bulky disease.
- **Non-Hodgkin lymphoma: diffuse large B-cell is the commonest NHL** (aggressive; **R-CHOP**, or pola-R-CHP; **CAR-T cells** for relapse); **follicular: t(14;18) BCL2**, indolent, commonest indolent NHL; **Burkitt: t(8;14) c-MYC, starry-sky, very high Ki-67**, jaw mass in endemic (EBV, malaria) African children, abdominal in sporadic; **mantle cell: t(11;14) cyclin D1, CD5 positive CD23 negative**; **MALT: t(11;18)**, **gastric MALT lymphoma regresses with H. pylori eradication**; adult T-cell leukaemia: HTLV-1; primary CNS lymphoma: HIV, EBV, high-dose methotrexate; enteropathy-associated T-cell lymphoma: coeliac. **Rituximab (anti-CD20)** is part of most B-cell regimens; bispecific antibodies (glofitamab, epcoritamab) are newer.
- **Multiple myeloma (IMWG 2014): clonal marrow plasma cells 10% or more (or a biopsy-proven plasmacytoma) plus a myeloma-defining event**: **CRAB** (hyper**c**alcaemia, **r**enal failure, **a**naemia, **b**one lytic lesions) or a biomarker (**SLiM**: plasma cells 60% or more, involved:uninvolved free light-chain ratio 100 or more, more than one focal lesion on MRI).

IgG is the commonest paraprotein, then IgA, then light chain only. **MGUS**: under 10% plasma cells, paraprotein under 3 g/dL, no CRAB (progresses about 1% a year); smouldering myeloma between. Clues: **rouleaux, high ESR, punched-out (pepper-pot) skull lesions**, back pain, infections, hyperviscosity, normal ALP. **Renal failure mainly from light-chain cast nephropathy ("myeloma kidney")**: casts obstruct the tubules when free light chains precipitate with **Tamm–Horsfall (uromodulin)** protein in distal tubules; also hypercalcaemia, dehydration, AL amyloid, Fanconi. **Bone scan is unhelpful** (no osteoblastic activity; ALP normal): **whole-body low-dose CT, PET-CT or MRI** have replaced the skeletal survey. Prognosis: **β2-microglobulin and albumin (ISS)**, with LDH and high-risk cytogenetics (R-ISS). Treatment: **daratumumab with bortezomib, lenalidomide and dexamethasone (D-VRd; PERSEUS 2024)**, then **autologous stem cell transplant** if fit, lenalidomide maintenance; CAR-T and bispecifics (teclistamab) for relapse; bisphosphonate or denosumab for bone.

- **Waldenström macroglobulinaemia** (lymphoplasmacytic lymphoma, **MYD88 L265P** in over 90%): **IgM paraprotein** causing **hyperviscosity** (headache, blurred vision with sausage-like retinal veins, mucosal bleeding, neuropathy), lymphadenopathy and splenomegaly, **no lytic bone lesions**, renal failure uncommon; **plasmapheresis** for symptomatic hyperviscosity. Myeloma is usually IgG or IgA. **Bence Jones protein = free monoclonal light chains (kappa or lambda)**, not heavy chains.
- **Langerhans cell histiocytosis** (histiocytosis X; classed as a **myeloid neoplasm** in WHO 2022): clonal Langerhans-type cells **positive for CD1a, CD207 (langerin) and S100**, with **Birbeck granules (tennis-racket shaped) on electron microscopy**; **BRAF V600E in about half**, MAP2K1 in others. Children mostly. Classic forms: **Letterer–Siwe** (under 2–3 years, disseminated: rash, hepatosplenomegaly, cytopenias, poor prognosis); **Hand–Schüller–Christian** (**lytic skull lesions, diabetes insipidus, exophthalmos**); **eosinophilic granuloma** (commonest, solitary lytic bone lesion in older children and young adults, good prognosis). Radiology: **punched-out "geographic" skull, bevelled-edge lesions, vertebra plana**. Pulmonary LCH: young smokers, upper-lobe nodules and cysts. Treatment: curettage or steroid injection for single bone lesions; **vinblastine with prednisolone** for multisystem disease; **BRAF or MEK inhibitors** (vemurafenib, dabrafenib, trametinib) for refractory disease.

Bleeding and thrombosis

Disorder	Platelets	Bleeding time	PT	aPTT
Haemophilia A/B (VIII / **IX, Christmas disease**)	normal	normal	normal	**prolonged** (corrects on mixing)
von Willebrand disease	normal	**prolonged**	normal	normal or mildly prolonged
ITP	**low**	prolonged	normal	normal
DIC	**low**	prolonged	**prolonged**	prolonged; **low fibrinogen, raised D-dimer**, schistocytes
Vitamin K deficiency, warfarin	normal	normal	**prolonged first** (factor VII shortest half-life)	prolonged later
Heparin (unfractionated)	normal (low in HIT)	normal	normal or slightly long	**prolonged**

- **Haemophilia:** X-linked recessive, **haemarthroses** and muscle bleeds; A (factor VIII, about 80%) and **B (factor IX, Christmas disease)**; C (factor XI) is autosomal and milder. Treat with factor concentrate; **emicizumab** (bispecific antibody mimicking factor VIIIa, weekly subcutaneous) for prophylaxis, including with inhibitors; gene therapy now licensed for A and B. Desmopressin for mild haemophilia A and type 1 von Willebrand disease. **Von Willebrand disease is the commonest inherited bleeding disorder** (autosomal dominant type 1; mucosal bleeding, menorrhagia; abnormal ristocetin cofactor activity).
- **Platelet function: Glanzmann thrombasthenia: GP IIb/IIIa deficiency, no aggregation with any agonist except ristocetin, normal count and size. Bernard–Soulier: GP Ib-IX-V deficiency, giant platelets, low count, no agglutination with ristocetin (not corrected by normal plasma, unlike vWD).** Aspirin irreversibly inhibits COX-1 (stop 7 days before surgery); clopidogrel blocks P2Y12.
- **ITP:** isolated thrombocytopenia, normal smear apart from few (large) platelets, no splenomegaly; diagnosis of exclusion (**test for HIV and hepatitis C**; H. pylori in some). **Children: usually after a viral illness, resolves, observation if no or mild bleeding. Adults with platelets under 30,000/μL or bleeding: corticosteroids first (prednisolone up to 6 weeks, or dexamethasone 40 mg for 4 days; ASH 2019)**, adding **IVIG when a fast rise is needed** (before surgery, severe bleeding); second line: **thrombopoietin receptor agonists (eltrombopag, romiplostim, avatrombopag)**, rituximab, **splenectomy** (delayed at least a year), fostamatinib. **Platelet transfusion only for life-threatening bleeding**, with IVIG and steroids.
- **TTP and HUS (thrombotic microangiopathies): microangiopathic haemolytic anaemia (schistocytes) with thrombocytopenia** and normal clotting; **TTP**: **ADAMTS13 under 10%** (autoantibody), the classic pentad (fever, neurological signs, renal involvement added) is now rarely complete; **PLASMIC score**; **urgent plasma exchange with steroids, caplacizumab (anti-vWF) and rituximab**; **platelet transfusion is contraindicated**. **HUS**: children after **Shiga toxin E. coli O157:H7**, renal failure prominent, supportive; atypical HUS (complement): eculizumab.
- **DIC:** sepsis, trauma, obstetric catastrophes (abruption, amniotic fluid embolism), APL, snake envenomation; treat the cause; platelets, cryoprecipitate (fibrinogen under 1.5 g/L) and FFP for bleeding; ISTH score.
- **Thrombophilia: factor V Leiden is the commonest inherited thrombophilia in people of European descent** (activated protein C resistance), prothrombin G20210A second; it is rare in South and East Asians, in whom **protein C, protein S and antithrombin deficiencies** are relatively commoner. **Vitamin K-dependent factors: II, VII, IX, X, and proteins C and S**; **warfarin-induced skin necrosis** in protein C deficiency (start with heparin cover). **Antiphospholipid syndrome:** arterial and venous thrombosis, **recurrent miscarriage**, thrombocytopenia, livedo; **lupus anticoagulant (prolonged aPTT not corrected by mixing, dilute Russell viper venom test), anticardiolipin, anti-β2-glycoprotein I**, positive twice 12 weeks apart; **warfarin (INR 2–3), not DOACs, especially**

for triple-positive or arterial disease (TRAPS 2018); heparin with aspirin in pregnancy.

- **Heparin-induced thrombocytopenia:** platelets fall by over 50% **5–10 days after starting heparin** (sooner with recent exposure), **with thrombosis, not bleeding**; antibodies to the heparin–PF4 complex; **4T score**, then anti-PF4 ELISA and functional assay; **stop all heparin, give a non-heparin anticoagulant (argatroban, fondaparinux, or a DOAC)**; no warfarin until platelets recover; no platelet transfusion.
- **Venous thromboembolism treatment: DOAC first line** (apixaban, rivaroxaban, edoxaban, dabigatran) for 3 months if provoked, longer if unprovoked; LMWH in pregnancy; warfarin with mechanical valves, APS and severe renal failure. **Reversal:** warfarin with **vitamin K and four-factor prothrombin complex concentrate** (FFP if PCC unavailable); **dabigatran with idarucizumab**; factor Xa inhibitors with andexanet alfa or PCC; heparin with **protamine**.
- **Transfusion:** restrictive thresholds (Hb 7 g/dL, 8 in cardiac disease and surgery; AABB 2023); **TRALI** (non-cardiogenic oedema within 6 h, donor antibodies, commonly from plasma from multiparous women) and **TACO** (circulatory overload, the commonest cause of transfusion death in recent haemovigilance reports); **acute haemolytic reaction from ABO mismatch, usually a clerical error**; febrile non-haemolytic reaction is the commonest reaction overall (leucodepletion reduces it); irradiated products prevent transfusion-associated graft-versus-host disease; IgA-deficient patients risk anaphylaxis.
- Drug interactions asked: **clopidogrel with omeprazole** (CYP2C19; pantoprazole is preferred), **tamoxifen with fluoxetine or paroxetine** (CYP2D6), **enzyme inducers (rifampicin, carbamazepine, phenytoin) with the oral contraceptive and warfarin**; azithromycin with pantoprazole is not clinically important.

Infectious diseases

Fever: patterns and bedside signs

- **Liebermeister's rule:** the pulse rises about 8–10 beats a minute for each 1 °C of fever. **Relative bradycardia (Faget sign, pulse–temperature dissociation)**: pulse lower than expected for the temperature (judged at 38.9 °C or more). Classic causes: **typhoid, yellow fever (Faget's original description), Legionella, psittacosis and Mycoplasma, brucellosis, leptospirosis, tularaemia, Q fever, scrub typhus and other rickettsioses**, malaria in some; non-infectious: **drug fever, beta-blockers, lymphoma, factitious fever**. **Dengue is not a classic cause** (some series report it; MCQs with "all except" key dengue).
- **Fever patterns:** continuous (under 1 °C variation, never normal: lobar pneumonia, typhoid in week 2, UTI); remittent (over 2 °C, never normal: most infections, infective endocarditis); intermittent (returns to normal daily: malaria, pyogenic abscess, septicaemia); **tertian (every 48 h): P. vivax, P. ovale, P. falciparum (irregular)**; **quartan (every 72 h): P. malariae**; **Pel–Ebstein: Hodgkin**; **step-ladder: typhoid in week 1**; saddleback (biphasic): dengue, leptospirosis. **Pyrexia of unknown origin (classic)**: 38.3 °C on several occasions over 3 weeks, undiagnosed after a week of study (Petersdorf–Beeson); **infection (TB commonest in Nepal) is still the commonest cause in developing countries**, non-infectious inflammatory disease and malignancy in the West.
- **Tourniquet test (capillary fragility; Hess test):** a BP cuff inflated midway between systolic and diastolic for **5 minutes**; **positive at 20 or more petechiae per square inch (2.5 cm square) in WHO's 1997 description; CDC's dengue training and later guides use 10 or more** (the lower cut-off is more sensitive, the higher more specific). It is part of the WHO definition of probable dengue (2009) and of the old dengue haemorrhagic fever criteria, and it has **low sensitivity: a negative test does not exclude dengue**. Do not confuse it with **Trousseau sign of hypocalcaemia** (cuff above systolic for 3 minutes, carpopedal spasm) or **Trousseau syndrome** (migratory thrombophlebitis with pancreatic or gastric cancer).

Enteric fever and other fevers of Nepal

- **Typhoid (Salmonella Typhi; Paratyphi A also common in Nepal):** step-ladder fever, **relative bradycardia**, coated tongue, rose spots, splenomegaly, leucopenia; complications in week 3: **ileal perforation and haemorrhage**, encephalopathy, myocarditis. **Blood culture is the investigation of choice (positive in 40–80% in week 1)**; **bone marrow culture is the most sensitive** (even after antibiotics); stool and urine cultures turn positive in weeks 2–3; **Widal is unreliable in endemic areas because of high background titres from past exposure and vaccination, cross-reaction, and late rise (after week 1)**; a fourfold rise in paired sera is needed. **Fluoroquinolone resistance is now usual in South Asia: azithromycin orally (7 days) for uncomplicated disease; ceftriaxone (or cefixime) for severe disease**; **XDR typhoid** (resistant to ceftriaxone and fluoroquinolones; Sindh, Pakistan, since 2016): **meropenem or azithromycin**. Carriers: gallbladder (gallstones), cholecystectomy or prolonged ciprofloxacin. **Typhoid conjugate vaccine** (one dose from 6 months; **Nepal added it to routine immunisation at 15 months after a national campaign in April 2022** for children aged 15 months to 15 years).
- **Scrub typhus** (Orientia tsutsugamushi, chigger larva of the trombiculid mite; rural hills and plains, monsoon and post-monsoon; now a common cause of acute febrile illness in Nepal): **eschar** (painless black scab in a skin fold), lymphadenopathy, rash, pneumonitis, meningoencephalitis, AKI; IgM ELISA or PCR (Weil–Felix OX-K is old and insensitive); **doxycycline for 7 days**, **rapid defervescence within 48 h supports the diagnosis**; **azithromycin in pregnancy and young children**; chloramphenicol or IV doxycycline plus azithromycin for severe disease (INTREST 2023: the combination did better than either drug alone). **Murine typhus** (fleas) and **spotted fevers** also respond to doxycycline.
- **Dengue (Aedes aegypti and albopictus; four serotypes; spreading from Nepal's Terai into Kathmandu and the hill and mountain districts, with record epidemics in 2019 (about 18,000 cases), 2022 and 2023 (about 50,000 each)): NS1 antigen and RT-PCR in days 1–5; IgM from about day 5**; IgG high early suggests a secondary infection (higher risk of severe dengue from antibody-dependent enhancement). **WHO 2009 classification: dengue without warning signs, dengue with warning signs** (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver over 2 cm, **rising haematocrit with a rapid fall in platelets**), and **severe dengue** (**plasma leakage leading to shock or fluid accumulation with respiratory distress**, severe bleeding, severe organ impairment). **The critical phase is around defervescence, days 3–7.** The older WHO 1997 term **dengue**

haemorrhagic fever required fever, haemorrhagic signs (or positive tourniquet test), platelets 100,000/µL or less and **plasma leakage (haematocrit rise of 20% or more, effusion, ascites)**, with grades III–IV called dengue shock syndrome. Treatment: **paracetamol and oral fluids; avoid NSAIDs and aspirin**; with warning signs, **crystalloid 5–7 mL/kg/h, adjusted by haematocrit**; shock: crystalloid boluses (10–20 mL/kg), colloid if refractory; **no prophylactic platelet transfusion**. Vaccine: **TAK-003 (Qdenga), WHO SAGE 2023, for ages 6–16 in high-transmission settings**; Dengvaxia only for seropositive people.

- **Fluid overload is a leading avoidable cause of death in dengue.** In the recovery phase (from about 24–48 hours after defervescence) leaked plasma is reabsorbed, so continued or excessive intravenous fluid causes **pulmonary oedema, effusions and ascites with respiratory distress and a falling haematocrit**; stop or sharply reduce fluids and give a small dose of furosemide if needed. Further leakage, by contrast, shows a rising haematocrit.
- **Malaria:** In Nepal most malaria is **P. vivax**, in the Terai and inner Terai, and about half of cases are imported (50% in 2016), with elimination targeted. **P. falciparum causes severe malaria**: impaired consciousness (cerebral malaria), prostration, convulsions, **acidosis, hypoglycaemia, severe anaemia (Hb under 7 in adults), AKI, jaundice, pulmonary oedema, shock, bleeding, parasitaemia over 10%** (WHO). **Severe malaria: IV (or IM) artesunate 2.4 mg/kg at 0, 12 and 24 h, then daily (3 mg/kg in children under 20 kg)**, then a full ACT course; quinine only if artesunate is unavailable; rectal artesunate before referral in children. **Uncomplicated falciparum: an artemisinin-based combination for 3 days** (artemether-lumefantrine first line in Nepal's 2019 treatment protocol) **plus single low-dose primaquine (0.25 mg/kg) to block transmission** (no G6PD test needed). **P. vivax: chloroquine (or an ACT) for blood stages (Nepal: chloroquine then 14 days of primaquine), then radical cure of hypnozoites with primaquine 0.25 mg/kg daily for 14 days** (or 0.5 mg/kg for 7 days) **after checking G6PD**; **tafenoquine as a single dose** is an alternative where quantitative G6PD testing shows normal activity (70% or more); primaquine is contraindicated in pregnancy, breastfeeding of infants of unknown G6PD status, and infants under 6 months. **First trimester: artemether-lumefantrine is now recommended** (WHO 2022), quinine with clindamycin the old answer. Diagnosis: thick and thin smears (gold standard; thick for detection, thin for species), rapid diagnostic tests (HRP2 for falciparum: **hrp2 deletions cause false negatives**). Vaccines **RTS,S and R21** for African children (WHO 2021, 2023).
- **Kala-azar (visceral leishmaniasis; Leishmania donovani, sandfly Phlebotomus argentipes; anthroponotic in South Asia; in Nepal, chiefly the eastern and central Terai):** fever over 2 weeks, **massive splenomegaly**, pancytopenia, hypergammaglobulinaemia, darkening of the skin; **rK39 rapid test** (with clinical features) for diagnosis; **amastigotes (Leishman–Donovan bodies) in splenic aspirate (highest yield, over 95%)**, bone marrow (60–85%). **Single dose liposomal amphotericin B 10 mg/kg is the first-line regimen of the South Asia elimination programme** (WHO 2010); alternatives **miltefosine with paromomycin** (combinations), miltefosine is teratogenic; **sodium stibogluconate abandoned in South Asia** (resistance in Bihar). **Post-kala-azar dermal leishmaniasis** (hypopigmented macules or nodules months to years later) is a reservoir.
- **Leptospirosis** (rat urine, flooded fields, monsoon): biphasic fever, **conjunctival suffusion, calf tenderness**, **Weil disease (jaundice, AKI, haemorrhage, pulmonary haemorrhage)**; MAT serology or PCR; **doxycycline (mild) or penicillin/ ceftriaxone (severe)**; doxycycline prophylaxis 200 mg weekly. **Brucellosis**: undulant fever, sweats, arthritis (sacroiliitis), unpasteurised milk; doxycycline with rifampicin or streptomycin. **Hepatitis E** and **typhus** complete the common causes of acute febrile illness in Nepal.
- **Cholera:** *Vibrio cholerae* O1 (El Tor) or O139; painless **rice-water stool** without fever. Cholera toxin raises **cyclic AMP**, driving chloride and water secretion, but the **sodium–glucose co-transporter (SGLT1) in the villi is unaffected**: glucose uptake pulls sodium and then water across the gut, which is why **oral rehydration solution (glucose or rice based) works despite massive secretion** (WHO low-osmolarity ORS: 245 mOsm/L). Severe dehydration: rapid IV Ringer's lactate, then ORS. Antibiotic only shortens illness (single-dose azithromycin or doxycycline); zinc for children; oral cholera vaccine in outbreaks.
- **Lymphatic filariasis:** *Wuchereria bancrofti* (about 90%, **Culex** mosquito, the species in South Asia) and *Brugia malayi*; microfilariae show **nocturnal periodicity**, so the blood film is taken at night. Lymphangitis, **hydrocele**, lymphoedema progressing to elephantiasis, chyluria, **tropical pulmonary eosinophilia**. **Diethylcarbamazine (DEC)** kills microfilariae and some adult worms and is the standard treatment (reactions from dying worms); **mass drug administration uses DEC with albendazole yearly**, and WHO (2017) endorses **triple therapy (ivermectin, DEC, albendazole)**. DEC is avoided where onchocerciasis or loiasis co-exist. Doxycycline (200 mg for 4–6 weeks) kills the Wolbachia symbiont. Nepal runs a national elimination programme using DEC with albendazole.
- **Hookworm:** *Ancylostoma duodenale* and *Necator americanus*; larvae penetrate bare feet (ground itch), pass through the lungs (Löffler syndrome) and are swallowed; adults attach to the small-intestinal mucosa with teeth or cutting plates and **suck blood**, so heavy chronic infection causes **iron-deficiency (microcytic hypochromic) anaemia and hypoalbuminaemia**, with eosinophilia. Ova in stool (thin-shelled, 4–8 cell stage). **Albendazole 400 mg once** (or mebendazole 100 mg twice daily for 3 days), plus iron. Ascaris causes malnutrition and obstruction, *Enterobius* perianal itch, and **only the fish tapeworm *Diphyllobothrium latum* causes B12 deficiency**.
- **Polio and acute flaccid paralysis (AFP) surveillance (WHO):** every case of AFP in a child under 15 years is reported at once and investigated; **two stool specimens at least 24 hours apart, within 14 days of onset**, go in a cold chain to an accredited laboratory, and the child is **re-examined at 60 days** for residual weakness. Differentials: poliomyelitis (asymmetric, proximal, fever, no sensory loss), Guillain–Barré (symmetric, ascending, areflexia), transverse myelitis (sensory level, bladder involvement), traumatic neuritis (one limb, after an injection).

Sepsis

- **Sepsis-3 (2016): life-threatening organ dysfunction (rise in SOFA score of 2 or more) from a dysregulated host response to infection**; **septic shock: vasopressors needed to keep MAP 65 mmHg or more and lactate over 2 mmol/L despite adequate fluids**. qSOFA (respiratory rate 22 or more, altered mentation, systolic 100 or less) predicts poor outcome but

should not be used alone to screen (Surviving Sepsis Campaign 2021).

- **Management (SSC 2021): antibiotics within 1 hour** when shock or sepsis is likely (within 3 h if sepsis is possible without shock), blood cultures first if this causes no delay; **30 mL/kg of crystalloid in the first 3 hours** for hypotension or lactate 4 or more (a weak recommendation), **balanced crystalloids** preferred over saline; **norepinephrine first-line vasopressor**, vasopressin added; target **MAP 65 mmHg**; **hydrocortisone 200 mg/day if vasopressors are still needed**; source control; lactate guides resuscitation (capillary refill also used). Children: Phoenix criteria (2024) in Paediatrics.

Rabies, snakebite and poisoning

- **Rabies:** lyssavirus (rhabdovirus), bullet-shaped; dog bites cause almost all human cases in Nepal and Asia; incubation usually 1–3 months (shorter with head and neck bites); **hydrophobia, aerophobia, furious or paralytic forms; fatal once symptoms begin**. **Negri bodies: eosinophilic cytoplasmic inclusions in neurons, most in the hippocampal pyramidal cells (Ammon's horn) and cerebellar Purkinje cells**; their absence does not exclude rabies. Diagnosis: post-mortem brain **direct fluorescent antibody test (gold standard)**; in life, saliva RT-PCR, nuchal skin biopsy, corneal impression smear. **WHO 2018 post-exposure prophylaxis: wound washing with soap and water for 15 minutes** (most important single step); **category I** (touching, licks on intact skin): none; **category II** (nibbles, minor scratches without bleeding): vaccine; **category III** (bites or scratches that bleed, licks on broken skin or mucosa, bat exposure): **vaccine plus rabies immunoglobulin infiltrated into and around the wounds** (equine 40 IU/kg, human 20 IU/kg; monoclonal antibodies acceptable). Schedules: **intradermal 2 sites on days 0, 3, 7 (one-week IPC regimen)**, or **intramuscular 1 dose on days 0, 3, 7 and 14–28 (Essen, 4 doses)** or **2-1-1 (Zagreb: 2 doses on day 0, 1 on days 7 and 21)**. Previously vaccinated: 1 site ID or IM on days 0 and 3, no RIG. Pre-exposure: days 0 and 7.
- **Snakebite in Nepal: common krait (Bungarus caeruleus)**: bites **sleeping people on the floor at night**, little or no local pain or swelling, **abdominal pain, ptosis, ophthalmoplegia, bulbar weakness and respiratory paralysis (presynaptic β-bungarotoxin)**; **polyvalent anti-snake venom early and ventilatory support**; **neostigmine with atropine helps postsynaptic (cobra) toxicity, much less in krait bites**. **Cobra**: painful local swelling and necrosis plus postsynaptic paralysis. **Russell's viper and saw-scaled viper** (vipers): local swelling, blistering, **coagulopathy (non-clotting blood), bleeding, AKI**; **20-minute whole blood clotting test** (blood that has not clotted at 20 minutes means venom-induced coagulopathy and is an indication for antivenom, repeated 6-hourly); green pit viper in the hills. First aid: **reassure, immobilise the limb, transport quickly; no incision, suction, tight tourniquet, ice or herbal remedies**. Antivenom (polyvalent against the "big four"; anaphylaxis treated with adrenaline 0.5 mg IM, no routine premedication) is the only specific treatment.
- **Organophosphate poisoning** (commonest pesticide poisoning in Nepal): muscarinic (**SLUDGE/DUMBELS: salivation, lacrimation, urination, diarrhoea, bronchorrhoea, bradycardia, miosis**), nicotinic (**fasciculations, weakness, paralysis**, tachycardia), CNS effects; **low plasma or red-cell cholinesterase**. **Atropine IV, 1.8–3 mg, doubling the dose every 5 minutes until the chest is clear, heart rate over 80, systolic over 80 and pupils no longer pinpoint**, then an infusion; oxygen, airway, decontamination; **pralidoxime best given early, before "ageing"** (loss of an alkyl group makes the phosphorylated enzyme irreversible), mainly for nicotinic effects; trials have shown little benefit. **Intermediate syndrome** (24–96 h: proximal, neck and respiratory weakness) and delayed polyneuropathy follow. **Do not use physostigmine or neostigmine**; avoid succinylcholine. **Carbamates**: similar but self-limiting, oximes less needed.
- **Other poisonings asked: paracetamol**: N-acetylcysteine guided by the Rumack–Matthew nomogram (treatment line 150 mg/L at 4 h, 100 in the UK since 2012), within 8 h best; **methanol**: visual loss, high-gap acidosis with osmolar gap, **fomepizole or ethanol**, dialysis; **aluminium phosphide (celphos)**: shock, no antidote, supportive; **paraquat**: lung fibrosis, no antidote, **avoid supplemental oxygen** unless hypoxic; **carbon monoxide**: 100% oxygen (hyperbaric if severe); **iron**: desferrioxamine; **benzodiazepines**: flumazenil (caution: seizures); **opioids**: naloxone; **digoxin**: Fab fragments; **beta-blockers**: glucagon, high-dose insulin; **tricyclics**: sodium bicarbonate for wide QRS.
- **Heat stroke:** core temperature **above 40 °C with central nervous system dysfunction** (confusion, convulsions, coma). **Exertional** (young, fit, sweating may persist) or **classic** (elderly, hot dry skin, in heat waves). **The most important step is immediate active cooling: cold- or ice-water immersion** is fastest (cooling about 0.2 °C a minute; aim under 39 °C within 30 minutes, then stop to avoid overshoot); evaporative cooling with ice packs if immersion is impossible. **Antipyretics do not work** (the hypothalamic set point is normal) and **dantrolene has no proven role**. Complications: rhabdomyolysis and AKI, DIC, liver failure, hypoglycaemia. **Heat exhaustion**: under 40 °C, sweating, no neurological dysfunction; rest and fluids.

HIV and the HIV–TB link

- **Diagnosis:** fourth-generation antigen-antibody test (window about 2–4 weeks), confirmed by **three consecutive reactive tests** (WHO 2019 recommends this three-test strategy in all settings); **infants under 18 months: nucleic acid test** (maternal antibody persists).
- **Treatment (WHO 2021 consolidated): treat everyone, whatever the CD4 count, starting the same day or within 7 days**; **first line TLD: tenofovir disoproxil, lamivudine and dolutegravir** (dolutegravir also preferred in pregnancy and for children; the neural tube defect signal was not confirmed). Monitoring: **viral load at 6 months and yearly; WHO 2023: under 50 copies/mL undetectable, 50–1,000 suppressed but detectable, over 1,000 unsuppressed** (adherence support, repeat, then switch); **undetectable = untransmittable (U=U)**.
- **HIV and TB: TB is the commonest opportunistic infection and cause of death in HIV in Nepal and worldwide**; screen everyone with HIV for TB at every visit; **start ART within 2 weeks of starting TB treatment** (delay **4–8 weeks in TB meningitis**); **rifampicin halves dolutegravir levels, so give dolutegravir 50 mg twice daily** (efavirenz needs no change); **avoid nevirapine and boosted protease inhibitors with rifampicin** (rifabutin instead); give TPT to everyone with HIV once active TB is excluded. **Immune reconstitution inflammatory syndrome** follows ART start (paradoxical worsening of TB, cryptococcal disease); steroids for TB-IRIS.

- **Opportunistic infections by CD4 count:** under 500 TB (any count), zoster, oral candida; **under 200 Pneumocystis, oesophageal candida, histoplasmosis**; **under 100 toxoplasmosis (ring-enhancing lesions; cotrimoxazole prevents it), cryptococcal meningitis (screen with serum CrAg at CD4 under 100, consider under 200; WHO 2022)**; **under 50 CMV retinitis, disseminated MAC (azithromycin)**; PML (JC virus) and primary CNS lymphoma at low counts. **Cotrimoxazole prophylaxis**: CDC/high-income: CD4 under 200; **WHO: CD4 350 or less or WHO stage 3–4** (and for everyone in settings with high malaria or bacterial infection rates).
- **Prevention: PEP: start within 72 h (ideally 2 h), 28 days of TLD**; **PrEP**: daily oral tenofovir-based, the dapivirine ring, **long-acting injectable cabotegravir (WHO 2022) and twice-yearly lenacapavir (WHO 2025)**; prevention of vertical transmission by maternal ART and infant prophylaxis.
- **Hepatitis B needlestick:** a vaccinated health worker with **anti-HBs 10 mIU/mL or more is protected and needs nothing more**; see Gastroenterology for the full rules. **HIV needlestick risk about 0.3%** (HBV 6–30%, HCV about 1.8%).
- **Extrapulmonary TB: lymph nodes are the commonest site** (cervical, "scrofula"; matted, cold abscess, sinus), then pleura, then bone and joint (spine, Pott disease), genitourinary and abdominal disease; HIV raises the share of extrapulmonary and disseminated disease. Treated with the same 6-month regimen, longer (9–12 months) for TB meningitis and bone and joint TB (WHO 2010, still followed in Nepal). The regimens themselves are under Respiratory medicine.
- **WHO treatment outcomes: cured** (bacteriologically confirmed at the start; smear or culture negative at the end and once before); **treatment completed**; **treatment failed: smear or culture positive at month 5 or later**, or the regimen changed for resistance; **died**; **lost to follow-up** (interrupted 2 months or more); **not evaluated**. **Relapse** is recurrence after cure or completion.
- **Isoniazid and pyridoxine:** isoniazid **depletes pyridoxine and inhibits pyridoxal kinase, causing peripheral neuropathy**, so pyridoxine (10–25 mg daily) is given to people at risk: malnourished, diabetic, pregnant or breastfeeding, alcoholic, HIV, CKD, the elderly; it does not affect isoniazid's antibacterial action. The TB regimens are in Respiratory medicine.

Rheumatology

Connective tissue disease and antibodies

Antibody	Disease
ANA	**most sensitive screen for SLE (over 95%)**; not specific (also other CTDs, elderly, drugs)
Anti-dsDNA, anti-Smith	**specific for SLE** (dsDNA rises with activity and nephritis; Smith most specific, not activity-linked)
Anti-histone	**drug-induced lupus** (hydralazine, procainamide, isoniazid, minocycline, anti-TNF); spares kidney and brain
Anti-centromere	**limited cutaneous systemic sclerosis (CREST)**; pulmonary hypertension
Anti-Scl-70 (topoisomerase I)	diffuse systemic sclerosis, **interstitial lung disease**
Anti-RNA polymerase III	diffuse systemic sclerosis with **scleroderma renal crisis** and cancer
Anti-Ro (SSA) / La (SSB)	**Sjögren**; subacute cutaneous lupus; **neonatal lupus with congenital heart block**
Anti-Jo-1 (histidyl-tRNA synthetase)	**antisynthetase syndrome: myositis, interstitial lung disease, mechanic's hands**, arthritis, Raynaud, fever
Anti-Mi-2	classic dermatomyositis (shawl sign, heliotrope rash, Gottron papules), good prognosis
Anti-MDA5	**amyopathic dermatomyositis with rapidly progressive ILD** (high mortality, Asia)
Anti-TIF1γ, anti-NXP2	**dermatomyositis with cancer**
Anti-HMGCR, anti-SRP	**necrotising myopathy** (HMGCR after statins)
Anti-U1-RNP	mixed connective tissue disease
c-ANCA (proteinase 3)	**granulomatosis with polyangiitis** (sinus disease, saddle nose, **strawberry gingivitis**, lung nodules and cavities, necrotising GN)
p-ANCA (myeloperoxidase)	**microscopic polyangiitis**, **EGPA** (asthma, eosinophilia), drug-induced vasculitis; also UC and PSC (atypical)
Anti-CCP, rheumatoid factor	rheumatoid arthritis (**anti-CCP more specific, about 95%**, predicts erosions); RF also Sjögren, HCV, endocarditis, elderly
Anti-GBM	Goodpasture disease

- **SLE: 2019 EULAR/ACR classification: ANA 1:80 or more as the entry criterion**, then weighted clinical and immunological items (10 or more points classifies). Features: malar rash sparing the nasolabial folds, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis (**Jaccoud**), serositis, nephritis, cytopenias, neuropsychiatric lupus, **Libman–Sacks endocarditis**, antiphospholipid antibodies; **low C3 and C4 in active disease**. **Treatment: hydroxychloroquine for everyone** (yearly eye checks after 5 years) and the lowest steroid dose (under 5 mg prednisolone, EULAR 2023); azathioprine, methotrexate or mycophenolate as steroid-sparing drugs; **nephritis: mycophenolate or low-dose cyclophosphamide, with belimumab or voclosporin** (KDIGO 2024); **belimumab (anti-BLyS) and anifrolumab (anti-interferon receptor)** for refractory disease. Pregnancy: plan in remission, continue hydroxychloroquine, low-dose aspirin.
- **Antiphospholipid syndrome (Sydney criteria 2006; ACR/EULAR 2023):** thrombosis (venous or arterial) or pregnancy morbidity (three or more consecutive losses before 10 weeks, a fetal death after 10 weeks, or premature birth before 34 weeks for severe pre-eclampsia or placental insufficiency), **plus persistent antibodies on two occasions at least 12 weeks apart: lupus anticoagulant, anticardiolipin or anti-β2-glycoprotein I**. The **lupus anticoagulant prolongs the aPTT, which does not correct on mixing** (it is thrombotic, not haemorrhagic); also thrombocytopenia and a false-positive VDRL. **Thrombosis: long-term warfarin (INR 2–3)**; DOACs are avoided in arterial events and triple-positive disease. **Obstetric APS without previous thrombosis: low-dose aspirin plus prophylactic LMWH throughout pregnancy and 6 weeks postpartum; with a previous thrombosis, aspirin plus therapeutic-dose LMWH (ACR 2020, EULAR 2019); warfarin is avoided (teratogenic).** Catastrophic APS: anticoagulation, steroids and plasma exchange or IVIG.
- **Systemic sclerosis: Raynaud phenomenon (first feature in most)**, sclerodactyly, digital ulcers, oesophageal dysmotility,

interstitial lung disease (commonest cause of death; nintedanib, mycophenolate, tocilizumab), pulmonary arterial hypertension; **scleroderma renal crisis**: malignant hypertension and AKI, **treated with an ACE inhibitor (captopril)**, precipitated by **high-dose steroids (over 15 mg prednisolone)**. Limited form (CREST: calcinosis, Raynaud, oesophagus, sclerodactyly, telangiectasia; anti-centromere) vs diffuse (anti-Scl-70, early organ disease).

- **Inflammatory myositis:** symmetrical proximal weakness, **raised CK**, EMG, MRI, **muscle biopsy (dermatomyositis: perifascicular atrophy, perivascular inflammation; polymyositis: endomysial CD8 T cells)**; **dermatomyositis is linked to cancer** (ovary, lung, GI, nasopharynx in Asia: screen); **steroids plus methotrexate or azathioprine**, IVIG. **Inclusion-body myositis**: older men, finger flexors and quadriceps, rimmed vacuoles, steroid-resistant.
- **Sjögren syndrome:** dry eyes (**Schirmer test** under 5 mm in 5 minutes) and mouth, parotid swelling, anti-Ro/La, **lymphocytic sialadenitis on lip biopsy (focus score 1 or more)**, distal RTA, **B-cell (MALT) lymphoma risk (about 5–15 times)**.

Vasculitis

- **By vessel size (Chapel Hill 2012): large: Takayasu arteritis** (young Asian women, **pulseless disease**, arm claudication, unequal BPs, renal artery stenosis) and **giant cell arteritis**; **medium: polyarteritis nodosa** (**hepatitis B**, mononeuritis multiplex, renal artery microaneurysms and infarcts, **spares the lungs and glomeruli, ANCA negative**) and **Kawasaki disease** (children under 5: fever 5 days or more, conjunctivitis, **strawberry tongue**, rash, extremity changes, cervical node; **coronary artery aneurysms**; **IVIG and aspirin**); **small: ANCA-associated vasculitides** (GPA, MPA, EGPA), **immune-complex: IgA vasculitis (Henoch–Schönlein: palpable purpura on the buttocks and legs, arthritis, abdominal pain, nephritis; children)**, cryoglobulinaemic (HCV), anti-GBM; **variable: Behçet disease**, Cogan.
- **IgA vasculitis and the gut:** colicky pain, vomiting and melaena from submucosal haemorrhage and oedema, which can form a lead point for **ileo-ileal intussusception** (idiopathic intussusception is ileocolic); ultrasound shows it and needs surgical review. Steroids ease the pain but do not prevent it. Nephritis decides the long-term outcome, so blood pressure and urine are followed for months.
- **ANCA vasculitis treatment (ACR 2021, KDIGO 2024):** induction with **rituximab (preferred) or cyclophosphamide plus steroids**, with **avacopan (C5a receptor antagonist, ADVOCATE 2021)** to cut steroid exposure; plasma exchange no longer routine (PEXIVAS 2020); maintenance with rituximab. **EGPA**: asthma, eosinophilia, neuropathy, p-ANCA in about 40%; **mepolizumab** for relapsing disease.
- **Giant cell arteritis:** over 50, new temporal headache, **scalp tenderness, jaw claudication (most specific symptom)**, **ESR often over 50 (CRP more sensitive)**, **polymyalgia rheumatica in about half**, systemic features; threat is **permanent visual loss (arteritic anterior ischaemic optic neuropathy from posterior ciliary artery occlusion)**. **Start high-dose prednisolone (40–60 mg; IV methylprednisolone if vision is affected) at once on suspicion**; **temporal artery biopsy within 1–2 weeks remains valid** (skip lesions: take at least 1 cm); **ultrasound "halo sign" is now the first imaging test (EULAR 2023)**, with PET-CT for large-vessel disease. **Tocilizumab (IL-6 receptor, GiACTA 2017)** spares steroids; upadacitinib (SELECT-GCA 2025). Classification: ACR/EULAR 2022. **Polymyalgia rheumatica**: shoulder and hip girdle aching and stiffness over 50, high ESR, **dramatic response to prednisolone 15 mg**; normal CK.
- **Behçet disease: recurrent oral ulcers (required in most criteria), genital ulcers, uveitis** (posterior, hypopyon), erythema nodosum, **pathergy** (papule or pustule at a sterile needle prick read at 24–48 h; commoner in Turkish, Middle Eastern and Japanese patients than in northern Europeans), venous and arterial thrombosis and aneurysms, neuro-Behçet; **HLA-B51**; Silk Road distribution. **Colchicine** for mucocutaneous disease and arthritis, **apremilast** for oral ulcers, azathioprine, **anti-TNF (infliximab, adalimumab)** for eye and severe disease (EULAR 2018). Pyoderma gangrenosum also shows pathergy.

Crystal and inflammatory arthritis

- **Gout: needle-shaped, strongly negatively birefringent monosodium urate crystals** (yellow when parallel to the compensator); **pseudogout (CPPD) has rhomboid, weakly positively birefringent calcium pyrophosphate crystals** and **chondrocalcinosis** (knee, wrist; haemochromatosis, hyperparathyroidism, hypomagnesaemia). First MTP joint (podagra) commonest; serum urate may be normal during an attack; **dual-energy CT** and ultrasound **double-contour sign** show urate. **Acute attack: NSAID, low-dose colchicine (1 mg then 0.5 mg after an hour) or steroid**; IL-1 blockers if these fail. **Urate-lowering therapy (ACR 2020)**: for 2 or more flares a year, tophi or erosions; **allopurinol first line (xanthine oxidase inhibitor; start at 100 mg or less, lower in CKD, and titrate)**, febuxostat alternative (cardiovascular warning), probenecid, pegloticase for refractory tophaceous gout; **treat to a target urate under 6 mg/dL** (under 5 with tophi). **Anti-inflammatory prophylaxis (colchicine, NSAID or prednisolone) for 3–6 months, because falling urate mobilises crystals and provokes flares**; ACR 2020 **allows starting during a flare**; **do not stop allopurinol during an attack**. **Test for HLA-B*58:01 before allopurinol in South-East Asian (Han Chinese, Korean, Thai) and African-American patients** (Stevens–Johnson and DRESS risk). Thiazides and loop diuretics, low-dose aspirin, ciclosporin and alcohol raise urate; losartan and fenofibrate lower it.
- **Rheumatoid arthritis:** symmetrical small-joint polyarthritis (MCP, PIP, wrist; **spares the DIP**), **morning stiffness over 1 hour**; **2010 ACR/EULAR classification (6 or more of 10 points from joints, serology, acute-phase reactants, duration over 6 weeks)**; ulnar deviation, swan-neck and boutonnière deformities, Z-thumb; X-ray periarticular osteopenia and **marginal erosions**. Extra-articular: nodules, **ILD (UIP pattern)**, Caplan syndrome (with pneumoconiosis), scleritis and **keratoconjunctivitis sicca (commonest eye feature)**, **Felty syndrome (RA, splenomegaly, neutropenia)**, secondary amyloidosis, vasculitis; **atlantoaxial subluxation** (check before intubation); cardiovascular disease is the leading cause of death. **Treatment (ACR 2021, EULAR 2022): methotrexate weekly, the anchor DMARD, with folic acid** (monitor blood count and liver; pneumonitis; teratogenic: stop 3 months before conception), short steroid bridging; **treat to target** (remission or low disease activity, DAS28 under 2.6 for remission); add sulfasalazine and hydroxychloroquine (triple therapy) or a **biologic (anti-TNF, abatacept, tocilizumab, rituximab) or a JAK inhibitor** (tofacitinib, baricitinib, upadacitinib; **ORAL Surveillance 2022: more cardiovascular events and cancer than anti-TNF in older smokers**); **screen**

for latent TB (and hepatitis B) before biologics and JAK inhibitors, especially in Nepal. Leflunomide is the alternative anchor. Gold, penicillamine and azathioprine are obsolete for RA.

- **Spondyloarthritis (seronegative, HLA-B27): ankylosing spondylitis (axial spondyloarthritis)**: young men, **inflammatory back pain** (onset under 40, insidious, over 3 months, **morning stiffness, improves with exercise but not with rest**, night pain in the second half of the night, alternating buttock pain), reduced spinal movement (**modified Schober test**), reduced chest expansion; **sacroiliitis on MRI (earliest) or X-ray**, **bamboo spine**, syndesmophytes, Romanus lesions; **anterior uveitis is the commonest extra-articular feature**, aortic regurgitation, apical fibrosis; **ASAS criteria**. **NSAIDs first, then TNF or IL-17 inhibitors (secukinumab)**, physiotherapy; DMARDs do not help axial disease. **Reactive arthritis**: 1–4 weeks after **Chlamydia trachomatis** or enteric infection (Shigella, Salmonella, Yersinia, Campylobacter); arthritis, urethritis, conjunctivitis; keratoderma blennorrhagicum, circinate balanitis. **Psoriatic arthritis**: DIP involvement, **dactylitis**, nail pitting, arthritis mutilans, **pencil-in-cup** deformity. Enteropathic arthritis with IBD.
- **Septic arthritis:** a hot swollen joint is septic until proven otherwise: **aspirate before antibiotics**; **Staphylococcus aureus commonest**; **Neisseria gonorrhoeae in young sexually active adults** (tenosynovitis, pustules, migratory arthritis); Salmonella in sickle cell disease; synovial white count over 50,000/µL; IV antibiotics and washout.
- **Osteoarthritis:** older, weight-bearing joints and hands, **Heberden (DIP) and Bouchard (PIP) nodes**, pain worse with use, stiffness under 30 minutes, **joint-space narrowing, osteophytes, subchondral sclerosis and cysts**, normal ESR; exercise and weight loss first, topical then oral NSAIDs, intra-articular steroid, joint replacement.
- In hand osteoarthritis the **DIP, PIP and first carpometacarpal joints** are involved and the **MCP joints and wrist are spared** (the reverse of rheumatoid arthritis); MCP disease in an osteoarthritic hand suggests haemochromatosis or CPPD.
- Sarcoidosis (Respiratory medicine) and fibromyalgia (widespread pain, tender points no longer required, normal tests; exercise, amitriptyline, duloxetine) round out common questions.

Metabolic bone disease

- **Bone biochemistry compared: osteomalacia (adults; rickets in children): low or normal calcium, low phosphate, raised alkaline phosphatase, raised PTH (secondary), low 25-hydroxyvitamin D**; **Looser zones (pseudofractures)** on X-ray, bone pain, proximal myopathy with waddling gait; treat with vitamin D. **Osteoporosis: calcium, phosphate and ALP all normal. Paget disease: ALP very high, calcium and phosphate normal.** Primary hyperparathyroidism: high calcium, low phosphate. CKD-mineral bone disorder: high phosphate, low calcium.

Clinical examination

Peripheral signs of infective endocarditis

Sign	Feature	Mechanism
Osler nodes	**Painful (tender), purplish nodules on the finger and toe pulps**, appear and fade within hours to days	**Immune-complex deposition** (immunological, a minor Duke criterion)
Janeway lesions	**Painless** flat macules on the **palms and soles**	**Septic emboli** (vascular phenomenon)
Roth spots	Retinal haemorrhages with a pale centre	Immunological
Splinter haemorrhages	Linear subungual streaks	Microemboli or vasculitis; also seen in trauma, so a few under the nails are non-specific
Clubbing	Late, in subacute disease	

- Remember the split: **Osler = painful and immune; Janeway = painless and embolic.**

Glasgow Coma Scale (GCS)

Response	Score
Eyes: spontaneous 4, to voice 3, **to pain 2**, none 1	1–4
Verbal: orientated 5, confused 4, **inappropriate words 3**, incomprehensible sounds 2, none 1	1–5
Motor: obeys commands 6, localises pain 5, **withdraws from pain 4**, abnormal flexion (decorticate) 3, extension (decerebrate) 2, none 1	1–6

- **Minimum 3, maximum 15.** Worked example: eyes open to pain (2), inappropriate words (3), withdrawal (4) = **9**. Severity: **13–15 mild, 9–12 moderate, 8 or below severe**; **a score of 8 or below usually means securing the airway**.
- Report each component as well as the total (for example E2 V3 M4 = 9). Test the motor response with a central stimulus (trapezius squeeze or supra-orbital pressure), and record the **best** response; **the motor score is the best single predictor of outcome.** An intubated patient's verbal score is recorded as "T"; the GCS-Pupils score (2018) subtracts points for non-reactive pupils.
- The GCS tests the level of consciousness but not brainstem reflexes; it is used in head injury (ATLS, NICE head injury guidance) and in medical coma.

Other bedside signs asked

- **Clubbing**: loss of the angle between nail and nail fold (Lovibond angle over 180°), **Schamroth window loss**, then a spongy nail bed and drumstick fingers; causes: lung cancer, bronchiectasis, empyema, fibrosis, cyanotic heart disease, endocarditis, cirrhosis, inflammatory bowel disease, coeliac disease.
- **Kussmaul breathing** (deep sighing, acidosis), **Cheyne–Stokes** (waxing and waning, heart failure and brain injury), **Biot** (irregular, brainstem lesions).
- Pulse and neck-vein signs are in Cardiology; fever patterns are in Infectious diseases.

Sources

- Harrison's Principles of Internal Medicine (21st edition, 2022); Davidson's Principles and Practice of Medicine (24th edition); Oxford Handbook of Clinical Medicine (11th edition); Robbins

and Cotran Pathologic Basis of Disease (10th edition); First Aid for the USMLE Step 1 2022.

- Braunwald's Heart Disease; Fishman's Pulmonary Diseases; Sherlock's Diseases of the Liver; Brenner and Rector's The Kidney; Williams Textbook of Endocrinology; Bradley and Daroff's Neurology in Clinical Practice; Williams Hematology; Kelley and Firestein's Textbook of Rheumatology; Park's Preventive and Social Medicine.
- Cardiology: ACC/AHA 2017 and AHA/ACC 2025 high blood pressure guidelines; ESC 2024 hypertension; ESC 2023 ACS; ACCF/AHA 2013 STEMI; ESC 2024 chronic coronary syndromes; ESC 2021 heart failure and 2023 focused update; AHA/ACC/HFSA 2022 heart failure; ESC 2024 atrial fibrillation; ACC/AHA 2020 and ESC/EACTS 2025 valvular heart disease; AHA 2015 revised Jones criteria; WHO 2024 rheumatic heart disease guideline; ESC 2023 endocarditis and 2023 Duke–ISCVID criteria; ESC 2015 pericardial diseases; ESVS 2024 abdominal aortic aneurysm; AHA 2020 and ERC 2021 resuscitation; INVICTUS (2022), SPRINT (2015), STRONG-HF (2022).
- Respiratory: WHO consolidated TB guidelines (Module 4: treatment, 2022 and 2025; Module 1: prevention); **Nepal's National Guidelines on Drug-Resistant TB Management 2024 and National TB Preventive Treatment Protocol 2024 (National Tuberculosis Control Centre)**, and the National TB Programme's 2019 regimen tables as presented in its training material; GOLD 2025 and 2026; GINA 2024; BTS/SIGN 2019 and BTS/NICE/SIGN 2024 asthma; BTS emergency oxygen 2017; BTS 2023 pleural disease; ESC 2019 pulmonary embolism; Berlin 2012 and 2023 global ARDS definitions; BTS CURB-65 (Lim 2003).
- Gastroenterology: WHO 2024 hepatitis B guidelines and Global Hepatitis Report 2024; AASLD and EASL cirrhosis, HBV, HCV and PBC guidance; Baveno VII (2022); ACG 2024 and Maastricht VI (2022) H. pylori; ACG 2021 upper GI bleeding; revised Atlanta classification 2012; WATERFALL (2022); multi-society MASLD nomenclature (2023); Rome IV.
- Nephrology: KDIGO AKI 2012, glomerular diseases 2021, CKD 2024, lupus nephritis 2024 and ANCA vasculitis 2024; European clinical practice guideline on hyponatraemia (2014); Mehta et al. on GOLDMARK (Lancet 2008).
- Endocrinology: ADA Standards of Care in Diabetes 2025; ADA/EASD/JBDS/AACE/DTS consensus on hyperglycaemic crises in adults (2024); ATA 2016 hyperthyroidism and ATA 2017 thyroid disease in pregnancy; Endocrine Society guidelines on Cushing syndrome (2008, 2021 consensus), primary aldosteronism (2016), phaeochromocytoma (2014) and adrenal insufficiency (2016); AVP deficiency and resistance nomenclature (2022).
- Neurology: AHA/ASA 2019 acute ischaemic stroke, 2022 intracerebral haemorrhage and 2023 aneurysmal SAH guidelines; ESO 2023 thrombolysis; McDonald 2017 and its 2024 revision (Montalban et al., Lancet Neurology 2025); NICE 2022 epilepsies; ESETT (2019); IDSA 2004 bacterial meningitis and 2017 neurocysticercosis; WHO 2022 cryptococcal disease; Brighton criteria for GBS.
- Haematology: WHO classification of haematolymphoid tumours (5th edition, 2022); WHO 2024 haemoglobin cut-offs; ASH 2019 ITP; IMWG 2014 myeloma criteria; Lugano 2014; ISTH TTP and DIC guidance; AABB 2023 transfusion thresholds; Histiocyte Society LCH guidance.
- Infectious diseases: WHO dengue 2009 and SEARO 2011 guidelines; WHO guidelines for malaria (2024 update); WHO Expert Consultation on Rabies (2018); WHO consolidated HIV guidelines (2021, with 2023 viral-load and 2025 lenacapavir updates); Surviving Sepsis Campaign 2021; Sepsis-3 (2016); WHO 2010 control of the leishmaniases; Nepal's National Malaria Treatment Protocol 2019 (EDCD) and National Immunization Programme schedule (MoHP); WHO SEARO snakebite guidelines 2016; WHO SAGE 2023 dengue vaccine; Cunha on relative bradycardia (2000).
- Rheumatology: 2019 EULAR/ACR SLE classification; EULAR 2023 SLE recommendations; ACR 2020 gout; 2010 ACR/EULAR RA classification; ACR 2021 and EULAR 2022 RA management; ACR/EULAR 2022 GCA classification and EULAR 2023 GCA imaging recommendations; ACR 2021 vasculitis; Chapel Hill 2012 nomenclature; ASAS axial spondyloarthritis criteria; EULAR 2018 Behçet recommendations.
- Curriculum fill (2026-11-26): ACG 2024 acute pancreatitis guideline; WATERFALL (NEJM 2022); ACG 2020 achalasia and Chicago classification v4.0 (2021); EAU urolithiasis 2024; WHO lymphatic filariasis guidelines (2017); WHO guidelines on iodine intake; ATLS 10th edition and Teasdale and Jennett's Glasgow Coma Scale; Harrison's and Davidson's for the bedside signs.