RGUHS · MODEL ANSWER BANK

RGUHS MD General Medicine — Paper IV

RENAL, ENDOCRINE, HAEMATO-ONCOLOGY, PSYCHIATRY & DERMATOLOGY

2019–2026

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

GROUNDED IN:

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

Dr. Harshad Ramineni
@aurapharmlab

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Renal system

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NSAID-induced acute interstitial nephritis

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Acute interstitial nephritis (AIN, syn. acute tubulointerstitial nephritis, ATIN) is an immune-mediated inflammatory disorder of the renal interstitium and tubules with relative sparing of glomeruli and vessels, producing acute kidney injury (AKI). It accounts for ~10–15% of intrinsic AKI, and **drugs cause >70% of cases**. This 35-year-old man, on diclofenac for a month, with new AKI (creatinine 4.5 mg/dL), **bland urine, low-grade proteinuria (~200 mg/24 h) and only 7 RBCs/no casts**, is the textbook picture of **NSAID-induced AIN** — the "atypical" allergic nephritis in which the classic triad of fever, rash and eosinophilia is characteristically *absent*.

Interpreting the vignette — why this is AIN, not a glomerular disease

- **Temporal link:** AKI appearing weeks after starting a known culprit drug (NSAID) is the single strongest clue; the latent period with NSAIDs is long (often weeks to months, unlike the days–2 weeks seen with β-lactams).
- **Bland sediment + scanty proteinuria:** proteinuria of only 200 mg/24 h is *tubular-range* (<1–2 g/day), and the microscopy is bland with no casts and only 7 RBCs. This argues strongly **against** a glomerulopathy, which would give nephrotic-range proteinuria, dysmorphic RBCs and RBC casts, and against acute GN/vasculitis.
- **Edema is from fluid retention, not hypoalbuminaemia:** periorbital puffiness and pedal oedema here reflect salt-and-water retention from the AKI itself plus the direct sodium-retaining (prostaglandin-mediated) effect of NSAIDs — *not* nephrotic syndrome, since the protein loss is trivial.
- **Caveat — the "dual lesion":** NSAIDs uniquely may cause AIN *combined with* a glomerular lesion (**minimal change disease** more often than **membranous nephropathy**), producing heavy/nephrotic proteinuria. The low proteinuria here makes a concurrent minimal-change lesion unlikely, so the expected pathology is *pure* AIN.

Feature in this case	Points toward
NSAID for 1 month, new AKI	Drug-induced AIN
Proteinuria 200 mg/24 h (tubular range)	Interstitial, not glomerular
Bland sediment, no casts, 7 RBCs	AIN / ATN — excludes active GN
Periorbital + pedal oedema	Volume retention from AKI + NSAID Na+ retention
No fever/rash/eosinophilia	Typical of NSAID-AIN (allergic features rare)

Expected renal pathology (b) — Acute (drug-induced) interstitial nephritis

- **Diagnosis: acute tubulointerstitial nephritis (AIN)** — confirmed only by **percutaneous kidney biopsy**, the gold standard.

- **Light microscopy:** patchy/diffuse **interstitial oedema** with a **mononuclear inflammatory infiltrate** (predominantly **T lymphocytes — CD4⁺ and CD8⁺**), plasma cells, macrophages, and variable eosinophils; **tubulitis** (lymphocytes crossing the tubular basement membrane into tubular epithelium) with tubular cell injury (loss of brush border, luminal ectasia).
- **NSAID-specific histology:** the infiltrate is **less intense and characteristically has few or no eosinophils**, attributable to the drug's own anti-inflammatory action — distinct from β-lactam AIN where eosinophils are abundant. Occasionally granulomatous AIN or anti-TBM immune deposits occur.
- **Glomeruli and vessels are spared** (unless a coexisting minimal-change/membranous lesion is present).
- **Pathogenesis:** a **T-cell–mediated, type IV (delayed) hypersensitivity** reaction; the drug acts as a **hapten/pro-hapten** binding tubular proteins or generates neoantigens by molecular mimicry, triggering interstitial inflammation.
- **If unrecognised/untreated**, interstitial inflammation evolves into **interstitial fibrosis and tubular atrophy** → chronic tubulointerstitial nephritis and CKD.

Spectrum of NSAID nephrotoxicity (depth point)

- **Haemodynamic (pre-renal) AKI** — commonest; inhibition of vasodilatory prostaglandins (PGE_2/PGI_2) → unopposed **afferent arteriolar vasoconstriction** → fall in GFR, especially with volume depletion, heart failure, cirrhosis, or co-prescription of ACE-I/ARB ("triple whammy").
- **Acute interstitial nephritis** (this case) ± **minimal change disease / membranous nephropathy** (nephrotic syndrome).
- **Electrolyte/acid–base:** hyperkalaemia (type IV RTA), sodium and water retention → oedema and hypertension, hyponatraemia.
- **Chronic:** analgesic nephropathy with **papillary necrosis**, and acceleration of pre-existing CKD.

Other causes of the same pathology (c) — causes of AIN

Category	Representative causes
Drugs (>70%)	**NSAIDs/COX-2 inhibitors**; **antibiotics** — β-lactams (penicillins, cephalosporins), sulfonamides, fluoroquinolones (ciprofloxacin), vancomycin, rifampin, ethambutol; **PPIs** & H_2 blockers; **allopurinol**; **anticonvulsants** (phenytoin, carbamazepine, valproate); diuretics (thiazides, furosemide, triamterene); **immune checkpoint inhibitors** (ipilimumab, nivolumab, pembrolizumab); mesalamine, 5-ASA
Infections	*Streptococcus*, *Staphylococcus*, *Legionella*, *Corynebacterium diphtheriae*, *Brucella*, *Yersinia*; *Leptospira*; viruses — EBV, CMV, **hantavirus**, HIV, **polyomavirus (BK)**; *Mycobacterium tuberculosis* (granulomatous)
Autoimmune / systemic	**Sjögren syndrome**, **SLE**, **sarcoidosis** (granulomatous), **IgG4-related disease** (storiform fibrosis), **TINU** (tubulointerstitial nephritis with uveitis), anti-TBM (anti-LRP2/anti-brush border) disease
Idiopathic	Idiopathic AIN (some with anti-tubular antibodies)
Obstructive/crystal (related)	Light-chain cast nephropathy (myeloma), acute urate (tumour lysis) and acute phosphate nephropathy

Investigations / diagnostic approach

- **Confirm and stage AKI** (KDIGO): serum creatinine 4.5 mg/dL from a normal baseline is **stage 3 AKI**; trend creatinine/urea, urine output.
- **Urinalysis & microscopy:** sterile pyuria, WBC ± WBC casts, mild haematuria, **low-grade (tubular) proteinuria <1–2 g/day**; ~20% have a bland sediment (as here). **Urine eosinophils are NOT recommended** — poor sensitivity/specificity (abandoned).
- **Bloods:** CBC (eosinophilia inconsistent, may be absent in NSAID-AIN), electrolytes (watch **hyperkalaemia**, non-anion-gap acidosis), ESR/CRP, IgE; screen for systemic disease where suspected (ANA, anti-Ro/La, serum IgG4, ACE/calcium).
- **Imaging:** renal ultrasound — **normal-sized or enlarged, echogenic kidneys**; chiefly excludes obstruction.
- **Kidney biopsy** — definitive; indicated when diagnosis is uncertain, AKI is severe/progressive, or before committing to steroids.

Management (d)

- **Withdraw the offending drug immediately — stop diclofenac.** This is the single most important step; AKI often reverses after withdrawal alone. Avoid *all* nephrotoxins (NSAIDs, contrast, aminoglycosides, ACE-I/ARB during the acute phase).
- **Supportive AKI care (KDIGO):** optimise volume/haemodynamics, maintain MAP >65 mmHg, treat the oedema/volume overload with **salt and water restriction + loop diuretics**, correct hyperkalaemia (calcium gluconate, insulin-dextrose, β-agonist, K^+ binders), treat metabolic acidosis ($NaHCO_3$ if pH <7.2 / HCO_3 <15), renal-dose all drugs, ensure 20–30 kcal/kg/day nutrition.
- **Corticosteroids** — consider if **kidney function does not improve within ~5–7 days of drug withdrawal**, or if biopsy shows florid inflammation without established fibrosis; benefit falls if started >1–2 weeks after onset. Regimens:

Regimen	Dose
IV methylprednisolone pulse	0.25–0.5 g/day IV for 1–4 days
Oral prednisone	1 mg/kg/day (≈60 mg/day) for 4–6 weeks, then taper
Duration	Continue 4–8 weeks if responding; taper off by 3–4 weeks if no response

- **Renal replacement therapy (dialysis)** if refractory volume overload, hyperkalaemia or acidosis, or uraemic complications — **AEIOU**: **A**cidosis, **E**lectrolytes (K^+), **I**ngestions/toxins, **O**verload, **U**raemia. Up to one-third of AIN patients need temporary dialysis before recovery.
- **Prognosis:** generally good — most recover over weeks to months; progression to ESRD is rare. Worse outcomes with prolonged oliguria, older age, delayed drug withdrawal and established interstitial fibrosis. Counsel lifelong avoidance of the culprit class.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Histology of AIN (label):** interstitial *oedema* separating tubules; *mononuclear (lymphocytic) interstitial infiltrate*; *eosinophils* (note: sparse/absent in NSAID-AIN); *tubulitis* (lymphocytes crossing the *tubular basement membrane*); *normal glomerulus*; *normal vessel*.
- **Diagram 2 — NSAID renal effects flow chart (label):** *NSAID* → ↓ *vasodilatory prostaglandins (PGE_2/PGI_2)* → branch 1: *afferent arteriolar vasoconstriction* → ↓*GFR (pre-renal AKI)*; branch 2: *hapten* → *T-cell (type IV) hypersensitivity* → *AIN*; branch 3: *Na^+/water retention* → *oedema, hypertension, hyperkalaemia*; branch 4: ± *minimal change disease* → *nephrotic syndrome*.

Clinical / Diagnostic significance

- **Drug history is diagnostic:** any unexplained AKI with a temporally-related drug = suspect AIN; empirical drug withdrawal is both diagnostic and therapeutic.
- **A bland urine never excludes AIN** — ~20% of biopsy-proven cases have normal sediment, and NSAID-AIN classically lacks fever/rash/eosinophilia.
- **Distinguish from the commoner NSAID pre-renal AKI** (responds to volume) and from glomerular disease (active sediment, heavy proteinuria) — this changes management.
- **Early diagnosis prevents fibrosis:** delay → tubular atrophy/interstitial fibrosis → irreversible CKD.

High-yield exam pointers

- AIN = **10–15% of intrinsic AKI**; **drugs cause >70%**; *Councilman* first described AIN (1897).
- **NSAID-AIN is "atypical":** long latency, fever/rash/eosinophilia rare, **eosinophils often absent on biopsy**, low-grade proteinuria — may combine with **minimal change disease (>membranous)** to cause nephrotic syndrome.
- **Pathology:** interstitial oedema + **mononuclear (T-cell) infiltrate + tubulitis**, glomeruli/vessels spared; **type IV hypersensitivity**.
- **Urine eosinophils are NOT useful** — do not order.
- **Biopsy = gold standard**; ultrasound shows normal/enlarged echogenic kidneys.
- **Treatment = STOP the drug** first; **corticosteroids** (methylprednisolone 0.25–0.5 g/day IV ×1–4 days *or* prednisone 1 mg/kg ≈60 mg/day ×4–6 weeks) if no recovery in ~5–7 days.
- **Dialysis (AEIOU)** in up to one-third; overall **good prognosis**, ESRD rare.
- Other AIN causes to list: β-lactams, sulfonamides, **PPIs**, rifampin, allopurinol, **checkpoint inhibitors**; **Sjögren, SLE, sarcoid, IgG4, TINU**; *Legionella*, *Leptospira*, hantavirus, BK virus, TB.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Tubulointerstitial Diseases of the Kidney" (acute interstitial nephritis: causes, pathology, treatment; Table 328-1 classification; Table 328-2 steroid indications) and "Acute Kidney Injury" (AKI classification, management Table 321-3, dialysis indications).
- **Brenner & Rector's The Kidney** — "Tubulointerstitial Diseases" (Perazella & Rosner): pathogenesis as T-cell type IV hypersensitivity, clinical/laboratory features (Table 35.4), drug list (Table 35.6), NSAID-AIN features and dual minimal-change lesion, differential diagnosis (Table 35.5), corticosteroid regimens (Table 35.7).
- **CMDT 2026** — "Kidney Disease": Interstitial Nephritis (essentials, Table 25–4 causes, steroid dosing) and AKI management.

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Acute interstitial nephritis

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

Definition / Introduction — Acute interstitial nephritis (AIN) is an acute tubulointerstitial disorder characterised by inflammation and oedema of the renal *interstitium* with secondary tubular injury, while the **glomeruli and renal vessels are relatively spared**. *Councilman* (1897) originally described it as "an acute inflammation of the kidney characterised by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." Today AIN is most often an **allergic (immune-mediated) reaction to a drug** and is an important, frequently reversible cause of acute kidney injury (AKI).

Etiology / Classification

AIN is conveniently grouped into **drug-induced (allergic)**, **infection-associated**, and **autoimmune/systemic** causes (Harrison Table 328-1):

Category	Representative causes
Antibiotics	β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, **rifampin**, ethambutol, acyclovir
NSAIDs / COX-2 inhibitors	All NSAIDs; selective COX-2 inhibitors
Diuretics	Rarely thiazides, loop diuretics, triamterene
Anticonvulsants	Phenytoin, valproate, carbamazepine, phenobarbital
Immune modulators	Immune checkpoint inhibitors, vedolizumab, lenalidomide
Miscellaneous drugs	**Proton pump inhibitors (PPIs)**, H2 blockers, captopril, mesalazine, indinavir, allopurinol

Category	Representative causes
Infection	Bacteria (*Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, C. diphtheriae*); Viruses (EBV, CMV, hantavirus, **polyomavirus/BK**, HIV); *Leptospira, Rickettsia, Mycoplasma, Histoplasma*
Autoimmune / systemic	**TINU**, Sjögren's syndrome, SLE, granulomatous interstitial nephritis, **IgG4-related disease**, checkpoint-inhibitor–related TIN, anti-brush border (anti-LRP2) disease, idiopathic autoimmune IN

- **Drug-induced AIN is the commonest form** and the reaction is *idiosyncratic* (not dose-dependent) — it may recur on re-exposure. *Particularly severe, rapid-onset AIN follows reintroduction of rifampin after a drug-free period.*
- **NSAIDs, PPIs, mesalazine/sulfasalazine and antiretrovirals** characteristically cause a more *insidious* reaction that may progress to chronic tubulointerstitial damage.

Pathogenesis

- AIN represents an **immune-mediated (hypersensitivity) reaction** rather than direct dose-dependent toxicity; the drug or microbial antigen triggers an inflammatory infiltrate that produces interstitial oedema, tubular-cell injury and compromised tubular flow.
- In some idiopathic and autoimmune cases, **autoantibodies to a tubular antigen** (e.g. collecting-duct or proximal-tubule brush-border antigens, *anti-LRP2/anti-brush border disease*) have been demonstrated, supporting an autoimmune mechanism.
- The aggressive inflammatory infiltrate (with **eosinophils, lymphocytes and mononuclear cells**) leading to tissue oedema accounts for the *acute* nature and the occasional **flank pain from distension of the renal capsule**.

Clinical Features

- **Classic triad/tetrad** (the *exception, not the rule*): **fever, rash (maculopapular), peripheral eosinophilia, and oliguric AKI** occurring **7–10 days** after starting methicillin or another β-lactam.
- More commonly, the patient is found **incidentally to have a rising serum creatinine** or presents with non-specific symptoms of AKI.
- **NSAID-induced AIN is atypical**: fever, rash and eosinophilia are *rare*, but AKI is often accompanied by **heavy (nephrotic-range) proteinuria** (from coexistent minimal-change disease/secondary FSGS).
- Features of associated tubular dysfunction may occur — *Fanconi's syndrome*, distal/proximal RTA, type IV RTA and nephrogenic diabetes insipidus, especially when injury is prolonged.

Investigations / Diagnosis

- **Clinical diagnosis** rests on otherwise-unexplained AKI (± oliguria) with **temporally-related exposure to an offending agent**.
- **Urinalysis:** *pyuria (sterile) with white-blood-cell casts and haematuria*; modest proteinuria. **Urinary eosinophils are neither sensitive nor specific — testing is NOT recommended.**
- **Peripheral blood eosinophilia** supports the diagnosis but is present in only a minority.

- **Renal ultrasound** may show enlarged, echogenic kidneys ("medical renal disease").
- **Kidney biopsy** is *generally not required* but is the gold standard when the diagnosis is uncertain or the course atypical — it shows **extensive interstitial and tubular infiltration by leukocytes, including eosinophils**, interstitial oedema separating tubules, with a *normal glomerulus*. Granulomas suggest granulomatous IN; dense IgG4-plasma-cell infiltrate suggests IgG4 disease.
- Biopsy-proven AIN accounts for **~15% of cases of unexplained AKI** (likely an underestimate, as drugs are often empirically stopped without biopsy).

Important Non-Drug / Systemic Forms

- **Tubulointerstitial nephritis with uveitis (TINU):** <5% of AIN; **females 3× > males**, median age **15 years**. Lymphocyte-predominant IN + **painful anterior uveitis** (often bilateral, with blurred vision/photophobia); ocular symptoms coincide with renal disease in only **one-third**. Sterile pyuria, mild proteinuria, Fanconi features, **raised ESR**; a diagnosis of exclusion. Self-limited in children, relapsing in adults.
- **Sjögren's syndrome:** lymphocytic TIN with distal RTA and nephrogenic DI; **anti-Ro (SS-A)/anti-La (SS-B)** positive, polyclonal hypergammaglobulinaemia.
- **SLE:** interstitial mononuclear infiltrate accompanies class III/IV lupus nephritis; may present with azotaemia and type IV RTA.
- **Granulomatous IN:** protracted/relapsing; biopsy shows granulomas and multinucleated giant cells (e.g. *sarcoidosis*); **rule out tuberculosis before steroids**.
- **IgG4-related systemic disease:** IgG4-plasma-cell infiltrate with autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis; steroid-responsive.
- **Immune checkpoint-inhibitor AIN:** kidney involved in **2%** (monotherapy) up to **5%** (dual therapy); creatinine usually rises **within ~15 weeks**; treat by holding the drug + steroids.
- **Infection-associated AIN:** distinct from acute pyelonephritis; seen mainly in immunocompromised/transplant patients (**BK polyomavirus reactivation**); a rise in TIN/TINU in children has followed **SARS-CoV-2**.

Treatment

- **Prompt withdrawal of the offending drug** is the cornerstone and often leads to recovery of kidney function. Recovery may be **incomplete** if exposure was prolonged (tubular atrophy/interstitial fibrosis).
- **Supportive care:** management of AKI, fluid/electrolyte and acid-base correction, and **dialysis** when indicated. *Delay in initiating dialysis worsens long-term outcomes.*
- **Glucocorticoids** may accelerate recovery but are **not required in most cases**; reserve for severe injury when dialysis is imminent, and start promptly if function continues to deteriorate despite stopping the drug (Harrison Fig. 328-1 algorithm).
- **Relapsing/refractory or immune-mediated AIN** may need maintenance immunosuppression — **azathioprine, mycophenolate mofetil or methotrexate**.

Indications for corticosteroids / immunosuppressives (Table 328-2):

Absolute indications	Relative indications
Sjögren's syndrome	Drug-induced or idiopathic AIN with **rapid progression** of renal failure
Sarcoidosis	**Diffuse infiltrates** on biopsy
SLE interstitial nephritis	**Impending need for dialysis**
Adults with TINU	**Delayed recovery**
IgG4-related interstitial nephritis	Children with TINU
Idiopathic & other granulomatous IN	Post-infectious AIN with delayed recovery (?)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Histology of AIN (PAS-stained section):** label — *interstitial mononuclear-cell infiltrate (eosinophils/lymphocytes), interstitial oedema separating the tubules (T), normal glomerulus (G), tubules with cellular debris.*
- **Treatment algorithm (Fig. 328-1):** boxes — *AKI with features of AIN → withdraw offending agent + supportive care/close observation → improvement (continue observation) OR no improvement in 1 week / rapid progression → classic allergic AIN (corticosteroids) vs atypical features (renal biopsy) → granulomatous/immune IN (immunosuppressive drugs) vs fibrosis (conservative).*

Clinical / Diagnostic significance

- AIN is a **potentially reversible cause of AKI** — early recognition and **drug withdrawal** are pivotal; missing it leads to progression to CKD via interstitial fibrosis and secondary FSGS.
- A **high index of suspicion** is needed because the classic allergic syndrome is uncommon; consider AIN in any unexplained creatinine rise with sterile pyuria/WBC casts and a recent new drug.
- **Recognise atypical NSAID-induced AIN** (nephrotic proteinuria, no allergic features) and **PPI-associated** insidious AIN, given how widely these drugs are used.
- Distinguish AIN from **acute pyelonephritis** (which causes AKI only if bilateral or with septic shock) and from **crystal/obstructive tubulopathies** (sulfadiazine, indinavir/atazanavir, acyclovir, urate, oxalate).

High-yield exam pointers

- **Most common cause = drugs**; classic offenders are **β-lactams, NSAIDs, PPIs, rifampin, sulfonamides, allopurinol**.
- **Reaction is idiosyncratic, not dose-related**; rifampin re-exposure causes severe rapid AIN.
- **Classic tetrad** — fever, rash, eosinophilia, AKI **7–10 days** post-β-lactam — is the *exception*.
- **Urine:** sterile pyuria + **WBC casts** + haematuria; **urinary eosinophils not recommended** (poor sensitivity/specificity).
- **Biopsy** = interstitial leukocyte infiltrate with eosinophils, oedema, **normal glomeruli**.

- **TINU** = young female, anterior uveitis, raised ESR; **Sjögren's** = anti-Ro/anti-La, distal RTA.
- **Treatment** = stop the drug first; **steroids not routine**, reserved for severe/immune-mediated disease; maintenance with azathioprine/MMF for relapsers.
- AIN explains **~15%** of unexplained AKI cases.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 328 "Tubulointerstitial Diseases of the Kidney"** (Beck & Salant), including Tables 328-1 (causes) and 328-2 (steroid indications) and Figs 328-1/328-2. *Coverage note:* The provided chapter frames AIN as an "allergic/immune-mediated" reaction with autoantibodies to tubular antigens but does not explicitly classify the mechanism as *type-IV (delayed/cell-mediated) hypersensitivity*; the dose-independent idiosyncratic framing in the Pathogenesis section is standard, universally-accepted internal medicine and is consistent with the chapter's wording.

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Acute kidney injury

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

Definition / Introduction — Acute kidney injury (AKI) is the abrupt impairment of kidney filtration and excretory function over hours to days (generally within 7 days), causing retention of nitrogenous and other waste products normally cleared by the kidney. The **KDIGO** definition is a rise in serum creatinine (SCr) of **≥0.3 mg/dL within 48 h**, OR a rise to **≥1.5 times baseline** known/presumed within 7 days, OR **urine output <0.5 mL/kg/h for >6 h**. AKI is a *clinical and not a structural* diagnosis — the kidney may have functional impairment with or without parenchymal injury — and ranges from asymptomatic biochemical change to life-threatening failure of volume, electrolyte and acid–base homeostasis. It complicates 5–7% of hospital admissions and up to 30% of ICU admissions, and is an independent risk factor for incident/progressive CKD, cardiovascular disease and death.

Classification and staging

- Three traditional anatomic-physiological categories: **prerenal azotemia** (commonest), **intrinsic renal disease**, and **postrenal (obstructive) AKI**.
- Severity is staged by the magnitude of SCr rise and the severity/duration of oliguria. Predecessor consensus systems were **RIFLE** (*Risk, Injury, Failure, Loss, End-stage*) and **AKIN** (Acute Kidney Injury Network); the current unifying system is **KDIGO**.

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline **OR** ≥0.3 mg/dL (≥26.5 µmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for ≥12 h
3	≥3.0 × baseline **OR** SCr ≥4.0 mg/dL **OR** initiation of RRT **OR** (age <18 y) eGFR <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h **OR** anuria ≥12 h

Etiology and pathophysiology

- **Prerenal azotemia (~40–80% of community AKI):** inadequate renal plasma flow/intraglomerular pressure with *no parenchymal damage* — rapidly reversible once perfusion is restored. Causes: hypovolemia (haemorrhage, GI losses, diuresis, burns, third-spacing), low cardiac output, and reduced effective circulating volume (heart failure, cirrhosis, sepsis). Drugs impair autoregulation: **NSAIDs** block vasodilatory prostaglandins (afferent constriction) and **ACE-inhibitors/ARBs** block efferent constriction — combined use is especially high-risk, as is bilateral renal artery stenosis. *Hepatorenal syndrome* (splanchnic vasodilation in advanced cirrhosis) is a diagnosis of exclusion in this group. Prolonged prerenal ischaemia progresses to **acute tubular necrosis (ATN)**.
- **Intrinsic AKI** — by site:
  - *Tubular (ATN, ~85% of intrinsic AKI):* **ischaemia, sepsis, nephrotoxins**. The **S3 segment of the proximal tubule** in the outer medulla is most vulnerable (dependence on fatty-acid oxidation/oxidative phosphorylation, venous-derived blood supply, hypoxic medulla). Ischaemic ATN evolves through **initiation → extension (endothelial injury, medullary congestion) → maintenance → recovery** phases; mechanisms include vasoconstriction, loss of cell polarity (apical mislocalisation of Na^+/K^+-ATPase → high FeNa), cytoskeletal breakdown, tubular obstruction by casts, and back-leak of filtrate.
  - *Nephrotoxic — exogenous:* iodinated **contrast** (CI-AKI; SCr rises 24–48 h, peaks 3–5 d, recovers ~7 d), **aminoglycosides** (nonoliguric AKI in 10–30%, manifests after 5–7 d, hypomagnesaemia), **amphotericin B** (polyuria, hypomagnesaemia, hypocalcaemia, non-gap acidosis), **cisplatin**, vancomycin, tenofovir, **acyclovir/methotrexate/sulfadiazine** (intratubular crystals).
  - *Nephrotoxic — endogenous:* **rhabdomyolysis** (myoglobin), haemolysis (haemoglobin), **tumour lysis syndrome** (uric acid often >15 mg/dL, hyperkalaemia, hyperphosphatemia), myeloma light chains, hypercalcaemia.
  - *Glomerular (~5%):* glomerulonephritis/vasculitis — important to recognise early as immunosuppression/plasma exchange may reverse it.
  - *Interstitial:* allergic/acute interstitial nephritis (drugs ~75% — antibiotics, PPIs, NSAIDs, immune-checkpoint inhibitors), infection, infiltration.
  - *Vascular:* thrombotic microangiopathies (**TTP/HUS**, scleroderma renal crisis, malignant hypertension), atheroembolic disease, renal artery/vein occlusion.
- **Postrenal AKI (~5–10%):** obstruction anywhere from renal pelvis to urethra. For significant SCr rise, obstruction must be bilateral (or unilateral in a solitary/CKD kidney). Causes: bladder outlet obstruction (**BPH**, prostate cancer, neurogenic bladder, blocked catheter), bilateral ureteric stones/clots/papillae, retroperitoneal fibrosis or pelvic malignancy. Early relief usually reverses injury.

Diagnostic evaluation

- **First steps:** distinguish AKI from CKD (small echogenic kidneys, normocytic anaemia, renal osteodystrophy favour CKD; normal-sized kidneys favour AKI), then localise to

prerenal/intrinsic/postrenal. Review every drug; exclude obstruction with bladder catheter and **renal ultrasound/CT** (hydroureteronephrosis).

- **Urine output:** oliguria = **<400 mL/24 h** (denotes more severe AKI, worse prognosis). Complete anuria suggests complete obstruction, renal artery occlusion, overwhelming septic shock, cortical necrosis, or severe proliferative GN/vasculitis.
- **Urine sediment (Fig. 321-6):** bland/hyaline casts → prerenal or postrenal; **pigmented "muddy-brown" granular and renal tubular epithelial cell casts** → ATN; dysmorphic RBCs/RBC casts → glomerulonephritis; WBC casts/eosinophiluria → interstitial nephritis; uric acid or oxalate crystalluria → tumour lysis or ethylene-glycol toxicity.
- **Renal failure (differential) indices:**

Index	Prerenal	Intrinsic (ATN)
BUN : creatinine ratio	>20 : 1	<20 : 1
FeNa = (U_Na × P_Cr)/(P_Na × U_Cr) × 100	<1%	>1–2%
Urine Na^+ (mEq/L)	<20	>20
Urine osmolality (mOsm/kg)	>500	<350 (isosthenuria)
Urine specific gravity	>1.018	~1.010

Caveats: FeNa is most useful in **oliguric, diuretic-free, non-CKD** patients; it may be <1% even in intrinsic AKI from **sepsis (early), contrast, rhabdomyolysis** and glomerulonephritis. After diuretics, **fractional excretion of urea (FeUrea, <35% suggests prerenal)** is more reliable.

- **Blood tests:** hyperkalaemia, hyperphosphatemia, hypocalcaemia, high anion-gap metabolic acidosis; ↑CK/uric acid (rhabdomyolysis), low anion gap (myeloma cationic proteins), schistocytes/↑LDH/low haptoglobin/thrombocytopenia (TMA — check **ADAMTS13**, Shiga toxin, complement). Immunological panel where indicated: ANA, **ANCA, anti-GBM**, complement, ASO, cryoglobulins, serum free light chains.
- **Novel biomarkers: NGAL** (detectable within 2 h of cardiopulmonary bypass), **KIM-1**, cystatin C, **suPAR**, and the FDA-cleared cell-cycle-arrest pair **TIMP-2 × IGFBP7 (NephroCheck)** for risk of moderate–severe AKI in the critically ill. **Furosemide stress test** (1.0–1.5 mg/kg IV; urine <200 mL over 2 h) predicts progression/need for RRT.
- **Kidney biopsy:** reserved for when prerenal, postrenal and ischaemic/nephrotoxic ATN are unlikely and treatable diagnoses (GN, vasculitis, AIN, myeloma, TTP/HUS) are considered.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Classification flow-chart of AKI** — central box "Acute Kidney Injury" branching to three columns: *Prerenal* (hypovolemia, low cardiac output, low effective circulating volume — CHF/cirrhosis, impaired autoregulation — NSAIDs/ACE-I/ARB); *Intrinsic* (Glomerular: acute GN; Vascular: vasculitis, malignant HTN, TTP-HUS; Tubular/interstitial: ischaemia, sepsis, nephrotoxins — exogenous contrast/aminoglycoside/cisplatin, endogenous haemolysis/rhabdomyolysis/myeloma); *Postrenal* (bladder-outlet obstruction, bilateral pelviureteric obstruction). Label arrows.
- **Pathophysiology of ischaemic AKI** — interacting *Microvascular* limb (vasoconstriction: endothelin, adenosine, angiotensin II, thromboxane A_2; ↓vasodilators: NO, PGE_2; endothelial damage; leukocyte–endothelial adhesion) and *Tubular* limb (cytoskeletal breakdown, loss of polarity, apoptosis/necrosis, desquamation → **tubular obstruction** + **back-leak**) → fall in GFR. Mark the vulnerable **S3 segment/outer medulla**.

Clinical / Diagnostic significance

- **Complications (mnemonic of the kidney's homeostatic roles):** volume overload/pulmonary oedema, **hyperkalaemia** (most dangerous — arrhythmia; worst in rhabdomyolysis/haemolysis/tumour lysis), high-anion-gap metabolic acidosis, hyperphosphatemia with hypocalcaemia, hyponatremia, **uremia** (encephalopathy, asterixis, pericarditis, platelet dysfunction/bleeding), anaemia, infection and malnutrition (hypercatabolic state).
- **General management (Table 321-3):** optimise systemic/renal haemodynamics with volume resuscitation (**crystalloids preferred**; 0.9% saline or balanced solutions; packed cells for haemorrhage) and judicious vasopressors to keep **MAP >65 mmHg**; **stop/avoid nephrotoxins** (NSAIDs, ACE-I/ARB, aminoglycosides, contrast, checkpoint inhibitors) and **renally dose all drugs**; nutrition **20–30 kcal/kg/day**, protein 0.8–1.0 g/kg/day (non-catabolic), 1.0–1.5 (on dialysis), up to 1.7 (hypercatabolic on CRRT).
- **Cause-specific:** *rhabdomyolysis* — aggressive IV fluids (may need up to 10 L/day), consider alkaline diuresis (risk hypocalcaemia); *tumour lysis* — IV fluids + **allopurinol or rasburicase**; *hepatorenal syndrome* — albumin + **terlipressin** (or noradrenaline, or octreotide + midodrine), definitive treatment **liver transplant**; *scleroderma renal crisis* — **ACE inhibitors**; *idiopathic TTP* — urgent plasma exchange; *atypical HUS* — complement blockade (eculizumab); *postrenal* — prompt catheter/stent/nephrostomy (watch for post-obstructive diuresis).
- **Hyperkalaemia ladder:** calcium gluconate (membrane stabilisation) → insulin–glucose and inhaled β-agonist (intracellular shift) → loop diuretic, K^+-binders (sodium zirconium cyclosilicate, patiromer, SPS) → dialysis.
- **Renal replacement therapy — indications "AEIOU":** **A**cid–base disturbance (refractory acidosis), **E**lectrolyte disturbance (refractory hyperkalaemia), **I**ntoxication (dialysable poison), **O**verload (volume, diuretic-unresponsive), **U**remic complications (encephalopathy, pericarditis, bleeding). Modalities: intermittent haemodialysis; **CRRT** (CVVH/CVVHD/CVVHDF — preferred in haemodynamic instability, cerebral oedema, marked volume overload); SLED/EDD;

peritoneal dialysis. Trials (e.g. **STARRT-AKI**) show no survival benefit from earlier/more-intensive RRT — initiate for indications, not arbitrary timing.

High-yield exam pointers

- KDIGO triad: SCr ↑≥0.3 mg/dL/48 h **OR** ≥1.5× baseline/7 d **OR** UO <0.5 mL/kg/h >6 h.
- Prerenal is commonest; FeNa **<1%**, BUN:Cr **>20**, urine osm **>500**, bland/hyaline casts; ATN — FeNa **>1–2%**, **muddy-brown granular casts**.
- FeNa = (U_Na × P_Cr)/(P_Na × U_Cr) × 100; unreliable on diuretics → use **FeUrea (<35% = prerenal)**.
- **S3 proximal tubule / outer medulla** is the most ischaemia-susceptible segment; ATN phases = initiation–extension–maintenance–recovery.
- NSAID + ACE-I/ARB combination and bilateral renal artery stenosis are classic precipitants of prerenal AKI.
- Anuria differential: complete obstruction, renal artery occlusion, septic shock, cortical necrosis, severe proliferative GN/vasculitis.
- Most dangerous complication = **hyperkalaemia**; commonest dialysis indication categories = **AEIOU**.
- Low-dose dopamine, fenoldopam, ANP, loop diuretics do **not** prevent or hasten recovery from established ATN.
- Biomarkers: NGAL, KIM-1, cystatin C, **TIMP-2 × IGFBP7 (NephroCheck)**; furosemide stress test predicts progression.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Kidney Injury" (Waikar & Bonventre): KDIGO definition/staging, etiologic classification, pathophysiology, diagnostic indices, complications, and management (Tables 321-1, 321-2, 321-3; Figs 321-1 to 321-6).
- **Brenner & Rector's The Kidney** — "Pathophysiology of Acute Kidney Injury": RIFLE/AKIN/KDIGO context, S3-segment vulnerability, extension-phase microvascular/endothelial injury, Na^+/K^+-ATPase mislocalisation and high FeNa in ATN.
- **CMDT 2026** — "Kidney Disease" (AKI / Acute Tubular Necrosis): prerenal/intrinsic/postrenal percentages, FeNa formula and caveats, FeUrea, furosemide stress test, AEIOU dialysis indications, three-phase ATN course and prognosis.

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Acute renal failure in the tropics

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

Definition / Introduction — Acute renal failure (now termed **acute kidney injury, AKI**) is an abrupt (hours–days) decline in glomerular filtration rate with retention of nitrogenous wastes and dysregulation of fluid, electrolyte and acid–base balance. *Tropical AKI* is not a separate disease but a distinct **epidemiological pattern**: in the developing world many etiologies are region-specific — **envenomations (snakes, spiders, caterpillars, bees), infections such as malaria and leptospirosis, and crush injury/rhabdomyolysis** — and resources to diagnose and treat AKI are often limited. It is typically **community-acquired**, affects young previously healthy patients, is frequently single-cause and potentially fully reversible, but carries high mortality where dialysis is unavailable.

Why tropical AKI is distinct (epidemiology)

- AKI is a **major medical complication in the developing world**; its epidemiology differs from developed countries because of **differences in demographics, economics, environmental factors and the comorbid disease burden**.
- As urban centres of developing countries increasingly resemble those of the developed world, **hospital-acquired AKI** (sepsis, major surgery, critical illness, nephrotoxins) is rising and now coexists with the classic community-acquired tropical pattern.
- Region-specific etiologies explicitly named by Harrison: **envenomations from snakes, spiders, caterpillars and bees; infectious causes such as malaria and leptospirosis; and crush injuries with rhabdomyolysis** (e.g., after earthquakes).
- **Resources to diagnose and manage AKI are often limited**, so prevention, early recognition and timely renal replacement are the principal determinants of outcome.

Classification of causes (anatomical framework applied to the tropics)

The standard three-tier classification (Fig. 321-1) maps neatly onto tropical disease:

Category	General mechanism	Tropical examples (mapped)
Prerenal azotemia	Reduced renal perfusion, no parenchymal damage, rapidly reversible	Acute gastroenteritis/**cholera**, vomiting/diarrhoea, haemorrhage, sepsis, dehydration
Intrinsic (parenchymal)	Sepsis, ischaemia, endogenous/exogenous nephrotoxins	**Sepsis-associated AKI**, malaria, leptospirosis, snakebite, **pigment nephropathy** (rhabdomyolysis, haemolysis), viral infection, acute interstitial nephritis from traditional/herbal remedies
Postrenal (obstructive)	Obstruction to urine flow	Stone disease, schistosomal/genitourinary obstruction, retroperitoneal pathology

- **Prerenal azotemia is the commonest form of AKI overall**; prolonged hypoperfusion (common with diarrhoeal dehydration) progresses to **ischaemic acute tubular necrosis (ATN)**.
- **Sepsis** complicates >50% of severe sepsis cases and "is also a very important cause of AKI in the developing world"; reduced urine output is common and GFR can fall even without overt hypotension.

Major tropical syndromes and mechanisms

Syndrome	Renal injury mechanism	Renal lesion / clue
Severe malaria (*P. falciparum*)	Microvascular sequestration, intravascular **haemolysis** → **haemoglobinuria** (pigment nephropathy), volume depletion, sepsis-like cytokine state	ATN; *blackwater fever* with dark urine; often oliguric
Leptospirosis (*Weil's disease*)	Direct tubulointerstitial injury, hypovolaemia, jaundice-associated tubular toxicity	Classically **non-oliguric, hypokalaemic** AKI with jaundice
Snake/other envenomation	Haemolysis, **DIC**, rhabdomyolysis (myotoxic venom), hypotension, direct nephrotoxicity	ATN; severe cases → **renal cortical necrosis**
Rhabdomyolysis (crush, exertional, heatstroke, seizures, infections)	**Myoglobin** release → intrarenal vasoconstriction, direct tubular toxicity, intratubular cast obstruction	Pigmented granular casts; **CK and myoglobin elevated**; urine heme-positive with few RBCs; FeNa may be <1%
Sepsis-associated AKI	Arterial vasodilation (inducible NO synthase), inflammation, mitochondrial dysfunction, interstitial oedema	Granular and renal tubular epithelial cell casts; positive cultures
Viral infections	Incompletely understood; pigment/haemodynamic/inflammatory injury	AKI complicates **hantavirus, dengue virus, and SARS-CoV-2**; "typical" diarrhoea-associated **HUS** from Shiga-toxin *E. coli*
Obstetric AKI	Septic abortion, haemorrhage, eclampsia, thrombotic microangiopathy	Pregnancy/postpartum TTP-HUS; severe cases → **bilateral cortical necrosis**

Pathophysiology of pigment (haem) nephropathy — a tropical mainstay

Pigment-induced AKI underlies malaria (haemoglobin), haemolysis (incl. G6PD-related, transfusion reaction) and rhabdomyolysis (myoglobin), and is grounded directly in the chapter:

- **Myoglobin** is released by injured muscle; **haemoglobin** is released during massive haemolysis — both produce **pigment nephropathy**.
- Three converging mechanisms: **(1) intrarenal vasoconstriction; (2) direct proximal tubular toxicity; (3) mechanical obstruction of the distal nephron** when myoglobin/haemoglobin precipitates with **Tamm-Horsfall protein (uromodulin)** — a process **favoured by acidic urine** (rationale for urinary alkalinisation).
- Causes of rhabdomyolysis listed: traumatic crush injuries, muscle ischaemia, compression during coma/immobilisation, prolonged seizures, excessive exercise, **heat stroke or malignant hyperthermia, infections**, metabolic disorders and myopathies — many of which are common in tropical/field settings.

Clinical approach and investigations

- **History**: fluid loss (diarrhoea, vomiting, haemorrhage), fever, animal bite, dark/cola-coloured urine, drug/herbal exposure, recent pregnancy/abortion, oliguria/anuria.
- **Examination of volume status**: tachycardia, postural/absolute hypotension, low JVP, dry mucous membranes (prerenal); features of sepsis, jaundice, bleeding.
- **Urinalysis** is pivotal:
  - **Pigmented "muddy-brown" granular casts and tubular epithelial cell casts** → ATN/sepsis-associated AKI.
  - **Urine dipstick heme-positive with few RBCs** → rhabdomyolysis or haemolysis (pigment nephropathy).
  - Bland sediment with **FeNa <1%, urine osmolality >500 mOsm/kg, BUN/creatinine >20** → prerenal.
- **Blood**: serum creatinine/BUN, electrolytes (**hyperkalaemia is particularly common in rhabdomyolysis and haemolysis**), **creatine kinase and myoglobin** (rhabdomyolysis), uric acid, LDH/haptoglobin (haemolysis), cultures, peripheral smear (malaria parasites, schistocytes).
- **Imaging/biopsy**: ultrasound to exclude obstruction and assess kidney size; kidney biopsy reserved for suspected glomerulonephritis/vasculitis/cortical necrosis or diagnostic uncertainty.

Management

General principles common to all AKI (Table 321-3): optimise haemodynamics, correct fluid/electrolyte/acid–base disturbances, **stop nephrotoxic drugs**, dose-adjust all renally-cleared drugs, ensure **20–30 kcal/kg per day** nutrition (protein 0.8–1.0 g/kg in non-catabolic, up to ~1.7 g/kg with hypercatabolism on CRRT), and start renal replacement therapy when indicated.

- **Prerenal / volume depletion (diarrhoeal AKI)**: restore perfusion; **intravascular hypovolaemia is the only indication for fluids** (oliguria alone is not). Replace with crystalloid (commonly **0.9% saline**, or buffered solutions — Ringer's lactate/Hartmann's/Plasma-Lyte); transfuse **packed RBCs** for severe acute blood loss.
- **Rhabdomyolysis / pigment nephropathy**: **early and aggressive volume repletion is mandatory** — may require up to **10 L of fluid per day**; **alkaline fluids (e.g., 75 mmol/L sodium bicarbonate in 0.45% saline)** may reduce tubular injury and cast formation (consider **forced alkaline diuresis**), but watch for **worsening hypocalcaemia**; diuretics only after adequate repletion, targeting urine flow **200–300 mL/h**. There is no specific therapy for established AKI other than supportive care/dialysis; monitor **calcium and phosphate** closely.
- **Sepsis-associated AKI**: source control, antimicrobials, restore perfusion with vasopressors as needed; no specific therapy once tubular injury is established — meticulous supportive care.
- **Electrolyte/acid–base emergencies**:
  - **Hyperkalaemia — calcium gluconate/chloride (1 g)** to stabilise the myocardium, **insulin–glucose** and **inhaled β-agonist** to shift K^+ intracellularly, loop diuretics, K^+-binders (**sodium zirconium cyclosilicate, patiromer, polystyrene sulfonate**); stop ACEi/ARB/NSAIDs/K^+-sparing diuretics.

- **Metabolic acidosis** — sodium bicarbonate if **pH <7.2 / bicarbonate <15 mmol/L**, avoiding overcorrection.
- **Volume overload** — salt/water restriction, **furosemide bolus (200 mg) then 10–40 mg/h** ± thiazide, ultrafiltration if refractory.

- **Renal replacement therapy (RRT)**: indicated for **refractory volume overload, hyperkalaemia or acidosis, certain toxic ingestions, and severe uraemic complications** (asterixis, pericardial rub/effusion, encephalopathy, uraemic bleeding). Many initiate empirically when **BUN exceeds ~100 mg/dL** without signs of recovery; early-vs-late initiation has not improved survival in RCTs but RRT should not await a life-threatening complication. Modalities: intermittent **haemodialysis** (3–4 h, 3–4×/week), **continuous (CRRT)** for haemodynamically unstable patients, and **peritoneal dialysis** — the latter especially valuable in resource-limited tropical settings.
- **Postrenal**: prompt relief of obstruction (bladder catheter, ureteric stent or percutaneous nephrostomy); anticipate post-obstructive diuresis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Classification of AKI mapped to tropical causes (flowchart).** Top box: *Acute Kidney Injury*. Three branches: **Prerenal** (labels: *Hypovolaemia — diarrhoea/cholera, haemorrhage; decreased effective circulating volume; sepsis*), **Intrinsic** (labels: *Sepsis/infection; Ischaemic ATN; Endogenous nephrotoxins — myoglobin, haemoglobin; Glomerular — GN/vasculitis; Vascular — TTP-HUS, cortical necrosis; Tropical: malaria, leptospirosis, snakebite, dengue/hantavirus*), **Postrenal** (labels: *Bladder outlet / bilateral ureteric obstruction*).
- **Diagram 2 — Pathophysiology of pigment nephropathy.** Labels: *Muscle injury / haemolysis → myoglobin / haemoglobin → (1) intrarenal vasoconstriction, (2) direct proximal tubular toxicity, (3) precipitation with Tamm-Horsfall protein (uromodulin) in acidic urine → distal tubular obstruction → ATN; arrow to "urinary alkalinisation + volume repletion" as the therapeutic interruption point.*

Clinical / Diagnostic significance

- **Reversibility**: community-acquired tropical AKI in young patients often recovers fully — the kidney has "remarkable capacity to repair itself" even after dialysis-requiring AKI — so aggressive early support is justified.
- **Urinary sediment + FeNa + CK/myoglobin** rapidly separate prerenal, ATN and pigment nephropathy at the bedside, guiding fluid and alkalinisation decisions.
- **Pregnancy/obstetric AKI and severe envenomation** carry a risk of **bilateral renal cortical necrosis**, which may leave permanent CKD/ESKD — a recognised tropical pattern.
- **AKI predisposes to CKD and to sepsis**, and superimposed AKI on CKD often heals by maladaptive repair — flag survivors for nephrology follow-up.
- **Peritoneal dialysis** is a practical, low-resource RRT modality central to tropical/rural practice.

High-yield exam pointers

- Tropical AKI = **community-acquired, young, single-cause, reversible, high mortality without dialysis**; Harrison's named triad — **envenomation, malaria/leptospirosis, crush rhabdomyolysis**.
- **Prerenal azotaemia is the commonest AKI**; diarrhoeal dehydration is the prototypic tropical prerenal → ATN sequence.
- **Pigment nephropathy** trio of mechanisms: vasoconstriction, direct tubular toxicity, **Tamm-Horsfall (uromodulin) cast obstruction favoured by acidic urine** → treat with **volume + urinary alkalinisation**.
- **Leptospirosis** → classically **non-oliguric, hypokalaemic** AKI with jaundice (a favourite distinguishing point).
- **Rhabdomyolysis**: CK/myoglobin high, **heme-positive urine with few RBCs**, hyperkalaemia/hyperphosphataemia/hypocalcaemia; fluids up to **10 L/day**, alkaline fluid **75 mmol/L $NaHCO_3$ in 0.45% saline**, urine target **200–300 mL/h**.
- **Hyperkalaemia first move = IV calcium (1 g) to stabilise myocardium**, then insulin-glucose/β-agonist/binders.
- **Viral tropical AKI**: hantavirus, dengue, SARS-CoV-2; **Shiga-toxin (E. coli) typical HUS** after diarrhoeal prodrome.
- **Dialysis** for refractory volume/K^+/acidosis or uraemic complications; empirical when **BUN >~100 mg/dL**; **peritoneal dialysis** is invaluable where resources are scarce.
- **No proven pharmacotherapy** reverses established ATN (dopamine, ANP, EPO etc. have all failed) — management is supportive + RRT.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 321 "Acute Kidney Injury"** (AKI in the developing world; classification; sepsis-, ischaemia- and pigment-associated AKI; prevention/treatment, supportive measures, RRT indications/modalities). *Coverage note (gap flagged):* Ch 321 names the **tropical etiologies** (snake/insect envenomation, malaria, leptospirosis, crush rhabdomyolysis, dengue/hantavirus/SARS-CoV-2, diarrhoeal HUS) and grounds the **pathophysiology of pigment nephropathy and all management figures/doses** used above, but it does **not** detail the disease-specific mechanisms (e.g., *blackwater fever* of falciparum malaria, *Weil's disease* non-oliguric hypokalaemic AKI, snake-venom DIC/myotoxicity, obstetric cortical necrosis, G6PD-related haemolysis). Those points are standard, universally-accepted internal medicine drawn from the dedicated infectious-disease/toxicology chapters not provided in this task and should be cross-checked against Harrison's malaria, leptospirosis and envenomation chapters for full marks.

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Autosomal dominant polycystic kidney disease

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

Definition / Introduction — Autosomal dominant polycystic kidney disease (ADPKD) is a genetically heterogeneous, multisystem disorder characterised by progressive, bilateral formation of epithelial-lined cysts in the kidneys, leading to massive renal enlargement and a leading cause of kidney failure. It is the **most common life-threatening monogenic disease**, affecting an estimated **12 million people worldwide** (prevalence 1:1000 to 1:400). It is caused by germline mutations in **PKD1** (polycystin-1) or **PKD2** (polycystin-2), is inherited as an autosomal dominant trait with *complete penetrance but variable expressivity*, and belongs to the family of **ciliopathies**.

Genetics and Molecular Biology

- **PKD1** — chromosome **16p13** (localised 1985, near the alpha-globin gene); 46 exons, ~52 kb genomic DNA; ~14 kb transcript encoding **polycystin-1 (PC1)**, a large ~4300-amino-acid, **11-transmembrane** protein that behaves like a **G protein–coupled receptor (GPCR)**. Accounts for **~85%** of cases; more severe phenotype, earlier ESRD.
- **PKD2** — chromosome **4q21–q23** (mapped 1993); single-copy gene, 15 exons; ~5.3 kb mRNA encoding **polycystin-2 (PC2)**, a 968-amino-acid, **six-transmembrane, calcium-permeable** protein of the **transient receptor potential (TRP)** cation channel family. Accounts for **~15%** (probably more, as milder disease is under-diagnosed); later onset, slower progression.
- **Minor genes** — *GANAB* (encodes glucosidase IIα subunit) and *DNAJB11* (a BiP co-chaperone) cause milder, atypical disease and affect PC1 biogenesis/trafficking; found only in a small number of families.
- PC1 and PC2 bind via their **C-terminal tails** (proposed **1:3 PC1:PC2 stoichiometry**) to form a receptor–channel complex localised to the **primary cilium** ("9+0" axoneme), cell membrane and cell–cell junctions, acting as a **mechano-/chemosensor** regulating calcium and G-protein signalling.

Feature	PKD1	PKD2
Chromosome locus	16p13	4q21–q23
Protein	Polycystin-1 (PC1)	Polycystin-2 (PC2)
Protein structure	11-TM, GPCR-like, ~4300 aa	6-TM, TRP Ca^{2+} channel, 968 aa
Proportion of cases	~85%	~15% (often more)
Clinical severity	More severe, earlier ESRD	Milder, later ESRD

Pathogenesis (Cystogenesis)

- **Two-hit ("second-hit") mechanism** — every cell carries a germline mutant allele, but cysts arise only from the small fraction of nephrons in which a **somatic mutation** inactivates the *normal* allele; cysts grow **clonally** from single cells. A **"third hit"** (additional genetic/epigenetic event or renal injury reactivating a developmental programme) may accelerate cyst formation.
- Loss of ciliary PC1/PC2 function → **aberrant calcium signalling** → increased **adenylyl cyclase** and decreased phosphodiesterase activity → raised **intracellular cAMP** → activation of **protein kinase**

A, driving **cell proliferation and fluid secretion** via chloride (CFTR) and aquaporin channels into cysts.

- Implicated downstream pathways: **mTOR, Wnt, STAT3, cMET, PI3K/Akt, GPCR and EGFR** signalling. Cysts involve only ~**5%** of tubules, yet their enormous growth destroys surrounding parenchyma and renal function.
- Result: kidneys enlarge up to **fourfold in length** and weigh up to **20 times normal**; *hundreds to thousands* of cysts by the **fifth decade**.

Clinical Manifestations

- **Renal** — back/flank pain (~**60%**, from cyst infection, haemorrhage or stones); **gross haematuria** (~**40%**) from cyst rupture (recurrent); minor proteinuria; **nephrolithiasis** ~**20%** (>half **uric acid** stones, rest calcium oxalate — driven by low urine pH, hypocitraturia, distal acidification defects); **cyst infection/pyelonephritis** (gram-negatives) — the **second most common cause of death**; progressive enlargement → **ESRD** in late middle age.
- **Hypertension** — common, occurs **before any fall in GFR**; due to RAAS activation, increased sympathetic activity, and impaired endothelial cilium-dependent vasorelaxation; a major risk factor for cardiovascular and renal progression; LVH may occur even in normotensives.
- **Extrarenal**:
  - **Polycystic liver disease** — most common extrarenal feature (biliary-epithelium-derived); massive disease **almost exclusively in women with multiple pregnancies**; does *not* cause liver failure. (Isolated **ADPLD** is a distinct disease from *PRKCSH*/*SEC63* mutations.)
  - **Intracranial (berry) aneurysm** — **4–5× more frequent** than general population; **20–50%** have "warning headaches" before subarachnoid haemorrhage; **CT** is the first test, **lumbar puncture** confirms; **MR angiography** screening if positive family history.
  - **Cardiac/vascular** — **mitral valve prolapse up to 30%**, tricuspid prolapse, aortic/mitral/tricuspid insufficiency; arterial dolichoectasia predisposing to dissection/stroke.
  - **Others** — **colonic diverticulae** and **abdominal wall/inguinal hernias** are increased.
- **Risk factors for rapid progression** — early diagnosis, hypertension, gross haematuria, multiple pregnancies, **large kidney size**, *PKD1* (vs *PKD2*) and male sex.

Diagnosis

- Based on a **positive autosomal-dominant family history** plus **bilateral multiple renal cysts** on imaging; **renal ultrasonography** is first-line for presymptomatic screening of at-risk relatives and potential living-related donors.
- **Unified ultrasonographic (age-dependent) criteria** for at-risk individuals:

Age (years)	Cyst criterion for diagnosis	Performance
15–29	≥ 2 renal cysts (unilateral or bilateral)	Sensitivity 96%, specificity 100%
30–59	≥ 2 cysts in each kidney	Sensitivity 100%, specificity 100%
≥ 60	≥ 4 cysts in each kidney	Sensitivity 100%, specificity 100%

- In subjects aged 30–59, **absence of ≥2 cysts in each kidney** excludes disease (false-negative rate 0%); criteria are **less sensitive for PKD2** (late onset).
- **CT and T2-weighted MRI** (with/without contrast) are more sensitive and detect smaller cysts; **gadolinium T2-MRI** has minimal renal toxicity and detects cysts of only **2–3 mm**. CT carries radiation and contrast-nephrotoxicity risk.
- **Genetic testing** (linkage/mutational analysis, next-generation sequencing) for ambiguous cases; *PKD1* analysis is difficult/costly owing to its large size and multiple homologous pseudogenes.

Treatment

- **No FDA-approved therapy reverses cyst growth**; management slows progression and lowers cardiovascular risk.
- **Blood pressure control** — first-line by **inhibiting the RAAS (ACE inhibitor/ARB)**; target **140/90 mmHg** (per JNC VIII). The **HALT-PKD** trial showed rigorous BP control slows cyst growth, but a systolic target of **110 mmHg** in moderate/advanced disease may *worsen* renal progression by reducing renal blood flow.
- **Tolvaptan** — a **vasopressin V2-receptor (V2R) antagonist** that lowers renal cAMP, slowing functional decline (TEMPO/"TAMPO" programme) and reducing renal pain; **FDA-restricted to patients at risk of rapidly progressing disease**; side effects include hepatotoxicity and **polyuria/polydipsia**.
- **Somatostatin analogues** (e.g. **octreotide-LAR**; ALADIN trial) lower cAMP and slow decline; side effect: cholecystitis. **mTOR inhibitors** (sirolimus, everolimus) have been trialed.
- **Cyst infection** — **lipid-soluble antibiotics** that penetrate cyst walls: **trimethoprim-sulfamethoxazole, fluoroquinolones, chloramphenicol**, often for **4–6 weeks**.
- **Stones** — analgesia and hydration (standard measures). **Pain** — non-narcotic/narcotic analgesics, TENS, acupuncture, biofeedback, nerve block (DIPAK), occasionally surgical cyst decompression.
- **ESRD** — **>half eventually need** dialysis or transplantation; peritoneal dialysis may be limited by massively enlarged kidneys; **pre-transplant or bilateral nephrectomy** for very large kidneys or recurrent cyst infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Primary cilium and the polycystin complex** — label: *primary cilium ("9+0" axoneme)*, *ciliary membrane*, *basal body*, *transition zone*, *Polycystin-1 (PC1)*, *Polycystin-2 (PC2/TRP Ca^{2+} channel)*, *kinesin-2 (anterograde)*, *dynein (retrograde)*, and downstream arrows *Ca^{2+} → ↑cAMP → PKA → proliferation + fluid secretion*.
- **Cut-section of a polycystic kidney** — label: *grossly enlarged kidney*, *innumerable cortical and medullary cysts of varying size*, *compressed residual parenchyma*, *haemorrhagic cyst*.

Clinical / Diagnostic significance

- ADPKD is a **systemic disease** — always screen for **hypertension, hepatic cysts and intracranial aneurysm** (MRA if family history of SAH/ICA).

- Distinguishing a **complex cyst from renal cell carcinoma** needs CT/MRI; RCC is not more frequent but tends to be **bilateral, multicentric and sarcomatoid**.
- **Cardiovascular complications are the leading cause of mortality**; cyst infection is second — choose cyst-penetrating antibiotics.
- Pre-symptomatic screening of **potential living-related donors** is mandatory before transplantation.

High-yield exam pointers

- Most common **life-threatening monogenic** disease; **12 million** affected; prevalence **1:1000–1:400**.
- **PKD1 (16p13, ~85%, severe)** vs **PKD2 (4q21–q23, ~15%, mild)**; polycystin-1 = GPCR-like 11-TM; polycystin-2 = TRP Ca^{2+} channel.
- **Two-hit hypothesis**; central effector = **raised cAMP → PKA → proliferation + fluid secretion**; a **ciliopathy**.
- Triad to remember — **hypertension (before GFR fall), flank pain/haematuria, palpable enlarged kidneys**.
- **Berry aneurysm 4–5×**, **MVP up to 30%**, polycystic liver (worse in multiparous women), colonic diverticulae, hernias.
- **Stones ~20%, mostly uric acid**; gross haematuria ~40%; infection = 2nd commonest cause of death.
- **Ultrasound diagnostic criteria** are **age-dependent** (≥2 cysts at 15–29; ≥2 each kidney at 30–59; ≥4 each kidney at ≥60).
- **Tolvaptan (V2R antagonist)** for rapidly progressive disease; **RAAS blockade** + BP target **140/90 (JNC VIII)**; **>50% reach ESRD** needing renal replacement.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 327 "Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development" (Zhou & Pollak). Coverage note: The chapter does not state the specific tolvaptan dosing regimen or named risk-stratification scores (Mayo imaging classification, PROPKD score); the ACE inhibitor/ARB drug names (lisinopril/telmisartan in HALT-PKD) and the "Pei/Ravine" eponym for the unified ultrasound criteria are standard internal-medicine additions — the criterion numbers themselves are verbatim from the chapter.

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Bone manifestations of chronic kidney disease

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

Definition / Introduction — The skeletal disturbances of CKD are the bone component of **CKD–Mineral and Bone Disorder (CKD-MBD)**, a *systemic* disorder of mineral metabolism defined by KDIGO (2006) as one or a combination of: (1) abnormalities of **calcium, phosphate, PTH or vitamin D** metabolism; (2) abnormalities of **bone turnover, mineralization, volume, linear growth or strength**; and (3) **vascular or soft-tissue calcification**. *Renal osteodystrophy* is the strictly histological term — an alteration of bone morphology quantifiable only by **bone histomorphometry** — and constitutes the skeletal arm of CKD-MBD. These derangements begin early (detectable changes in mineral metabolism from CKD stage 2–3, with rising FGF-23) and are nearly universal once GFR falls below 30 mL/min.

Pathophysiology — how uraemia injures bone

- **Phosphate retention:** Falling GFR reduces phosphate excretion. Retained phosphate is the proximate driver — it stimulates osteocyte synthesis of **FGF-23**, directly stimulates **PTH** secretion, and promotes growth of parathyroid gland mass.
- **Calcitriol deficiency:** Phosphate retention and high FGF-23 suppress renal **CYP27B1** (1α-hydroxylase) and accelerate calcitriol degradation (via CYP24), lowering **$1,25(OH)_2D_3$**. Low calcitriol causes hypocalcaemia (poor gut Ca absorption) and de-represses **PTH gene transcription**.
- **Hypocalcaemia:** From low calcitriol and phosphate complexing of calcium — a further stimulus to PTH.
- **FGF-23 / Klotho axis:** FGF-23 (a "phosphatonin") rises *earliest*. Renal **Klotho** (its obligatory co-receptor) is down-regulated in CKD, so the normal Klotho-dependent inhibitory effect of FGF-23 on the parathyroid is *attenuated*, permitting PTH to climb. High FGF-23 is an independent risk factor for **left ventricular hypertrophy** and mortality.
- **Net result — secondary hyperparathyroidism:** Hyperphosphataemia + hypocalcaemia + calcitriol deficiency + Klotho loss → sustained PTH excess → high-turnover bone disease. Persistent stimulation can produce autonomous, hypercalcaemic **tertiary hyperparathyroidism**. PTH itself behaves as a uraemic toxin (muscle weakness, myocardial fibrosis, ESA-resistant anaemia from marrow fibrosis).

Spectrum of renal osteodystrophy (KDIGO TMV classification)

KDIGO classifies bone lesions on three histomorphometric axes — **T**urnover, **M**ineralization, **V**olume — replacing older eponymic categories.

Lesion	Turnover	PTH	Histology / hallmark
Osteitis fibrosa cystica (2° hyperparathyroidism)	High	High	Giant multinucleated osteoclasts in **Howship's lacunae**, peritrabecular/marrow fibrosis, woven bone, cysts/**brown tumours**
Adynamic (low-turnover) bone disease	Low	Low/ normal	Absent osteoblast & osteoclast activity, little osteoid, no fibrosis; ↓bone volume & mineralization

Lesion	Turnover	PTH	Histology / hallmark
Osteomalacia	Low	Variable	Excess **unmineralized osteoid**, wide osteoid seams, markedly reduced mineralization rate
Mixed uraemic osteodystrophy	High + defect	High	Features of 2° HPT *plus* a mineralization defect on tetracycline labelling

- **Osteitis fibrosa cystica** is the *classic* high-turnover lesion of secondary hyperparathyroidism — bone pain, fragility, **brown tumours** (haemorrhagic cysts that appear brown) with compression syndromes, and ESA-resistant anaemia.
- **Adynamic bone disease** is now *increasingly prevalent*, especially in diabetics and older patients. It results from **over-suppression of PTH** — by vitamin D preparations, calcium-based binders or high-calcium dialysate — chronic inflammation, or both. Despite low turnover, patients suffer severe musculoskeletal pain (inability to repair microfractures), increased fractures, and a strong association with **vascular/cardiac calcification** (ingested calcium cannot enter low-turnover bone and is deposited ectopically).
- **Osteomalacia** is a distinct mineralization defect from reduced calcitriol; historically linked to **aluminium toxicity** (aluminium-containing binders, contaminated dialysate) — now rare. Aluminium deposits stain at the mineralization front.
- The historical predominance of osteitis fibrosa has shifted: osteomalacia has been largely "replaced" by adynamic bone disease, and mixed uraemic osteodystrophy has risen.

Extraskeletal manifestations of CKD-MBD

- **Vascular calcification:** Hyperphosphataemia and hypercalcaemia drive **medial** calcification of coronaries and valves (orders of magnitude greater than in non-CKD), distinct from intimal atherosclerotic calcification. Phosphate induces an *osteoblast-like phenotypic switch* in vascular smooth-muscle cells (up-regulation of **RUNX-2 / MSX2**), with loss of inhibitors (fetuin-A, matrix Gla protein, pyrophosphate). Linked to LVH and cardiovascular mortality.
- **Calciphylaxis (calcific uraemic arteriolopathy):** Devastating, near-exclusive to advanced CKD. Painful **livedo reticularis** and subcutaneous nodules progress to ischaemic skin necrosis/ulceration (legs, thighs, abdomen, breasts) from small-vessel medial calcification and thrombosis. **Warfarin** is a key risk factor (it blocks vitamin K–dependent activation of matrix Gla protein) and must be stopped.
- **Tumoral calcinosis:** Periarticular soft-tissue calcified masses in chronically, severely hyperphosphataemic, non-adherent dialysis patients.

Clinical / Diagnostic significance

- **Biochemistry (serial trends matter more than single values):** serum **phosphate**, **corrected calcium**, intact **PTH**, **alkaline phosphatase** (bone turnover surrogate), **25-OH vitamin D**; FGF-23 and Klotho remain largely research tools.
- **Bone biopsy** (iliac crest) with **double tetracycline labelling** is the *gold standard* for renal osteodystrophy — tetracycline binds hydroxyapatite and fluoresces, allowing dynamic measurement of bone-formation rate (turnover) plus static mineralization and volume.

- **Radiology: subperiosteal resorption** (radial side of middle phalanges, distal clavicle), resorption of phalangeal tufts (acro-osteolysis), **brown tumours**, "salt-and-pepper" skull and the *rugger-jersey spine* of secondary hyperparathyroidism; pseudofractures (Looser's zones) in osteomalacia. DEXA quantifies density but cannot distinguish lesion type.
- **Clinical clues:** bone pain, proximal myopathy/muscle weakness, fragility fractures, pruritus, periarticular masses, and ESA-hyporesponsive anaemia.
- **Caution: Bisphosphonates and denosumab** suppress turnover and can *precipitate adynamic bone disease* in CKD/ESKD — avoid unless a high-turnover state is confirmed.

Management (prevention-focused; KDIGO targets)

- **Control phosphate first** — the foundational step. Dietary phosphate restriction (avoid cola, processed/additive phosphate) + **phosphate binders taken with meals**:
  - *Calcium-based* (calcium acetate, calcium carbonate) — cheap but risk hypercalcaemia and positive calcium balance, especially in low-turnover bone; limit use.
  - *Non-calcium* — **sevelamer**, **lanthanum carbonate**; *iron-based* — **ferric citrate**, sucroferric oxyhydroxide; reduce vascular calcium loading.
  - **Tenapanor** (NHE3 inhibitor) reduces GI phosphate absorption; **aluminium hydroxide** only short-term (osteomalacia/neurotoxicity risk).
- **Active vitamin D** for secondary hyperparathyroidism once phosphate is controlled and 25-OH D repleted: **calcitriol** or analogues (**paricalcitol** — less hypercalcaemia). Dose-reduce/stop if hypercalcaemia or hyperphosphataemia develops.
- **Calcimimetics** — **cinacalcet** (oral), **etelcalcetide** (IV, at dialysis) — sensitize the parathyroid CaSR, lowering PTH *and* calcium; watch for hypocalcaemia. Useful when high Ca/PO_4 prohibit vitamin D analogues.
- **Target PTH:** KDIGO/KDOQI recommend **2–9 × upper limit of normal** in ESKD (skeletal PTH resistance means normal levels risk adynamic bone); very low PTH predicts fracture and ectopic calcification.
- **Parathyroidectomy** for severe refractory/tertiary hyperparathyroidism with persistent hypercalcaemia, intractable pruritus, calciphylaxis or progressive disease.
- **Calciphylaxis:** stop warfarin, use IV **sodium thiosulfate**, correct Ca/PO_4, wound care ± hyperbaric oxygen.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Pathophysiology cascade of CKD-MBD:** Box "↓GFR" → "Phosphate retention" branching to "↑FGF-23 (osteocytes)" and "↓Calcitriol (CYP27B1↓)"; arrows converging through "Hypocalcaemia" and "↓Klotho" to a central box "**Secondary hyperparathyroidism (↑PTH)**", with downstream boxes "**Osteitis fibrosa cystica / high-turnover bone**", "Vascular calcification", "LVH/CV mortality". Labels: *GFR, Phosphate, FGF-23, Klotho, Calcitriol, Calcium, PTH*.
- **Diagram 2 — Classification by bone turnover:** A horizontal axis "Bone turnover (low → high)"; left = **Adynamic bone disease** & **Osteomalacia** (low PTH); right = **Osteitis fibrosa cystica** (high PTH); centre = **Mixed uraemic osteodystrophy**. Annotate KDIGO **TMV** axes: *Turnover, Mineralization, Volume*.

High-yield exam pointers

- **CKD-MBD = triad:** biochemical (Ca/PO_4/PTH/vit D) + bone (renal osteodystrophy) + extraskeletal calcification (KDIGO 2006).
- **FGF-23 rises earliest**, before measurable PTH/Ca/PO_4 change; needs **Klotho** co-receptor (down-regulated in CKD).
- **Osteitis fibrosa cystica** = high-turnover, secondary HPT; *Howship's lacunae*, *brown tumours*, *subperiosteal resorption*, *rugger-jersey spine*.
- **Adynamic bone disease** = low PTH, over-suppressed; commonest emerging lesion; linked to fractures + vascular calcification.
- **Bone biopsy with double tetracycline labelling** = gold standard; classify by **TMV**.
- **Target PTH 2–9 × ULN** in ESKD; avoid *over-suppression*.
- **Warfarin → calciphylaxis** (blocks matrix Gla protein); avoid in dialysis where possible.
- **Avoid bisphosphonates/denosumab** in CKD unless high-turnover confirmed.
- Binder hierarchy: phosphate control *first*, prefer non-calcium binders to limit vascular calcium loading.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Chronic Kidney Disease" (Bone manifestations of CKD; disorders of calcium and phosphate metabolism; calciphylaxis; treatment) and "Disorders of the Parathyroid Gland and Calcium Homeostasis" (osteitis fibrosa cystica, Howship's lacunae, subperiosteal resorption).
- **Brenner & Rector's The Kidney** — "Chronic Kidney Disease–Mineral Bone Disorder" (KDIGO CKD-MBD/renal osteodystrophy definitions, FGF-23/Klotho axis, TMV classification, histomorphometry, vascular calcification/RUNX-2).
- **CMDT 2026** — "Kidney Disease" (mineral bone disorders: binders, calcitriol/analogues, calcimimetics, PTH targets) and "Disorders of Parathyroid Glands & Bone Metabolism".
- *Coverage note:* "Rugger-jersey spine," "salt-and-pepper skull" and "Looser's zones" are universally accepted standard radiographic eponyms included for completeness; the corpus explicitly documents subperiosteal resorption, phalangeal tuft resorption and brown tumours.

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Counter-current multiplier system — Gitelman syndrome

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

Definition / Introduction — The **countercurrent multiplier** is the renal mechanism that generates and maintains a **hypertonic medullary interstitium**, enabling the kidney to produce urine far more concentrated than plasma. It exploits the hairpin (countercurrent) geometry of the **loop of Henle**, where active NaCl reabsorption by the water-impermeable thick ascending limb is "multiplied" along the cortico-medullary axis by the opposing flow in the two limbs. The medullary gradient, in concert with vasopressin-driven water reabsorption in the collecting duct, determines final urine concentration. **Gitelman syndrome** is a contrasting *distal* tubulopathy — an inherited salt-wasting disorder of the distal convoluted tubule (DCT) caused by loss of the thiazide-sensitive Na^+/Cl^- cotransporter.

Anatomical and functional basis of the countercurrent apparatus

- The **loop of Henle** has three segments: **descending thin limb, ascending thin limb, and ascending thick limb (TAL)**; the loop reabsorbs ~**15–25% of filtered NaCl**, mainly in the TAL.
- **Descending thin limb** — highly **water-permeable** owing to dense, constitutively active **aquaporin-1** channels; relatively solute-impermeable. Tubular fluid equilibrates osmotically with the interstitium and becomes progressively *concentrated* as it descends.
- **Ascending thin and thick limbs** — water permeability is **negligible** ("diluting segment").
- **Thick ascending limb** — high-capacity secondary-active NaCl transport by the apical **$Na^+/K^+/2Cl^-$ cotransporter (NKCC2)** in series with basolateral **Cl^- channels** and the **Na^+/K^+-ATPase**. Tubular **K^+** (~4 meq/L) is the limiting substrate, so activity is sustained by **K^+ recycling** through an apical potassium channel (ROMK). NKCC2 is the molecular target of **loop diuretics**.
- K^+ recycling renders the lumen **electropositive**, driving **paracellular reabsorption of Mg^{2+} and Ca^{2+}** in the TAL.

Mechanism — the "single effect" and its multiplication

- **Step 1 — the single effect:** Active NaCl reabsorption by the *water-impermeable* TAL moves solute (without water) into the interstitium, **diluting tubular fluid** and **adding new osmoles** to medullary interstitial fluid. At any horizontal level this creates a modest osmotic gradient between lumen and interstitium (classically ~200 mOsm/kg).
- **Step 2 — countercurrent multiplication:** Because flow in the **descending and ascending limbs runs in opposite directions** (a hairpin), the small transverse single effect is repeatedly summed along the length of the loop, multiplying into a **large axial (cortico-medullary) gradient**.
- **Step 3 — solute trapping:** As water leaves the permeable descending limb to equilibrate with the hypertonic interstitium, solute is **progressively trapped** in the inner medulla, steepening the gradient from iso-osmotic at the cortex to maximally hypertonic at the papillary tip.
- **Net result:** A standing medullary osmotic gradient (in humans rising to ~**1200 mOsm/kg** at the papilla) against which the collecting duct can extract water. *NaCl reabsorption by the TAL is the primary initiating event of the whole process.*

Role of urea recycling and the vasa recta (countercurrent exchanger)

- **Urea recycling** — the **inner medullary collecting duct** transports urea (via urea transporters) out of the lumen into the interstitium, where it diffuses into the descending and ascending limbs and is recycled. Urea contributes substantially to **maximum medullary interstitial osmolality**.
- **Vasa recta** — the medullary peritubular capillaries that envelop the loop form the **second countercurrent system**. Their hairpin geometry allows passive **countercurrent exchange**: solutes and water are shunted between descending and ascending vessels so that blood flow nourishes the medulla **without washing out** the gradient. (The loop is an *active* countercurrent **multiplier**; the vasa recta is a *passive* countercurrent **exchanger** that preserves the gradient.)

Using the gradient — vasopressin and the collecting duct

- Collecting duct cells express vasopressin-regulated **aquaporin-2 (apical)** and **aquaporin-3/-4 (basolateral)** water channels.
- **Vasopressin (ADH)** binds the basolateral **V2 receptor** → G-protein activation of **adenylyl cyclase** → rise in **cyclic AMP** → insertion of aquaporin-2 into the apical membrane → water reabsorption and **concentrated urine**.
- Without vasopressin, the collecting duct is water-impermeable and urine stays **dilute**. *Vaptans* (nonpeptide V2 antagonists) block this effect to produce a water diuresis (e.g., for hyponatremia).

Feature	Countercurrent multiplier	Countercurrent exchanger
Structure	Loop of Henle (descending + ascending limbs)	Vasa recta (medullary capillaries)
Energy	**Active** (NKCC2 in TAL)	**Passive** (diffusion only)
Function	**Generates** the medullary gradient	**Preserves** the gradient (prevents washout)

Feature	Countercurrent multiplier	Countercurrent exchanger
Key requirement	Water-impermeable TAL + water-permeable thin descending limb	Hairpin geometry with slow blood flow

Gitelman syndrome

- **Definition / genetics:** An autosomal-recessive **salt-wasting tubulopathy** caused by **loss-of-function mutations of *SLC12A3***, which encodes the apical **thiazide-sensitive Na^+/Cl^- cotransporter (NCC)** of the **distal convoluted tubule** — effectively a lifelong "thiazide-like" state. The DCT normally reabsorbs ~5% of filtered NaCl.
- **Mechanism of electrolyte disturbance:**
  - Impaired distal NaCl reabsorption → mild **volume contraction** → activation of renin–angiotensin–aldosterone → enhanced distal Na^+ reabsorption with K^+ and H^+ secretion → **hypokalaemia and metabolic alkalosis**.
  - Blocking apical Na^+/Cl^- cotransport lowers intracellular Na^+, favouring basolateral **Na^+/Ca^{2+} exchange** and passive apical **Ca^{2+} entry (TRPV5)** → increased Ca^{2+} reabsorption → **hypocalciuria** (the hallmark distinguishing it from loop pathology).
  - **Hypomagnesaemia** — impaired Mg^{2+} handling in the DCT (the TRPM6/TRPM7 channel complex is critical for DCT Mg^{2+} reabsorption).
- **Clinical features (standard medicine):** Usually presents **later (adolescence/adulthood)** and is **milder** than Bartter syndrome — muscle cramps/weakness, tetany and carpopedal spasm (from hypomagnesaemia), fatigue, salt craving, **normal-to-low blood pressure**, and occasionally chondrocalcinosis.
- **Biochemistry:** Hypokalaemia, metabolic alkalosis, **hypomagnesaemia**, **hypocalciuria**, with high plasma renin/aldosterone and normal/low BP.
- **Management (standard medicine):** Liberal **sodium**, oral **potassium and magnesium** supplementation, and **potassium-sparing agents** (spironolactone/eplerenone or amiloride); magnesium repletion is central because it is needed to correct the hypokalaemia.

Feature	Bartter syndrome	Gitelman syndrome
Tubular site	Thick ascending limb	Distal convoluted tubule
Gene / transporter	NKCC2 (*SLC12A2*), ROMK (*KCNJ1*), CLCNKB/BSND, CASR	**NCC (*SLC12A3*)**
Diuretic mimicked	**Loop diuretic** (furosemide)	**Thiazide**
K^+ / acid-base	Hypokalaemia + metabolic alkalosis	Hypokalaemia + metabolic alkalosis
Urinary calcium	**Hyper**calciuria ± nephrocalcinosis	**Hypo**calciuria
Magnesium	Usually normal	**Hypomagnesaemia**
Typical onset / severity	Neonatal/childhood, severe	Adolescent/adult, milder

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Nephron loop with the medullary gradient:** Draw the U-shaped loop in the medulla. Label *descending thin limb (aquaporin-1, water-permeable)*, *ascending thin limb*, *thick ascending limb (NKCC2 + ROMK + Na^+/K^+-ATPase, water-impermeable)*, *vasa recta (countercurrent exchanger)*, and the *inner medullary collecting duct (urea recycling, ADH/AQP2)*. Add a vertical osmolality scale on the right reading *~300 mOsm/kg (cortex) → ~1200 mOsm/kg (papilla)* with horizontal arrows for the "single effect."
- **DCT cell for Gitelman:** Apical *thiazide-sensitive Na^+/Cl^- cotransporter (NCC, SLC12A3)* with a red cross (mutated), apical *TRPV5 (Ca^{2+})*, basolateral *Na^+/K^+-ATPase*, *Cl^- channel*, and *Na^+/Ca^{2+} exchanger*.

Clinical / Diagnostic significance

- The medullary gradient is the physiological substrate for the **urine-concentrating/diluting** capacity; its disruption underlies **nephrogenic diabetes insipidus** (AQP2/V2 defects) and the polyuria of medullary disease.
- **Loop diuretics** abolish the single effect (block NKCC2) → impaired concentration and brisk natriuresis; **thiazides** act at the DCT NCC — the same target lost in Gitelman.
- **Differentiating hypokalaemic metabolic alkalosis with normal BP:** Gitelman (hypocalciuria + hypomagnesaemia, adult, thiazide-like) vs Bartter (hypercalciuria, neonatal, loop-like) vs surreptitious **vomiting/diuretic abuse** (check urine chloride/diuretic screen).
- Recognising the volume-contracted, **normal/low-BP** picture separates these salt-wasting tubulopathies from **Liddle syndrome** (ENaC gain-of-function: hypertension + hypokalaemic alkalosis with low renin/aldosterone).

High-yield exam pointers

- Two countercurrent systems: **loop of Henle = active multiplier**; **vasa recta = passive exchanger** (prevents washout).
- The **water-impermeable TAL** with **NKCC2** is the engine ("single effect"); the **water-permeable descending limb (AQP1)** enables solute trapping.
- **Urea recycling** from the inner medullary collecting duct is essential for **maximal** medullary hypertonicity.
- **ADH → V2 → cAMP → AQP2** insertion converts the gradient into concentrated urine.
- Gitelman = **DCT, *SLC12A3*/NCC, thiazide-like**: hypokalaemic metabolic alkalosis + **hypocalciuria + hypomagnesaemia**, normal/low BP.
- Mnemonic contrast — **G**itelman = hypocalciuria (Goes low calcium in urine) vs **B**artter = hypercalciuria.
- Treat Gitelman with **Na, K, Mg** replacement ± **K^+-sparing diuretic**; correct Mg to fix the K^+.

SOURCE & COVERAGE

Harrison 22e — Ch 320 "Cell Biology and Physiology of the Kidney" (countercurrent multiplication, loop/vasa recta, TAL/NKCC2, urea recycling, ADH/AQP2, DCT/NCC and the *SLC12A3* Gitelman mention; Bartter genes). Ch 432 "Inherited Defects of Membrane Transport" was provided but covers cystinuria/lysinuric protein intolerance only and does **not** address Gitelman syndrome. *Coverage note:* The provided text grounds the countercurrent mechanism fully and names Gitelman syndrome with its core triad (salt-wasting, hypokalaemic alkalosis, hypocalciuria), the *SLC12A3*/NCC defect, and the DCT calcium/magnesium handling. The expanded Gitelman details — autosomal-recessive inheritance, secondary hyperaldosteronism, clinical presentation (age/severity, tetany, chondrocalcinosis), and treatment — plus the classic ~200 and ~1200 mOsm/kg figures and Bartter hypercalciuria are universally accepted standard internal medicine added for exam completeness, not verbatim from the supplied chapters.

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Crescentic glomerulonephritis

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

Definition / Introduction — *Crescentic glomerulonephritis* (CrGN) is the histological correlate of the clinical syndrome of **rapidly progressive glomerulonephritis (RPGN)** — a nephritic illness with loss of kidney function over days to weeks, accompanied by dysmorphic (glomerular) haematuria, red-cell casts and sub-nephrotic to nephritic-range proteinuria. It is defined pathologically by **extracapillary proliferation forming crescents in Bowman's space in >50% of glomeruli**, and represents the most aggressive structural phenotype in the continuum of glomerular inflammatory injury. The terms RPGN (clinical) and crescentic GN (pathological) are used almost interchangeably because aggressive GN that causes RPGN nearly always shows extensive crescents. It is a nephrological emergency: untreated, it progresses to irreversible scarring and end-stage kidney disease (ESKD), so urgent biopsy and immunosuppression are mandatory.

The crescent — morphology and pathogenesis

- A **crescent** is a collection of cells and matrix that fills part or all of Bowman's (urinary) space, compressing the glomerular tuft into a half-moon shape (*Fig. — cellular crescent, PAS ×500*).
- **Pathogenesis (final common pathway):** severe glomerular injury causes **focal rupture of glomerular capillary walls and breaks in the GBM/Bowman's capsule** → leakage of fibrin, plasma proteins and inflammatory mediators into Bowman's space → proliferation of parietal/visceral epithelial cells with influx and maturation of **macrophages**, producing the crescent. Fibrin (seen as *fibrin tactoids* on EM) is a potent stimulus.
- **Evolution:** *cellular* crescent → *fibrocellular* → *fibrous (fibrotic)* crescent. Cellular crescents are potentially reversible with treatment; fibrous crescents and Bowman's capsule rupture signify irreversibility.

- Associated features: **segmental fibrinoid necrosis** of the tuft, periglomerular inflammation, and in chronic stages, glomerulosclerosis, tubular atrophy and **interstitial fibrosis** (an ominous sign of irreversibility).
- Crescents are a marker of severity across many GNs — they are seen in ~97% of anti-GBM, ~90% of ANCA, ~56% of immune-complex and ~61% of proliferative lupus (class III/IV) biopsies (UNC Nephropathology data).

Immunopathologic classification (the three categories / Type I–III)

The precise category requires integrating **immunofluorescence (IF) pattern, serology, light and electron microscopy**. Three immunopathologic groups account for almost all cases:

Feature	Type I — Anti-GBM	Type II — Immune-complex	Type III — Pauci-immune (ANCA)
IF pattern	**Linear** IgG along GBM	**Granular** ("lumpy-bumpy") Ig + C3	**Pauci-immune** (little/no Ig or complement)
Antigen / serology	Anti-GBM Ab to **α3-NC1 domain of type IV collagen**	Circulating/in-situ immune complexes; ± low complement	**ANCA** — PR3 (c-ANCA) or MPO (p-ANCA)
Frequency (all ages)	~15%	~24%	~60% (≈90% ANCA-positive)
Typical age	Bimodal (20s; 60s–70s)	Children/young adults	Older adults (≈79% of CrGN >60 yr)
Representative diseases	Goodpasture syndrome; renal-limited anti-GBM	Post-infectious GN, IgA nephropathy/IgA vasculitis, lupus nephritis (III/IV), MPGN, cryoglobulinaemia, C3 glomerulopathy	GPA, MPA, EGPA, renal-limited (ANCA) vasculitis

- **Type I (anti-GBM):** autoantibody against the *Goodpasture antigen* — the **α3 chain NC1 domain of collagen IV** (an autoimmune "conformeropathy"). Genetic link to **HLA-DR2 (DRB1*1501, DQB1*0602)**. Bimodal age: young men (more often full Goodpasture syndrome with lung haemorrhage) and elderly (more often renal-limited, female predominance). **25–33% are also ANCA (usually MPO)-positive** ("double-positive").
- **Type II (immune-complex):** the underlying disease shapes the picture — e.g. mesangial IgA (IgA nephropathy), coarse granular capillary-wall deposits and sub-epithelial "humps" (post-streptococcal), C3-dominant with double contours (MPGN/C3GN), "full-house" with tubuloreticular inclusions (lupus). Intact glomeruli show **endocapillary hypercellularity and capillary-wall thickening**.
- **Type III (pauci-immune/ANCA):** most common cause of CrGN in adults; segmental **necrotising** GN with crescents but minimal deposits. Part of ANCA-associated small-vessel vasculitis (GPA = PR3 predominant; MPA/EGPA = MPO predominant) or renal-limited. A 4th category — **monoclonal Ig–mediated (MGRS)** — and rare "double/triple antibody-negative" cases are now also recognised.

Clinical features and investigations

- **Presentation:** rapidly rising serum creatinine over days–weeks, oliguria/anuria, **smoky/cola-coloured urine**, hypertension, oedema and uraemic symptoms (nausea, malaise, fatigue).
- **Urinalysis (the key bedside clue):** active nephritic sediment — **dysmorphic RBCs, red-cell casts**, pyuria, and proteinuria typically 1–3.5 g/day (rarely nephrotic).
- **Systemic clues:** haemoptysis/pulmonary haemorrhage (anti-GBM/Goodpasture, ANCA "pulmonary-renal syndrome"); sinusitis, nasal crusting, cavitating lung nodules, mononeuritis multiplex, palpable purpura (ANCA vasculitis); malar rash, arthralgia, serositis (lupus).
- **Serology panel (send before/at biopsy):** anti-GBM antibody; ANCA (anti-PR3, anti-MPO); ANA, anti-dsDNA, **C3/C4** (low in lupus, post-infectious, MPGN, cryoglobulinaemia; normal in anti-GBM and ANCA); ASO/anti-DNase, cryoglobulins, hepatitis B/C and HIV serology, blood cultures.
- **Kidney biopsy = diagnostic cornerstone:** light microscopy (crescents, % involvement, necrosis, chronicity), **immunofluorescence** (linear vs granular vs pauci-immune — defines the category) and electron microscopy (location of deposits; linear staining has no deposits).
- **Mimics of RPGN to exclude:** thrombotic microangiopathy/HUS (MAHA, thrombocytopenia), atheroembolic disease, acute interstitial nephritis and ATN — these typically lack dysmorphic haematuria and RBC casts.

Management

- **Principle:** treat *urgently and empirically* — outcome depends on how early therapy is started relative to the degree of scarring; oliguria/dialysis-dependence at presentation predicts a poor renal outcome.
- **General:** supportive care — control BP (RAAS blockade once stable), manage volume, treat hyperkalaemia/uraemia, dialysis as needed.

Category	Induction	Adjunct / maintenance
Anti-GBM (Type I)	**Daily plasma exchange ×~2 weeks** (until antibody negative) + high-dose corticosteroids + **cyclophosphamide**	Rituximab in refractory cases; transplant deferred ~6 months until antibodies undetectable
ANCA / pauci-immune (Type III)	Corticosteroids + **cyclophosphamide or rituximab** (3–6 months)	Maintenance **rituximab (preferred) or azathioprine** 1–2 yr; **avacopan** (oral C5a-receptor inhibitor) can spare steroids; plasma exchange for Cr >3.4 mg/dL, diffuse alveolar haemorrhage, or double-positive disease
Immune-complex (Type II)	Treat the underlying disease; for severe/idiopathic — **pulse methylprednisolone** then prednisone 1 mg/kg/day, ± cyclophosphamide ± plasma exchange	Lupus: induction (steroid + MMF or cyclophosphamide ± belimumab) then MMF/azathioprine maintenance

- **Plasma exchange:** standard in anti-GBM and in pulmonary haemorrhage; in ANCA it is reserved (PEXIVAS-era) for severe renal failure or alveolar haemorrhage. It is **mandatory when anti-GBM and ANCA coexist**.

- **Outcomes:** ANCA — remission in 75–90%, but relapse in 25–50% (commonest in GPA). Post-infectious crescentic GN is usually supportive (no immunosuppression even with crescents).

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Labelled glomerulus with a cellular crescent:** label *Bowman's capsule, Bowman's (urinary) space, cellular crescent (proliferating parietal epithelial cells + macrophages), compressed glomerular tuft, segmental fibrinoid necrosis, break in GBM/capillary wall, fibrin in Bowman's space.*
> - **Immunofluorescence comparison (three boxes):** *Linear GBM IgG (anti-GBM / Type I) — Granular "lumpy-bumpy" IgG + C3 (immune-complex / Type II) — Pauci-immune / negative IF with ANCA in serum (Type III).*

Clinical / Diagnostic significance

- **RPGN is a medical emergency** — the single most important determinant of renal recovery is *time to immunosuppression*; never wait for full results if anti-GBM/Goodpasture is strongly suspected.
- The **IF pattern instantly triages** therapy and prognosis: linear → plasma exchange + cyclophosphamide; pauci-immune → steroid + rituximab/cyclophosphamide ± avacopan; granular → treat the underlying immune-complex disease.
- **Percentage of crescents and degree of interstitial fibrosis** on biopsy are the strongest prognostic markers; >50% crescents, serum creatinine >5–6 mg/dL, oliguria or dialysis need at presentation portend a poor outcome.
- Always test **anti-GBM and ANCA together** — "double-positive" patients exist and require both plasma exchange and prolonged immunosuppression with closer relapse surveillance.

High-yield exam pointers

- **Crescentic GN = RPGN**; crescents in **>50% of glomeruli** defines it; crescent = extracapillary proliferation in Bowman's space.
- **Three immunopathologic types: Type I anti-GBM (linear IF), Type II immune-complex (granular IF), Type III pauci-immune/ANCA (negative IF)** — remember frequencies ≈15% : 24% : 60%.
- **Pauci-immune/ANCA is the commonest** cause of CrGN overall and in older adults; **immune-complex** predominates in children.
- **Goodpasture antigen = α3 chain NC1 domain of type IV collagen**; HLA-DR2 association; lung + kidney = pulmonary-renal syndrome.
- **C3/C4 low** in lupus, post-infectious, MPGN, cryoglobulinaemia; **normal** in anti-GBM and ANCA vasculitis.
- **Anti-GBM treatment = plasma exchange + steroids + cyclophosphamide**; **ANCA = steroids + rituximab/cyclophosphamide**, maintenance rituximab/azathioprine, avacopan steroid-sparing.
- **Double-positive (anti-GBM + ANCA)** seen in 25–33% of anti-GBM cases — give both plasma exchange and full immunosuppression.

- Crescent frequency hierarchy: **anti-GBM (97%) > ANCA (90%) > lupus III/IV (61%) > immune-complex (56%)**.
- Poor prognostic signs: oliguria, dialysis-dependence, creatinine >5–6 mg/dL, fibrous crescents and interstitial fibrosis.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Glomerular Diseases"* (acute nephritic syndromes; anti-GBM disease/Goodpasture's; ANCA small-vessel vasculitis; lupus nephritis classification).
- **Brenner & Rector's The Kidney** — *"Primary Glomerular Disease"* (Rapidly Progressive and Crescentic Glomerulonephritis: nomenclature, immunopathologic categories and frequency Tables 31.8–31.10, the diagnostic IF algorithm, anti-GBM pathogenesis and pathology, treatment).
- **CMDT 2026** — *"Kidney Disease"* (nephritic spectrum; pauci-immune/ANCA, anti-GBM and immune-complex GN — current induction/maintenance regimens, avacopan, plasma-exchange indications).

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Diabetic nephropathy

Asked in: Paper IV Dec 2023 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Diabetic nephropathy, better termed **diabetic kidney disease (DKD)** in clinical practice, is chronic kidney disease attributable to diabetes mellitus, usually recognized by persistent albuminuria and/or falling eGFR in a patient with compatible diabetes duration and other microvascular disease. It is the commonest cause of CKD and ESKD worldwide. The lesion is a combined **metabolic, hemodynamic, glomerular, vascular, podocyte, and tubulointerstitial** injury pattern rather than isolated proteinuria.

Epidemiology and risk factors

- DKD develops in approximately **20-40%** of patients with diabetes; because type 2 diabetes is much more prevalent, most patients with DKD have type 2 diabetes.
- It is a major cause of **stage 5 CKD/ESKD** requiring dialysis or transplantation, and CKD in diabetes markedly increases cardiovascular morbidity and mortality.
- **Type 1 diabetes:** clinically significant DKD usually appears after several years of diabetes; CKD after **10 years or more** of type 1 diabetes is very likely to be DKD if the clinical picture is typical.
- **Type 2 diabetes:** onset of diabetes is often insidious, so albuminuria or low eGFR may already be present at diagnosis; lesions are more heterogeneous because hypertension, obesity, atherosclerosis, and aging often coexist.
- Important risk factors are **duration of diabetes, chronic hyperglycemia, hypertension, family history/genetic susceptibility, smoking, obesity, dyslipidemia, ethnicity**, and established cardiovascular disease.

- Diabetic retinopathy is strongly concordant with DKD, especially in type 1 diabetes; absence of retinopathy in type 1 diabetes with proteinuria should trigger a search for non-diabetic kidney disease.

Pathogenesis

- **Chronic hyperglycemia** drives advanced glycation end-products, oxidative stress, inflammatory and profibrotic signaling, epigenetic or "metabolic memory" changes, and activation of growth factors such as **TGF-beta** and VEGF.
- **Hemodynamic injury:** diabetes causes renal hypertrophy, glomerular hyperperfusion, increased intraglomerular pressure, and hyperfiltration. Upregulated proximal tubular **SGLT2** increases sodium-glucose reabsorption, lowers sodium delivery to the macula densa, and perpetuates glomerular hyperfiltration.
- **RAAS/endothelin axis:** angiotensin II, aldosterone, and endothelin promote efferent arteriolar tone, mesangial matrix production, podocyte injury, and interstitial fibrosis.
- **Structural glomerular injury:** glomerular basement membrane (GBM) thickening, mesangial matrix expansion, reduced filtration surface area, and later diffuse or nodular glomerulosclerosis.
- **Podocyte injury** begins early: foot-process widening, podocyte detachment, nephrin loss, and podocytopenia contribute to albuminuria and secondary focal segmental sclerosis.
- **Tubulointerstitial injury** with tubular basement membrane thickening, tubular dysfunction, inflammation, and fibrosis correlates with progressive eGFR decline.

Natural history and classification

- Classical sequence: **glomerular hyperfiltration and renal hypertrophy -> moderate albuminuria -> severe albuminuria/overt proteinuria -> declining GFR -> ESKD**.
- In type 1 diabetes, hyperfiltration and renal hypertrophy occur in the first years; GBM thickening and mesangial expansion appear early; albuminuria often appears after **5-10 years**. In type 2 diabetes, patients may present at any point in this sequence.
- Atypical but important pattern: DKD may present with **reduced eGFR without albuminuria**, particularly in type 2 diabetes and in contemporary treated cohorts.

Parameter	Category	Exam value
Urine albumin-creatinine ratio (UACR)	Normal	**<30 mg/g**
UACR	Moderate albuminuria, formerly microalbuminuria	**30-299 mg/g**
UACR	Severe albuminuria, overt nephropathy	**>=300 mg/g**
eGFR	G1/G2	**>=90 / 60-89 mL/min/1.73 m2**
eGFR	G3a/G3b	**45-59 / 30-44 mL/min/1.73 m2**

Parameter	Category	Exam value
eGFR	G4/G5	**15-29 / <15 mL/min/1.73 m2**

- Albuminuria is continuous risk: higher UACR predicts faster GFR loss, kidney failure, cardiovascular events, and all-cause mortality.
- Regression from moderate albuminuria to normoalbuminuria can occur, especially with early treatment; regression is a favorable prognostic sign.

Clinical evaluation and diagnosis

- Screen with **spot UACR plus serum creatinine-based eGFR**; routine urine dipstick misses low-grade albuminuria.
- Screening schedule: begin **5 years after onset of type 1 diabetes**, and **at diagnosis of type 2 diabetes**; repeat annually if normal.
- Confirm an elevated UACR on **2-3 occasions over 3-6 months**, because transient albuminuria may follow strenuous exercise, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, or prostate disease.
- Typical clinical picture: long-standing diabetes, persistent albuminuria, bland urine sediment, hypertension, diabetic retinopathy or neuropathy, and often enlarged kidneys until late disease.
- Kidney biopsy is usually unnecessary when the phenotype is typical, but is indicated or strongly considered for **sudden onset proteinuria, active urine sediment, RBC casts, nephritic features, rapid eGFR fall, massive proteinuria, refractory hypertension, systemic disease clues, absent retinopathy in type 1 diabetes, or >30% eGFR fall after ACE inhibitor/ARB initiation**.
- Differential diagnoses in a diabetic patient include hypertensive nephrosclerosis, IgA nephropathy, membranous nephropathy, amyloidosis, monoclonal/light-chain deposition disease, FSGS from obesity, renal artery stenosis, chronic interstitial nephritis, and drug/contrast-related kidney injury.

Renal pathology

- **Light microscopy:** diffuse mesangial expansion and diffuse glomerulosclerosis are common; advanced disease may show **nodular glomerulosclerosis (*Kimmelstiel-Wilson nodules*)**.
- **Kimmelstiel-Wilson nodules:** round, hypocellular mesangial matrix nodules, often PAS/silver positive, surrounded by patent capillaries; a classic exam lesion, but nodular glomerulosclerosis has mimics such as amyloid, light-chain deposition disease, and idiopathic nodular glomerulosclerosis.
- **Electron microscopy:** early and sensitive **GBM thickening**, mesangial matrix increase, podocyte foot-process widening or detachment, and thickened tubular basement membranes.
- **Immunofluorescence:** may show nonspecific linear IgG or complement accentuation along basement membranes, without immune-complex deposits on electron microscopy.
- **Vascular lesions:** afferent and efferent arteriolar hyalinosis is characteristic; exudative lesions include hyaline caps/fibrin caps and capsular drops.

- **Chronic damage:** global glomerulosclerosis, secondary FSGS, interstitial fibrosis, tubular atrophy, and arteriosclerosis determine irreversible kidney function loss.

Management

- Aim to slow albuminuria progression, preserve eGFR, reduce cardiovascular risk, avoid AKI, and prepare timely kidney replacement therapy when needed.
- **Glycemic control:** target HbA1c around **7%** in many nonpregnant adults, individualized for age, comorbidity, hypoglycemia risk, and CKD stage. Intensive glycemic control clearly prevents or delays albuminuria in type 1 diabetes and helps early DKD; benefit is less dramatic once established albuminuria and GFR decline are present.
- As GFR falls, reassess diabetes drugs: insulin requirement may decline; sulfonylureas increase hypoglycemia risk; metformin should be stopped when **eGFR <30 mL/min/1.73 m2**.
- **Blood pressure:** a practical exam target is **<130/80 mm Hg** in diabetes with albuminuria or CKD, individualized lower if tolerated and cardiovascular/CKD risk is high. Use salt restriction, weight loss, exercise, DASH-style diet, and smoking cessation.
- **ACE inhibitor or ARB:** first-line antiproteinuric therapy in albuminuric DKD and/or hypertension; reduces intraglomerular pressure and fibrosis. Do not use ACE inhibitor plus ARB together, and do not prescribe RAAS blockade solely to prevent DKD in normotensive, normoalbuminuric diabetes.
- Check **serum creatinine/eGFR and potassium within 1-2 weeks** after starting or uptitrating ACE inhibitor/ARB/MRA. Review therapy if potassium rises significantly or creatinine rises/eGFR falls by **>30%**.
- **SGLT2 inhibitors:** in type 2 diabetes with CKD, canagliflozin, dapagliflozin, and empagliflozin slow GFR decline, reduce kidney failure risk, and reduce heart failure events; kidney benefit persists despite reduced glucose-lowering at low eGFR. They are generally useful down to about **20-25 mL/min/1.73 m2** depending on drug and guideline, and are stopped at dialysis initiation.
- **Mineralocorticoid receptor antagonism:** finerenone or other MRAs reduce albuminuria and improve kidney/cardiovascular outcomes in selected type 2 DKD patients already on ACE inhibitor/ARB; monitor carefully for hyperkalemia.
- **GLP-1 receptor agonists** such as dulaglutide or semaglutide are useful additional agents for glycemic, weight, cardiovascular, and kidney-risk reduction, especially when SGLT2 inhibitors are not tolerated or CKD is advanced.
- Treat dyslipidemia with statin-based therapy as indicated; manage obesity, avoid NSAIDs and unnecessary iodinated contrast, hydrate around contrast exposure, treat metabolic acidosis and anemia of CKD, vaccinate, and refer to nephrology for eGFR <30, rapid decline, or heavy albuminuria.
- ESKD management includes education for dialysis modalities and transplantation; **kidney transplantation improves survival**, and simultaneous pancreas-kidney transplantation may be considered in suitable type 1 diabetes patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Natural history graph:** x-axis = diabetes duration in years; y-axis left = UACR/albuminuria; y-axis right = GFR; labels = hyperfiltration, moderate albuminuria, severe albuminuria, falling GFR, ESKD, earlier presentation in type 2 diabetes.
- **Glomerular pathology diagram:** labels = thickened GBM, mesangial expansion, *Kimmelstiel-Wilson nodule*, podocyte foot-process effacement/detachment, afferent and efferent arteriolar hyalinosis, tubulointerstitial fibrosis.

Clinical / Diagnostic significance

- DKD is both a renal diagnosis and a **cardiovascular risk marker**; albuminuria independently predicts myocardial infarction, stroke, heart failure, and death.
- Retinopathy supports DKD, especially in type 1 diabetes; its absence, active sediment, or rapid loss of function should prevent blind attribution to diabetes.
- Diabetics are prone to **type 4 renal tubular acidosis** with hyperkalemia, especially with ACE inhibitors, ARBs, MRAs, NSAIDs, beta-blockers, or advanced CKD.
- Diabetes plus CKD is a high-risk setting for **contrast-associated AKI**; use the lowest necessary contrast dose, avoid volume depletion and NSAIDs, and monitor creatinine after exposure.
- Persistent albuminuria despite good BP and glycemic control should prompt adherence review, sodium intake assessment, optimized RAAS/SGLT2/MRA therapy, and exclusion of non-diabetic kidney disease.

High-yield exam pointers

- Write **UACR plus eGFR**; dipstick alone is inadequate for early disease.
- Screening: **type 1 after 5 years, type 2 at diagnosis, then annually**.
- Confirm albuminuria: **2-3 samples over 3-6 months**.
- Albuminuria categories: **30-299 mg/g** and **>=300 mg/g**.
- Classical sequence: **hyperfiltration -> albuminuria -> proteinuria -> falling GFR**.
- Pathology triad: **GBM thickening, mesangial expansion, nodular glomerulosclerosis**.
- Treatment triad for albuminuric DKD: **BP control + ACE inhibitor/ARB + SGLT2 inhibitor**; add **finerenone** when appropriate.
- Do **not** combine ACE inhibitor and ARB; monitor creatinine and potassium.
- Absence of retinopathy in type 1 diabetes with proteinuria means **look for another renal disease**.

SOURCE & COVERAGE

Harrison 22e — "Diabetes Mellitus: Complications"; "Glomerular Diseases"; Brenner & Rector's The Kidney — "Epidemiology of Diabetic Kidney Disease"; CMDT 2026 — "Kidney Disease" and "Diabetes Mellitus & Hypoglycemia".

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Nephrolithiasis

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Nephrolithiasis** (kidney stone disease, urolithiasis) is the formation of crystalline concretions within the upper urinary tract due to supersaturation of lithogenic solutes in urine when the concentration product exceeds the solubility product, combined with deficient crystallisation inhibitors. It is a common, recurrent, costly **systemic disorder** — lifetime risk reaches ~20% in men and ~10% in women, with >50% of first-time formers recurring within 5–10 years. A stone may sit silently in the kidney for years, then migrate into the ureter to produce **renal colic**, often described by patients as the worst pain ever experienced. Identifying the stone type is central, as it dictates prognosis and the targeted, often life-long, preventive regimen.

Classification / Types of stones

Stone type	Approx. frequency	Key urinary risk factors	Radiology	Special features
Calcium oxalate	~75% (most common)	↑urine calcium, ↑oxalate, ↓citrate	Radiopaque	Insensitive to urine pH; grows on Randall's plaque
Calcium phosphate	~15%	↑calcium, ↓citrate, ↑phosphate, **urine pH ≥6.5**	Radiopaque	Linked to distal RTA & primary hyperparathyroidism
Uric acid	~8%	High uric acid excretion, **persistent urine pH ≤5.5**	*Radiolucent* on KUB; visible on CT	Seen in gout, obesity, T2DM, tumour lysis
Struvite (Mg-ammonium-phosphate, "triple-phosphate"/infection stone)	~1%	Urease-producing UTI, **urine pH >8.0**	Faintly opaque	Forms **staghorn calculi**; *Proteus mirabilis*, *Klebsiella*, *Providencia*
Cystine	<1%	Autosomal-recessive cystinuria	Faintly opaque	Hexagonal crystals; staghorn / bilateral; childhood onset

- Calcium-containing stones together account for ~85% and are radiopaque, which is why most stones are seen on plain radiographs.
- Many stones are **mixtures** (e.g., calcium oxalate + calcium phosphate) and contain a protein matrix. Rarely stones are **drug-induced** (acyclovir, atazanavir/indinavir, triamterene, sulfadiazine, guaifenesin).

Pathogenesis and risk factors

- **Supersaturation–inhibition balance:** stones form when urine is supersaturated and protective inhibitors are deficient. **Citrate** is the most important inhibitor of calcium stones (complexes calcium, raising solubility); others include magnesium and pyrophosphate.
- **Randall's plaque hypothesis:** interstitial **calcium-phosphate** deposits begin at the thin limb of the loop of Henle, extend to the papillary tip and erode through the urothelium, providing an

anchored nidus on which calcium oxalate/phosphate crystals grow — explaining why stone formation begins years before a clinical stone.

- **Urinary risk factors:** low urine volume (<1 L/day more than doubles risk), hypercalciuria (>250 mg/day men, >200 mg/day women, or >4 mg/kg/day), hyperoxaluria (>40 mg/day), hypocitraturia (<450 mg/day), hyperuricosuria (>800 mg/day men, >750 mg/day women) and unfavourable urine pH.
- **Dietary risk factors:** high animal protein, oxalate, sodium, sucrose/fructose and high-dose vitamin C (raises oxalate). **Protective:** high dietary calcium (binds gut oxalate), potassium, phytate, citrus and high fluid intake. *Low* dietary calcium is harmful — it increases oxalate absorption and bone loss.
- **Associated/secondary conditions:** primary hyperparathyroidism, distal (type 1) renal tubular acidosis (urolithiasis in up to 75%), GI malabsorption (Crohn's, gastric bypass → **enteric hyperoxaluria** via fatty-acid sequestration of calcium), obesity, type 2 diabetes, gout, medullary sponge kidney, and recurrent UTI.
- **Genetic disorders: cystinuria** (AR defect in dibasic amino-acid reabsorption) and **primary hyperoxaluria** (AR hepatic overproduction of oxalate, types I–III) — both cause early, severe, recurrent stones.

Clinical features

- **Two classic acute presentations:** (1) **renal colic** and (2) painless gross haematuria.
- **Renal colic:** sudden-onset, severe **unilateral flank pain** that waxes and wanes (a misnomer — pain rarely fully subsides) with no relieving posture; patients are **restless and writhing** (cf. the still patient of peritonitis). Frequently accompanied by **nausea/vomiting** and visible or microscopic haematuria.
- **Radiation by stone site:** upper-ureteric stone → pain radiates anteriorly; lower-ureteric stone → radiates to ipsilateral **testis/labium**; ureterovesical-junction stone → urinary **urgency, frequency, dysuria** (mimics cystitis but culture-negative).
- **Differential diagnosis by location:** right UPJ stone mimics acute cholecystitis; right pelvic-brim stone mimics appendicitis; left pelvic-brim mimics diverticulitis. Also consider biliary colic, ectopic pregnancy/ovarian torsion, **leaking abdominal aortic aneurysm**, herpes zoster, musculoskeletal pain, and ureteric obstruction by clot or sloughed papilla.
- **Red-flag — "pus under pressure":** an obstructing stone with proximal infection (fever, leucocytosis, sepsis) is an **obstructive pyonephrosis / urologic emergency** requiring emergent drainage; antibiotics alone are inadequate.
- Note: absence of haematuria does **not** exclude a stone (complete obstruction may give a normal urinalysis), and stone size does not correlate with pain severity.

Investigations

- **Urinalysis:** micro/gross haematuria in ~90%; sediment may show crystals — *bipyramidal (envelope)* calcium oxalate or *hexagonal* cystine crystals; pyuria with culture if infection suspected.

- **Imaging — non-contrast helical CT (KUB) is the gold standard:** highly sensitive, detects stones as small as 1 mm including "radiolucent" uric-acid stones, and shows hydroureteronephrosis and perinephric stranding. Hounsfield units estimate composition (pure uric acid = low HU). **Ultrasound** (no radiation) is preferred first-line in pregnancy and for follow-up but is less sensitive and misses most ureteric stones. **KUB radiograph** misses radiolucent/small stones and gives no information on obstruction.
- **Blood:** serum electrolytes (for hypokalaemia/RTA), creatinine, calcium, phosphate, uric acid; **PTH** and **25-OH vitamin D** if calcium is high/high-normal.
- **Metabolic work-up: stone analysis** is essential whenever a stone/fragment is retrieved (patients should strain urine). **Two 24-h urine collections** on the usual diet form the cornerstone of prevention — measure volume, calcium, oxalate, citrate, uric acid, sodium, potassium, phosphate, magnesium, pH, creatinine, and calculated supersaturation. Indicated after the first stone in interested/high-risk patients and in all recurrent formers.

Management — acute and surgical

- **Analgesia:** parenteral **NSAIDs (e.g., ketorolac)** are at least as effective as opioids with fewer side effects, and are first-line; opioids are adjuncts.
- **Fluids:** maintain **euvolaemia** — forced diuresis does not flush stones and worsens pain/obstruction.
- **Medical expulsive therapy (MET): α-blocker (tamsulosin 0.4 mg OD)** ± an NSAID (ibuprofen 600 mg TID) ± short low-dose prednisone increases spontaneous passage, most effective for **distal ureteric stones >5 mm**. Stones **<5–6 mm** usually pass spontaneously.
- **Indications for urologic intervention:** UTI/infection behind obstruction, low likelihood of passage (**stone ≥6 mm**, anatomic abnormality, solitary kidney), intractable pain/vomiting, or non-passage after a few weeks.
- **Emergency drainage** (ureteric **stent** or **percutaneous nephrostomy**) for the infected, obstructed kidney — *definitive stone removal is deferred until sepsis is treated*.
- **Definitive procedures** (chosen by stone size, site, composition, anatomy):
  - **Ureteroscopy + laser/basket** — mid/distal ureteric stones; outpatient, most reliable.
  - **Extracorporeal shock-wave lithotripsy (ESWL)** — least invasive; best for stones <1 cm in the lower pole or <2 cm elsewhere; poor for hard stones (cystine, brushite, >1000–1200 HU) and obese patients; **contraindicated in pregnancy, untreated UTI, coagulopathy/anticoagulation, and discouraged for staghorn/infected stones**.
  - **Percutaneous nephrolithotomy (PCNL)** — for large (>15–20 mm) and **staghorn** calculi; highest stone-free rate. Open ureterolithotomy/pyelolithotomy is now rarely needed.

Prevention by stone type

- **Universal measure (all types):** high fluid intake to keep **urine volume ≥2–2.5 L/day** — proven by RCT to halve recurrence; tailor advice to the measured 24-h volume.

Stone type	Targeted preventive measures
Calcium oxalate	Normal-to-high dietary calcium (~1000–1200 mg/d), restrict sodium (<2.5–3.5 g/d) & animal protein, reduce sucrose/fructose; **thiazide** (higher dose than for HTN — chlorthalidone/indapamide OD, HCTZ BD) for hypercalciuria; **potassium citrate** for hypocitraturia; **allopurinol** if hyperuricosuric; avoid high-dose vitamin C; DASH / Mediterranean diet
Calcium phosphate	Thiazide + sodium restriction; potassium citrate (with **urine-pH monitoring**, as alkali can worsen phosphate stones); reduce dietary phosphate; exclude/treat distal RTA & hyperparathyroidism
Uric acid	**Alkalinise urine to pH 6.5** (potassium citrate/bicarbonate) — *mainstay*; reduce purine intake; add **xanthine-oxidase inhibitor (allopurinol 300 mg/d or febuxostat)** if alkalinisation insufficient (lowers urine uric acid 40–50%)
Struvite	**Complete surgical clearance** (PCNL) + prevent/treat UTI; **acetohydroxamic acid** (urease inhibitor) for refractory recurrent cases
Cystine	High urine volume (3–4 L/d), low sodium, alkalinise to **pH 7.0–7.5** (potassium citrate); thiol drugs that solubilise cystine — **tiopronin (preferred) or D-penicillamine**
Primary hyperoxaluria (type I)	Pyridoxine (vitamin B6) in selected patients; **siRNA agents lumasiran / nedosiran** to cut hepatic oxalate production

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled coronal nephron/urinary tract diagram of stone impaction sites:** label *Kidney (calyx, renal pelvis)*, *Randall's plaque at papillary tip*, and the **three ureteric narrowings** — *Pelvi-ureteric (UPJ) junction*, *crossing of iliac vessels / pelvic brim*, *Vesico-ureteric (UVJ) junction* — plus *bladder*; mark *hydroureteronephrosis* proximal to an obstructing stone.
- **Urine-pH vs stone-type bar/line:** label axis pH 4.5 → 8.5; mark *uric acid ≤5.5*, *calcium oxalate (pH-independent)*, *calcium phosphate ≥6.5*, *cystine (more soluble at high pH)*, *struvite >8.0*.

Clinical / Diagnostic significance

- Nephrolithiasis is a **marker of systemic disease** — independently associated with hypertension, CKD/ESRD, reduced bone mineral density, gout, type 2 diabetes and cardiovascular disease; evaluate accordingly.
- A **culture-negative pyuria with haematuria** plus flank pain should prompt CT for an occult ureteric stone before labelling "cystitis".
- Unexplained recurrent calcium stones mandate exclusion of **primary hyperparathyroidism** (serum Ca, PTH) and **distal RTA** (hyperchloraemic metabolic acidosis with inappropriately alkaline urine, hypocitraturia, hypokalaemia).
- **Stone composition and 24-h urine chemistry**, not symptoms, drive long-term prevention — preventive therapy is usually **life-long** with annual 24-h urine monitoring and radiation-sparing follow-up imaging (prefer ultrasound).

High-yield exam pointers

- Commonest stone = **calcium oxalate (~75%)**; calcium-containing stones ~85% and radiopaque; **uric acid** stones are radiolucent on KUB but visible on CT.
- **Non-contrast helical CT** = investigation of choice (detects 1-mm stones); **ultrasound** in pregnancy/follow-up.
- Restless writhing patient with colicky flank-to-groin pain + haematuria = ureteric stone; **NSAIDs first-line analgesia**.
- **Obstructed + infected kidney = emergency drainage** (stent/nephrostomy) — "pus under pressure".
- Stones **<5 mm** usually pass; offer **tamsulosin MET**; **≥6 mm** or persistent → intervention; **staghorn → PCNL**.
- **Citrate** = key inhibitor; **hypocitraturia → potassium citrate**; **hypercalciuria → thiazide + low sodium**.
- Do **not** restrict dietary calcium — it raises oxalate absorption and stone risk; restrict **sodium, animal protein, oxalate**; fluids to **≥2–2.5 L urine/day**.
- **Struvite** = infection stone (urease-positive *Proteus*); **cystine** = AR, hexagonal crystals, treat with tiopronin + alkali; **uric acid** stones managed primarily by **urinary alkalinisation to pH 6.5**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Nephrolithiasis" (Gary C. Curhan): pathogenesis, Randall's plaque, stone types, risk factors, evaluation, prevention by stone type.
- **Brenner & Rector's The Kidney** — "Urolithiasis": Randall's-plaque pathophysiology, hypocitraturia/dRTA, enteric & primary hyperoxaluria, pharmacotherapeutic trial evidence (thiazides, potassium citrate, allopurinol, thiol drugs).
- **CMDT 2026** — "Urologic Disorders: Urinary Stone Disease": clinical findings, metabolic thresholds, drug doses (tamsulosin, potassium citrate, allopurinol, thiazides), MET, ESWL/ureteroscopy/PCNL selection and contraindications.

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Emphysematous pyelonephritis

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Emphysematous pyelonephritis (EPN)* is an acute, severe, **necrotizing infection of the renal and perinephric tissues characterized by the production of gas within the renal parenchyma, collecting system and/or perirenal space** by gas-forming uropathogens. It is a **urological emergency** that occurs *almost exclusively in patients with poorly controlled diabetes mellitus*, frequently with co-existent urinary obstruction, and carries a high mortality if not promptly recognised and aggressively managed. It must be distinguished from the more benign *emphysematous pyelitis* (gas confined to the collecting system, parenchyma spared) and *emphysematous cystitis* (gas in the bladder wall/lumen).

Pathogenesis and predisposing factors

- **Diabetes mellitus** is the dominant risk factor — *62–100%* of patients in case series are diabetic, and serum glucose is often very high at presentation; EPN occurs **almost exclusively in poorly controlled diabetics**.
- **Mechanism of gas formation:** high urinary and tissue **glucose acts as a fermentable substrate** for facultative anaerobes, generating large volumes of gas (CO_2, hydrogen, nitrogen) through *fermentation*. In the *non-diabetic minority*, **fermentation of tissue protein** is the proposed gas source.
- **Contributory factors:** *impaired host immunity and microvascular disease of diabetes*, **urinary tract obstruction** (calculus, papillary necrosis, stricture — a common predisposant), high tissue glucose, and locally **reduced perfusion**, which favours anaerobic metabolism and necrosis.
- A **female preponderance** is consistently reported (ascending infection, shorter urethra). Most infection is *ascending* from the lower tract.
- The end result is **acute suppurative necrosis** of parenchyma; a fulminant course is characterised by *tissue necrosis, intravascular thrombosis and microabscess formation*.

Microbiology

- ***Escherichia coli*** is the single most common organism (**~45–54%** of episodes) — a *gas-forming, facultative anaerobic uropathogen*.
- ***Klebsiella pneumoniae*** is the next most frequent isolate.
- Less common: *Proteus mirabilis, Enterobacter, Pseudomonas aeruginosa* and, rarely, *Candida* and *Clostridium* species.
- **Bacteraemia** is demonstrable in **20–50%** of patients in whom blood cultures are obtained — reflecting the invasive, systemic nature of the disease.

Clinical presentation

- The presentation overlaps with severe acute pyelonephritis — the **classic triad of fever, vomiting and flank pain**.
- **Severe pyelonephritis** features: *high fever, rigors, nausea, vomiting, flank/costovertebral-angle (CVA) pain and marked CVA tenderness*; symptoms are usually acute in onset and may or may not be preceded by cystitis.

- **Systemic toxicity is common:** the patient is frequently *acutely ill, dehydrated, tachycardic and may present with septic shock*.
- **Crepitus** over the flank or a *palpable, tender renal mass* may rarely be appreciated when gas tracks into the retroperitoneum/subcutaneous tissue.
- **Frequent accompaniments / complications:** *acute kidney injury, diabetic ketoacidosis or hyperglycaemic crisis, thrombocytopenia, disturbance of consciousness, and shock* — these are also **adverse prognostic markers**.
- **Pneumaturia** suggests gas in the collecting system/bladder (more typical of emphysematous cystitis or pyelitis).
- A subset present with a **poor response to standard antibiotics for "pyelonephritis"**, or *persistent fever/bacteraemia*, which should prompt imaging to look for gas, abscess or obstruction.

Evaluation / Investigations

- **Urinalysis & urine culture:** pyuria, bacteriuria, haematuria; culture (with sensitivities) identifies the organism — *obtain before antibiotics where feasible*.
- **Blood culture:** positive in a substantial minority; identifies bacteraemia and guides therapy.
- **Blood investigations:** complete blood count (*leukocytosis with left shift; thrombocytopenia is a poor-prognosis marker*), **renal function (urea/creatinine — AKI is common)**, electrolytes, **blood glucose and HbA1c**, **arterial blood gas / serum lactate** (for acidosis and sepsis), and **CRP** (generally elevated). Screen for **DKA** (ketones, anion gap).
- **Plain abdominal radiograph (KUB):** may show mottled/streaky or crescentic gas over the renal shadow — but **identifies renal gas in only ~50%** of EPN cases (more sensitive in emphysematous cystitis).
- **Ultrasonography:** usually shows renal abnormality with high-amplitude echoes and "dirty" shadowing from gas, but is **less accurate than CT** for defining extent.
- **Contrast-enhanced CT is the imaging modality of choice** — it confirms the diagnosis, maps the **distribution and extent of gas, parenchymal destruction, fluid/abscess, obstruction and contralateral kidney**, and underpins the radiological classification that drives management.

Radiological classification (CT-based — Huang & Tseng) — directs management & prognosis:

Class	CT findings	Implication
Class 1	Gas confined to the **collecting system** (emphysematous *pyelitis*)	Best prognosis
Class 2	Gas confined to the **renal parenchyma** alone	Good outcome with drainage
Class 3A	Extension of gas/abscess into the **perinephric space**	Higher risk
Class 3B	Extension of gas/abscess into the **pararenal space** (beyond Gerota's fascia)	Higher risk
Class 4	**Bilateral** EPN, or EPN in a **solitary functioning kidney**	Worst prognosis

An alternative morphological scheme (Wan) divides EPN into Type I — parenchymal destruction with streaky/mottled gas and no fluid (the "dry," more necrotic, higher-mortality form) — and Type II — renal/perirenal fluid with bubbly/loculated gas (the "wet," lower-mortality form).

Adverse prognostic factors (≥2 predict failure of conservative management): *thrombocytopenia, acute kidney injury (raised creatinine), disturbance of consciousness, and shock.*

Management

Management is **multidisciplinary** (physician/intensivist, nephrologist, urologist, interventional radiologist) and combines **resuscitation, source control and metabolic control**.

- **Resuscitation & supportive care:** IV fluids, correction of dehydration and electrolytes, management of sepsis/septic shock, and **aggressive glycaemic control** (treat DKA/hyperglycaemia with insulin).
- **Empirical broad-spectrum IV antibiotics**, started promptly after cultures and de-escalated by sensitivities:
  - For hospitalised/systemically ill patients, an **IV β-lactam** is preferred — *ceftriaxone or cefepime, piperacillin-tazobactam, or a carbapenem*; an **aminoglycoside** (e.g. with ampicillin) is an effective addition/alternative. **Carbapenems** are used for ESBL-producing organisms.
  - Treatment is *culture-guided*; switch to oral once stable, with a total course typically extending well beyond uncomplicated pyelonephritis given tissue-invasive necrotising disease.
- **Relief of obstruction:** *ureteric stenting or percutaneous nephrostomy* if there is obstructive uropathy (e.g. obstructing calculus, papillary necrosis) — essential for source control.
- **Percutaneous catheter drainage (PCD)** of gas/abscess, combined with antibiotics, is now the **recommended initial intervention** and the modern "kidney-sparing" standard; it has *similar or lower mortality* than emergency nephrectomy or medical therapy alone.
- **Nephrectomy** (emergency or delayed/elective) is reserved for **failure of PCD plus medical therapy**, fulminant/extensive disease, or a non-functioning kidney — typically in patients with **≥2 adverse prognostic factors** or extensive (Class 3B/4) disease.
- **Outcome:** mortality ranges from **7–20%** in less severe disease to **~70%** in a fulminant course (necrosis, intravascular thrombosis, microabscesses). Comparative case-series mortality: **~50%** with medical therapy alone, **~25%** with medical therapy plus emergency nephrectomy, and **~13.5%** with medical therapy plus initial percutaneous drainage — underscoring the value of early drainage.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled CT cross-section of EPN (axial):** label *renal parenchyma with destruction, intraparenchymal/streaky gas (mottled lucencies), gas tracking into perinephric space, Gerota's fascia, pararenal space, obstructing calculus/collecting-system gas, and normal contralateral kidney.* Annotate the **Huang-Tseng classes 1–4** alongside (gas in collecting system → parenchyma → perinephric → pararenal → bilateral/solitary).
- **Management flow-diagram:** *Suspected EPN → resuscitate + IV antibiotics + glycaemic control → CT (classify) → relieve obstruction (stent/nephrostomy) → Class 1–2 or <2 risk factors: percutaneous drainage; Class 3–4 with ≥2 risk factors / failure of PCD: nephrectomy.*

Clinical / Diagnostic significance

- EPN should be **suspected in any diabetic with severe/septic pyelonephritis failing to respond promptly**, or with gas seen on KUB/USG — **CT is mandatory** to confirm and stage.
- **Early percutaneous drainage with relief of obstruction has shifted practice away from routine emergency nephrectomy**, improving renal preservation and survival.
- **Glycaemic control and treatment of the underlying diabetes** are integral, not adjunctive — high tissue glucose perpetuates gas-forming infection.
- Differentiate from *xanthogranulomatous pyelonephritis* (chronic, staghorn-calculus-associated, lipid-laden foamy macrophages, usually needs nephrectomy) and from benign **post-instrumentation gas** in the collecting system (gas in *tissue* defines emphysematous infection).

High-yield exam pointers

- EPN = **gas-forming necrotising infection of renal/perinephric tissue**, *almost exclusively in poorly controlled diabetics*.
- ***E. coli*** (commonest) and ***Klebsiella pneumoniae*** are the leading pathogens; *bacteraemia in 20–50%*.
- **Pathogenesis** = fermentation of **high tissue/urinary glucose** by facultative anaerobes → gas; obstruction and impaired immunity contribute.
- **CT is the investigation of choice**; KUB detects renal gas in only ~50%.
- **Huang-Tseng Class 1→4** (collecting system → parenchyma → perinephric → pararenal → bilateral/solitary) classifies and prognosticates.
- **Four poor-prognosis factors:** *thrombocytopenia, AKI, altered sensorium, shock*; **≥2** predicts failure of conservative care.
- **Modern management = antibiotics + glycaemic/sepsis control + percutaneous drainage + relief of obstruction**; nephrectomy only if these fail.
- Mortality **7–20%** (less severe) up to **~70%** (fulminant); PCD-based therapy gives the lowest mortality (~13.5%).
- Distinguish from **emphysematous pyelitis** (collecting-system gas, parenchyma spared, benign) and **emphysematous cystitis** (bladder).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis" (definition of EPN, gas-forming *E. coli*, percutaneous drainage ± elective nephrectomy; pyelonephritis antibiotic regimens).
- **Brenner & Rector's The Kidney** — "Urinary Tract Infection in Adults" (dedicated *Emphysematous Cystitis and Pyelonephritis* section: pathogenesis, microbiology, diabetic/female predominance, CT as modality of choice, mortality figures, and the shift from emergency nephrectomy to percutaneous drainage).
- **CMDT 2026** — "Urologic Disorders" (acute pyelonephritis evaluation and empirical antibiotic management; EPN as a life-threatening complication in diabetics).

Coverage note: The **Huang & Tseng CT classification (Classes 1–4)**, the **Wan Type I/II morphological types**, and the four adverse prognostic factors are *universally accepted standard urological/nephrological references* used to stage and triage EPN but were **not present verbatim in the local corpus**; they are included as standard, accurate exam content. All organism frequencies, mortality percentages, imaging yields, pathogenesis and management principles are grounded in Brenner, Harrison and CMDT as cited above.

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Focal segmental glomerulosclerosis

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

Definition / Introduction — *Focal segmental glomerulosclerosis (FSGS)* is not a single disease but a **clinico-pathological pattern of podocyte injury** characterised by segmental (part of the tuft) scars in *some but not all* (focal) glomeruli, with **proteinuria** as its ubiquitous clinical hallmark. It is best regarded as a *podocytopathy* — a final common pathway of glomerular injury with multiple causes (primary/idiopathic, secondary/adaptive, viral and genetic). FSGS is now the **most common cause of primary glomerular disease leading to ESKD in the United States** and an important cause of steroid-resistant nephrotic syndrome in both children and adults.

Etiological Classification (Primary, Secondary, Genetic)

- **Primary (idiopathic) FSGS** — driven by a presumed **circulating permeability factor** (yet to be definitively identified); typically presents with abrupt, *full nephrotic syndrome* and diffuse foot-process effacement; the form most likely to respond to immunosuppression and to recur after transplantation.
- **Secondary / adaptive FSGS** — maladaptive response to nephron loss, glomerular hypertrophy or hyperfiltration; usually sub-nephrotic proteinuria with *preserved serum albumin* and *segmental* foot-process effacement.

Category	Representative causes (from Harrison Table 326-4 / Brenner Box 31.6)
Adaptive (hyperfiltration / ↓ nephron mass)	Obesity, oligomeganephronia, unilateral renal agenesis/post-nephrectomy, reflux nephropathy, sickle cell disease, cyanotic congenital heart disease, hypoxic pulmonary disease, glomerulomegaly
Viral	HIV (collapsing), hepatitis B, parvovirus B19, SARS-CoV-2
Drug-associated	Heroin, analgesics, **bisphosphonates (pamidronate)**, interferon, anabolic steroids, ecstasy, lithium
Other secondary	Hypertensive nephrosclerosis, cholesterol emboli, radiation nephritis
Genetic / familial podocytopathies	*NPHS1* (nephrin), *NPHS2* (podocin), *ACTN4* (α-actinin-4), *TRPC6*, *INF2* (inverted formin 2), *WT1*, *PLCE1*, *CD2AP*; Fabry disease (α-galactosidase A); nephrosialidosis
High-risk genetic background	**APOL1 risk alleles (G1/G2)** in those of sub-Saharan African ancestry

Pathology — Columbia Histological Variants

- **Light microscopy:** segmental glomerular **sclerosis/consolidation** with capillary collapse, hyalinosis (insudated plasma proteins), foam cells and adhesions to Bowman's capsule. Lesions are most prominent at the **cortico-medullary junction**, so a superficial biopsy may miss them and be mislabelled minimal change disease (MCD).
- **Immunofluorescence:** non-specific **IgM and C3** trapped *in the sclerotic segments only* (not pathogenic immune complexes).
- **Electron microscopy: foot-process effacement** — diffuse in primary, more *segmental/partial* in secondary FSGS; no immune-type dense deposits in non-sclerotic glomeruli.
- The **Columbia classification** recognises *five morphological variants* correlating with cause and prognosis:

Variant	Key features	Demographics / prognosis
NOS (classic)	Segmental sclerosis without distinctive features; commonest (~42%)	Primary or secondary; intermediate outcome
Perihilar	Sclerosis + hyalinosis at the vascular pole; glomerulomegaly	Typical of **adaptive/secondary** FSGS; often sub-nephrotic
Tip lesion	Consolidation at the tubular (urinary) pole opposite the hilum	Older **Caucasian** males; **steroid-responsive, best prognosis**
Cellular	Endocapillary hypercellularity, foam cells; heavy proteinuria	Intermediate remission/ESKD rates
Collapsing (collapsing glomerulopathy)	Global/segmental capillary **collapse** + podocyte hyperplasia ("pseudocrescents")	**African-American**, **HIV**-associated; massive proteinuria; **worst prognosis**

Pathogenesis — Podocyte Injury as the Final Common Pathway

- **Circulating permeability factor (primary FSGS):** plasma factor increasing glomerular albumin permeability; supported by **recurrence within hours–days of transplantation** and response to

plasmapheresis. Candidate factors include **soluble urokinase receptor (suPAR)** (activates podocyte β3-integrin) and a galactose-binding factor — *neither yet conclusively proven*.

- **Genetic podocytopathies:** mutations disrupt the **slit diaphragm / actin cytoskeleton / GBM**. *NPHS2* (podocin) is the **most frequent genetic cause of steroid-resistant nephrotic syndrome** (the R138Q and R229Q variants are characteristic); *NPHS1* causes congenital (Finnish-type) nephrotic syndrome; *ACTN4*, *TRPC6* and *INF2* cause autosomal-dominant adult FSGS.
- **APOL1 risk variants (G1/G2, chromosome 22):** explain the ~4-fold excess of FSGS and the 18–50-fold excess of HIV-associated collapsing FSGS in people of African ancestry (the same alleles that confer protection against *Trypanosoma brucei rhodesiense* — analogous to sickle trait and malaria).
- **Adaptive (maladaptive) hyperfiltration:** nephron loss → ↑ single-nephron GFR and intraglomerular hypertension → podocyte stretch, dropout and segmental sclerosis (mediated partly by **TGF-β1**). Worsened by high dietary protein; ameliorated by RAAS blockade and protein restriction.
- **Direct injury:** viruses (HIV → collapsing variant with endothelial *tubuloreticular inclusions*), drugs (pamidronate, interferon, anabolic steroids).

Clinical Features and Natural History

- **Proteinuria is the hallmark** — ranges from sub-nephrotic (1–2 g/day) to >10 g/day with full nephrotic syndrome (oedema, hypoalbuminaemia <2 g/dL, hyperlipidaemia).
- **Microscopic (and frank) haematuria in >50%**, hypertension in ~⅓, and impaired GFR at presentation in ~25–50%.
- **Collapsing variant** — rapid onset, very heavy proteinuria, low albumin, high creatinine, rapid decline to ESKD; **tip lesion** — abrupt MCD-like nephrosis but favourable, often reversible AKI and good response.
- **Prognosis:** FSGS *rarely remits spontaneously*. Nephrotic-range proteinuria with kidney injury carries a poor outcome — **~50% reach ESKD within 10 years**; proteinuria >10 g/day → most reach ESKD within ~3 years. **Achieving remission (spontaneous or treatment-induced) is the single best prognostic indicator**; entry serum creatinine >1.3 mg/dL also predicts poor renal survival.

Diagnosis and Investigations

- **Kidney biopsy is required** for diagnosis (LM + IF + EM); a deep/cortico-medullary sample is essential to avoid a false MCD label.
- **Quantify proteinuria** — spot urine protein:creatinine ratio or 24-h protein; urinalysis may show **oval fat bodies / "Maltese crosses"** under polarised light.
- **Exclude secondary and genetic causes before treating:** HIV serology (especially with collapsing pattern), hepatitis B/C, parvovirus; drug history (bisphosphonates, heroin, anabolic steroids, interferon); assessment for obesity, reflux, sickle cell, reduced nephron mass; **genetic testing** (increasingly in children and steroid-resistant cases).
- Supportive labs: hypoalbuminaemia, hyperlipidaemia, **normal complement** (helps distinguish from immune-complex GN).

Treatment

- **Supportive / antiproteinuric (all forms): RAAS blockade** (ACE inhibitor or ARB) ± mineralocorticoid-receptor antagonist; **SGLT2 inhibitor**; statin for dyslipidaemia; salt restriction and diuretics for oedema; anticoagulation for thrombotic complications of nephrotic syndrome.
- **Primary FSGS with nephrotic syndrome — immunosuppression:**
  - **Corticosteroids first-line — prednisone 1 mg/kg/day** (children 60 mg/m^2/day) for **4–16 weeks** followed by slow taper; response is *slower and less frequent than in MCD* — remission in only ~**20–45%**, median time to remission 3–4 months.
  - **Calcineurin inhibitors** for steroid-resistant or steroid-intolerant disease — **cyclosporine 5 mg/kg/day** (RCTs by Ponticelli and the North American Nephrotic Syndrome Study Group show induction of remission); relapse is common on withdrawal and chronic use risks nephrotoxicity / interstitial fibrosis.
  - **Mycophenolate mofetil** and **rituximab** are second-/third-line/steroid-sparing options with limited evidence (FSGS Clinical Trial: MMF + pulse dexamethasone *not* superior to cyclosporine).
- **Secondary and genetic FSGS: no role for steroids/immunosuppression** — treat the underlying cause (weight loss, stop offending drug, antiretrovirals for HIV) and maximise antiproteinuric therapy.
- **Transplantation: FSGS recurs in ~30% of allografts** (more with primary, less with secondary, rarely with genetic disease); recurrent post-transplant FSGS from a presumed circulating factor often responds to **plasmapheresis**.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Diagram 1 — Glomerulus with a segmental sclerotic lesion:** label *Bowman's capsule, capillary tuft, segmental sclerosis/hyalinosis, foam cells, adhesion (synechia) to Bowman's capsule, afferent & efferent arterioles (vascular/hilar pole), tubular (urinary) pole, effaced podocyte foot processes*.
> - **Diagram 2 — Columbia variant map (small glomerular line-drawings):** label *Perihilar (sclerosis at vascular pole), Tip lesion (consolidation at tubular pole), Collapsing (capillary collapse + podocyte hyperplasia), Cellular (endocapillary hypercellularity), NOS*.

Clinical / Diagnostic significance

- A **deep cortico-medullary biopsy** is mandatory — superficial sampling misses segmental lesions and causes mislabelling as MCD; steroid-resistant "MCD" on repeat biopsy is often FSGS.
- **Distinguishing primary from secondary FSGS is therapeutically decisive:** primary = full nephrosis + diffuse effacement → immunosuppress; secondary = sub-nephrotic + preserved albumin + segmental effacement → treat the cause, avoid steroids.
- **APOL1 genotyping** identifies high-risk African-ancestry patients (collapsing/HIV-associated disease) and informs transplant donor selection.
- **Remission of proteinuria** is the key modifiable determinant of long-term renal survival; **collapsing variant** flags aggressive disease and should prompt HIV testing.

High-yield exam pointers

- FSGS = **podocytopathy**; **proteinuria is the hallmark**; commonest cause of **primary glomerular ESKD in the US**.
- **Five Columbia variants:** NOS (commonest), Perihilar, **Tip (best prognosis, steroid-responsive)**, Cellular, **Collapsing (worst, HIV/African-American, APOL1)**.
- **IF:** segmental **IgM + C3** (trapped, non-pathogenic); **EM:** foot-process effacement (diffuse in primary, segmental in secondary).
- **NPHS2/podocin** = commonest genetic cause of **steroid-resistant nephrotic syndrome**; key genes — *NPHS1, ACTN4, TRPC6, INF2, WT1*.
- **APOL1 G1/G2** alleles → ↑ FSGS & HIV-associated collapsing FSGS in African ancestry.
- **Treatment:** RAAS blockade + SGLT2i for all; **prednisone 1 mg/kg/day** for primary nephrotic FSGS; CNI/rituximab/MMF for resistant disease; **no immunosuppression for secondary/genetic**.
- **Prognosis:** ~50% reach ESKD in 10 years; **remission of proteinuria = best prognostic sign**; rarely remits spontaneously.
- **Recurs in ~30% of kidney transplants** (primary > secondary); recurrent disease may respond to **plasmapheresis**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Glomerular Diseases"** (FSGS pattern of nephrotic syndrome; Table 326-4 causes; Columbia variants; APOL1; treatment).
- **Brenner & Rector's The Kidney — "Primary Glomerular Disease"** (Box 31.6 classification, Columbia variants, gene table including NPHS1/NPHS2/ACTN4/TRPC6/INF2, suPAR & permeability-factor pathogenesis, GDCN/Columbia outcome data, steroid/cyclosporine/MMF/rituximab trial evidence) and **"Glomerular Cell Biology and Podocytopathies"** for podocyte mechanisms.
- **CMDT 2026 — "Kidney Disease" (Nephrotic Spectrum: Focal Segmental Glomerulosclerosis)** for current management (RAAS blockade, SGLT2i, prednisone 1 mg/kg/day 4–16 weeks, secondary/APOL1 immunosuppression caveats, transplant recurrence).

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Goodpasture's syndrome

Asked in: Paper III Dec 2023 · Paper III Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Goodpasture's syndrome is the **pulmonary-renal form of anti-glomerular basement membrane (anti-GBM) disease**, classically defined by crescentic glomerulonephritis, pulmonary hemorrhage, and circulating or tissue-bound anti-GBM antibodies. Anti-GBM disease may be renal-limited; the term Goodpasture's syndrome is best reserved for cases with both glomerulonephritis and alveolar hemorrhage. It is a nephrology emergency because renal function can fall from normal to dialysis-requiring kidney failure within days to weeks, while pulmonary hemorrhage can cause fatal hypoxemia or airway flooding.

Etiopathogenesis and epidemiology

- The autoantibody is directed mainly against the **noncollagenous NC1 domain of the alpha-3 chain of type IV collagen** in the specialized alpha-3/alpha-4/alpha-5 collagen IV network of the GBM and alveolar capillary basement membrane.
- Harrison and Brenner describe anti-GBM disease as an autoimmune **conformeropathy**: normally sequestered epitopes in the collagen IV NC1 hexamer become exposed after infection, smoking, oxidant injury, or solvent exposure.
- The kidney and lung are selectively involved because the target antigen is concentrated in the **glomerular basement membrane** and **alveolar capillary basement membrane**.
- Lung hemorrhage usually requires an additional pulmonary injury that increases antibody access to alveolar basement membrane; important associations include **cigarette smoking**, pulmonary infection, hydrocarbon solvents, cocaine inhalation, metallic dust, and d-penicillamine. CMDT also lists alemtuzumab exposure.
- Anti-GBM glomerulonephritis accounts for about **10-20% of acute rapidly progressive glomerulonephritis (RPGN)**. Brenner describes anti-GBM disease as rare, about **1-2% of all glomerular diseases** in most estimates.
- Age distribution is **bimodal**: young men in the third decade often present with full pulmonary-renal disease, while older adults in the sixth to seventh decades more often have renal-limited disease and less sex specificity.
- Genetic predisposition is suggested by HLA associations; CMDT notes **HLA-DR2 and HLA-B7** as predisposing antigens.

Clinical presentation

- **True Goodpasture triad**: proliferative/crescentic glomerulonephritis + pulmonary hemorrhage + anti-GBM antibodies.
- Pulmonary hemorrhage may **precede, coincide with, or follow** renal disease. Symptoms include cough, dyspnea, hemoptysis, fever, sudden fall in hemoglobin, hypoxemia, and diffuse pulmonary infiltrates. Hemoptysis may be mild or absent despite diffuse alveolar hemorrhage.
- Renal disease is usually **acute nephritic syndrome or RPGN**: microscopic hematuria, dysmorphic RBCs, red cell casts, subnephrotic proteinuria, edema, hypertension, oliguria, and rapidly rising creatinine.

- Proteinuria is common but usually **not nephrotic range**; severe nephrotic-range proteinuria should widen the differential diagnosis or suggest overlap pathology.
- Constitutional symptoms may occur: fatigue, malaise, chills, fever, weight loss, nausea/vomiting, and arthralgia. Purpura, arthritis, or other systemic vasculitic features suggest **double-positive anti-GBM plus ANCA disease** rather than isolated Goodpasture's syndrome.
- Pulmonary-renal syndrome differential includes granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, SLE, cryoglobulinemia, IgA vasculitis, infection-related GN, and anticoagulant or coagulopathy-related alveolar hemorrhage.

Investigations and diagnosis

- Treat suspected disease as urgent. Send **CBC**, urea/creatinine/electrolytes, urinalysis with microscopy, urine protein quantification, ABG if hypoxemic, chest radiograph or HRCT, anti-GBM antibody, ANCA with MPO/PR3 specificity, ANA/anti-dsDNA, C3/C4, hepatitis/HIV tests where indicated, and coagulation profile.
- Urine microscopy shows **glomerular hematuria** with dysmorphic RBCs and red cell casts; creatinine may rise over days to weeks.
- Serology: circulating **anti-GBM antibodies are present in >90%** of typical cases; complement levels are usually **normal**. A minority are also ANCA-positive, most often MPO-ANCA.
- Chest imaging shows bilateral or patchy alveolar infiltrates when pulmonary hemorrhage is present, but imaging is not specific.
- Bronchoscopy is useful when the pulmonary diagnosis is uncertain; **sequential BAL aliquots becoming progressively bloodier** support diffuse alveolar hemorrhage, and hemosiderin-laden macrophages support recent or recurrent bleeding.
- **Kidney biopsy is the diagnostic and prognostic test** when feasible, but patients with pulmonary hemorrhage and strong clinical suspicion should receive emergency treatment before confirmation.

Pathology and diagnostic contrasts

Feature	Goodpasture / anti-GBM disease	ANCA-associated vasculitis	Immune-complex GN / SLE
Key serology	Anti-GBM antibody high; complement normal	MPO-ANCA or PR3-ANCA; complement usually normal	ANA/anti-dsDNA, cryoglobulins or infection markers; complement often low
Light microscopy	Focal necrosis early; commonly **diffuse crescentic GN** with circumferential crescents	Necrotizing crescentic GN	Endocapillary proliferation; immune-complex patterns
Immunofluorescence	**Intense diffuse linear IgG** along GBM; often fine C3; C1q usually absent	Pauci-immune or negative	Granular deposits; lupus may show "full house"
Electron microscopy	Usually no immune-type electron-dense deposits; GBM gaps may be seen	No immune deposits	Electron-dense deposits by location

Feature	Goodpasture / anti-GBM disease	ANCA-associated vasculitis	Immune-complex GN / SLE
Relapse tendency	Rare once quiescent unless double-positive	Common, especially PR3/GPA	Depends on underlying disease

- The diagnostic biopsy phrase to write is: **crescentic necrotizing glomerulonephritis with linear IgG staining along the GBM**.
- Brenner notes that the common biopsy picture is diffuse crescentic GN involving more than half of glomeruli, with compressed tufts, focal necrosis, GBM breaks, and interstitial inflammation; chronic biopsies show glomerulosclerosis, tubular atrophy, and interstitial fibrosis.
- Similar **linear IgG deposition** can occur along alveolar capillary walls in the lung.

Management

- **Admit immediately**; ICU care is needed for hypoxemia, massive hemoptysis, respiratory failure, severe AKI, oliguria, or dialysis requirement.
- Supportive care: oxygen, ventilatory support if needed, transfuse for severe anemia, stop smoking/solvent exposure, treat intercurrent infection, manage fluid overload, control blood pressure, avoid unnecessary anticoagulation during active bleeding, and start dialysis for standard indications.
- Disease-specific therapy has three simultaneous goals: **remove circulating antibody**, **stop new antibody production**, and **control inflammatory injury**.
- **Therapeutic plasma exchange (plasmapheresis)**: start urgently; daily exchanges are used in severe disease, often for **8-10 treatments** or up to about **2 weeks**, guided by pulmonary bleeding, renal course, and fall in anti-GBM titers. It is especially important for pulmonary hemorrhage because lung bleeding may respond dramatically.
- **Glucocorticoids**: IV pulse methylprednisolone may be used for several days in severe disease, followed by high-dose oral prednisone; Brenner gives oral prednisone **1 mg/kg/day** or IV methylprednisolone **30 mg/kg/day up to 1000 mg/day** as typical steroid dosing.
- **Cyclophosphamide**: used with steroids to suppress antibody formation; Brenner gives **2 mg/kg/day** as a typical oral dose. Adjust for renal function, monitor CBC, infection risk, hemorrhagic cystitis, fertility risk, and cumulative toxicity.
- Continue immunosuppression until anti-GBM antibodies are negative and disease is controlled; Brenner notes that immunosuppression is usually continued for about **6 months** with tapering. Azathioprine may be used as less toxic maintenance in selected patients after antibody disappearance.
- **Rituximab** has limited evidence and is reserved for refractory disease or cyclophosphamide-intolerant patients; it should not replace urgent plasma exchange in life-threatening pulmonary hemorrhage.

Prognosis and follow-up

- Outcome depends mainly on **renal status at presentation** and speed of treatment. Lung hemorrhage often improves with plasma exchange, whereas renal recovery is poor if irreversible crescentic scarring is already established.

- Poor renal prognostic markers: oliguria, dialysis requirement at presentation, serum creatinine around **>5-6 mg/dL** or severe renal failure, **>50% crescents**, advanced interstitial fibrosis/tubular atrophy, and delayed therapy.
- Untreated disease progresses to uremia and may be fatal from pulmonary hemorrhage or renal failure; modern rapid diagnosis, dialysis, ventilatory support, plasma exchange, and immunosuppression have markedly improved survival.
- Anti-GBM disease is typically a **one-shot disease** with rare relapse once antibodies disappear; persistent or recurrent disease should prompt evaluation for ANCA double positivity, infection triggers, and ongoing exposure.
- Follow anti-GBM titers until negative, serial creatinine/eGFR, urine sediment/proteinuria, hemoglobin, chest symptoms, and cyclophosphamide toxicity. ANCA-positive patients require longer relapse surveillance.
- Kidney transplantation is considered only after the acute illness is quiescent and anti-GBM antibodies are absent; recurrence in the allograft is uncommon when transplantation is delayed until seronegativity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pulmonary-renal syndrome flow diagram**: trigger (infection/smoking/solvent) -> exposed alpha-3 NC1 collagen IV epitope -> circulating anti-GBM IgG -> kidney GBM injury (hematuria, RBC casts, RPGN) + alveolar capillary injury (diffuse alveolar hemorrhage, hemoptysis, hypoxemia).
- **Renal biopsy sketch**: glomerular tuft, Bowman space, circumferential cellular crescent, compressed tuft, segmental necrosis, GBM break, and a side panel labelled "linear IgG on immunofluorescence".

Clinical / Diagnostic significance

- In any patient with **hemoptysis plus hematuria or AKI**, send anti-GBM antibody and ANCA immediately; do not wait for classical hemoptysis because diffuse alveolar hemorrhage may be occult.
- Normal complement with RPGN narrows the diagnosis toward **anti-GBM disease or ANCA vasculitis** rather than lupus, cryoglobulinemia, or postinfectious GN.
- A positive anti-GBM antibody is highly useful, but biopsy remains important for prognosis because the percentage of crescents and fibrosis determines renal salvageability.
- Plasma exchange is controversial in isolated ANCA vasculitis but is standard in Goodpasture's syndrome and in ANCA disease with coexistent anti-GBM antibodies.
- In examination answers, separate **anti-GBM disease** from **Goodpasture's syndrome**: renal-limited anti-GBM GN is not true Goodpasture unless pulmonary hemorrhage is present.

High-yield exam pointers

- Write the triad: **crescentic GN + pulmonary hemorrhage + anti-GBM antibodies**.
- Target antigen: **NC1 domain of alpha-3 type IV collagen** in GBM and alveolar basement membrane.

- Risk/exposure clues: **young male smoker**, recent respiratory infection, hydrocarbon solvent exposure, and pulmonary-renal presentation.
- Urine: dysmorphic RBCs, **RBC casts**, subnephrotic proteinuria, rapidly rising creatinine.
- Complement is usually **normal**; anti-GBM antibody is positive in **>90%**.
- Biopsy hallmark: **linear IgG along GBM** with crescentic necrotizing GN.
- Treatment must be urgent: **plasmapheresis + high-dose corticosteroid + cyclophosphamide**.
- Poor renal prognosis: dialysis at presentation, oliguria, creatinine >5-6 mg/dL, >50% crescents, and interstitial fibrosis.
- Relapse is uncommon after antibody clearance; relapse suggests double-positive ANCA disease or renewed exposure.

SOURCE & COVERAGE

Harrison 22e — "Glomerular Diseases", "Hemoptysis", "Bronchoscopy"; Brenner & Rector's The Kidney — "Secondary Glomerular Disease", "Primary Glomerular Disease", "Treatment of Glomerulonephritis"; CMDT 2026 — "Kidney Disease", "Pulmonary Disorders".

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IgA nephropathy

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

Definition / Introduction — IgA nephropathy (IgAN, *Berger disease*) is an immune-complex glomerulonephritis defined by the **dominant or codominant deposition of IgA in the glomerular mesangium**, accompanied by mesangial proliferation. First described by *Berger and Hinglais* in the late 1960s, it is the **commonest primary glomerulonephritis worldwide**, classically presenting as *syntharyngitic* macroscopic haematuria in a young male. Once thought benign, it is now recognised that up to 25–40% of patients progress to end-stage kidney disease (ESKD).

Epidemiology

- **Most common primary glomerular disease worldwide**, especially in **Asia/Pacific Rim (30–45% of glomerular biopsies)**; 20% in southern Europe, ~10% in northern Europe/North America. Higher Asian rates partly reflect routine school urinalysis prompting biopsy of asymptomatic haematuria.
- Peak incidence in the **2nd–3rd decades**; ~80% are aged 16–35 years at biopsy. Uncommon under 10 years.
- Strong **male preponderance** (M:F ratio ~2:1, quoted up to 6:1). Rare in African-Americans; common in Native American Zuni and Navajo tribes.
- Mostly **sporadic**; familial clustering in 4–14%, usually autosomal dominant with incomplete penetrance. *IGAN1* locus on chromosome **6q22-23**; GWAS implicate the **MHC region (6p21)**, *DEFA*, *TNFSF13*, *CFH/CFHR*, and *C1GALT1 / C1GALT1C1 (Cosmc)* glycosylation genes — pointing to innate/adaptive immunity and host–intestinal mucosal interactions.

Pathogenesis — the "four-hit" model

The central abnormality is *not* a quantitative excess of IgA but a **qualitative defect in O-glycosylation of the hinge region of polymeric IgA1**:

- **Hit 1 — Galactose-deficient IgA1 (Gd-IgA1):** the 18-amino-acid, proline/serine/threonine-rich hinge region of IgA1 (absent in IgA2) carries O-linked sugars; premature sialylation and deficient β-1,3-galactosyltransferase (with reduced activity of its chaperone *Cosmc*) leave terminal **N-acetylgalactosamine exposed**, generating a neoepitope. This is an inherited trait (also raised in at-risk relatives).
- **Hit 2 — Anti-glycan autoantibodies:** circulating **IgG (and IgA1) autoantibodies** recognise the exposed Gd-IgA1 neoepitope.
- **Hit 3 — Immune-complex formation:** Gd-IgA1 and autoantibody form **circulating immune complexes** that escape hepatic clearance (defective asialoglycoprotein-receptor uptake) and via the asialoglycoprotein pathway.
- **Hit 4 — Mesangial deposition & injury:** complexes deposit in the mesangium (possibly via a transferrin receptor), activating **complement through the alternative and mannose-binding lectin pathways** (note: classical C1q pathway is *spared*), driving mesangial proliferation, cytokine/growth-factor release and secondary podocyte injury.
- The same Gd-IgA1 mechanism underlies **IgA vasculitis** (formerly Henoch-Schönlein purpura), the systemic counterpart of IgAN.

Pathology (kidney biopsy is mandatory for diagnosis)

Modality	Characteristic findings
Immunofluorescence (diagnostic)	**Dominant/codominant mesangial IgA** (100% by definition, mean ~3+), with **C3** in nearly all; often IgM (~84%) and IgG (~62%) at low intensity. **C1q rare/weak**. Distinctively, **λ (lambda) light chain staining > κ (kappa)**. Deposits are *J-chain–containing polymeric IgA1*.
Light microscopy	Spectrum from normal glomeruli → **focal/diffuse mesangioproliferative GN** (commonest) → proliferative/necrotising → crescentic → sclerosing GN. Mesangial matrix expansion + hypercellularity.
Electron microscopy	**Mesangial (paramesangial) electron-dense deposits**, beneath the perimesangial basement membrane; foot-process effacement when proteinuria is heavy.

- *Oxford classification (MEST-C score)* — the validated histological prognostic tool reported on every IgAN biopsy:
  - **M — Mesangial hypercellularity:** ≤0.5 = 0, >0.5 = 1
  - **E — Endocapillary hypercellularity:** absent = 0, present = 1
  - **S — Segmental glomerulosclerosis:** absent = 0, present = 1
  - **T — Tubular atrophy / interstitial fibrosis:** ≤25% = 0, 26–50% = 1, >50% = 2
  - **C — Crescents** (added 2016/17): none = 0, in <25% = 1, ≥25% = 2

Clinical features and natural history

- **Synpharyngitic macroscopic haematuria** — recurrent gross haematuria appearing **1–2 days after (concurrent with) an upper-respiratory or GI mucosal infection** in 40–50% at onset; this

short latency distinguishes it from the *longer 1–3 week latent period of post-streptococcal GN*. May be accompanied by loin pain/dysuria.

- **Asymptomatic microscopic haematuria ± proteinuria** (30–40%), frequently with hypertension — IgAN is the commonest cause of haematuria in hypertensive Caucasians.
- Less common: **nephrotic syndrome** (may signify coexistent minimal-change disease), malignant hypertension (<5%), and **RPGN/crescentic disease** with AKI (<10%).
- AKI accompanying an episode of gross haematuria is usually due to **tubular injury from haem pigment**, not true crescents, and typically recovers fully with a good long-term prognosis.
- Course is variable: spontaneous remission in some; **1–2% per year progress to ESKD**, with **~25–40% reaching ESKD over 20–25 years**.

Laboratory and diagnosis

- **No diagnostic serology**; **serum C3 and C4 are characteristically normal** (a key contrast to post-streptococcal GN, lupus nephritis, MPGN where complement is low).
- **Serum IgA raised in only 20–50%** — neither sensitive nor specific; serum/urinary Gd-IgA1 assays remain investigational.
- Urinalysis: **dysmorphic RBCs / RBC casts**; proteinuria usually <1 g/day (heavier with worse lesions).
- Skin biopsy IgA deposits are not reliable — **kidney biopsy is required to confirm**.

Treatment

- **Optimised supportive care is the cornerstone** (KDIGO): maximally-tolerated **RAAS blockade (ACE inhibitor or ARB)** titrated to **proteinuria <0.5–1 g/day** and BP control (~120/80 mmHg), plus dietary sodium restriction; treat for ~90 days before escalating. High-dose ARB (e.g. losartan 200 mg/day) is more antiproteinuric than standard dose.
- **SGLT2 inhibitors** (e.g. dapagliflozin) are now standard add-on in proteinuric CKD for renoprotection.
- **Sparsentan** — a **dual endothelin-A and angiotensin-II receptor antagonist** (PROTECT trial) — gives superior proteinuria reduction versus irbesartan; cost-limited.
- **Targeted-release (enteric) budesonide** (NefIgArd/NEFIGAN trials) targets gut mucosal (Peyer-patch) IgA production, reducing proteinuria with fewer systemic steroid effects.
- **Systemic corticosteroids** for persistent proteinuria >1 g/day despite supportive care, in patients with preserved GFR — efficacy weighed against infection risk (the **TESTING** trial was paused for excess serious infections; **STOP-IgAN** showed steroids cut proteinuria but did not preserve GFR).
- **Iptacopan**, an oral **factor B inhibitor of the alternative complement pathway**, reduces proteinuria without raising infection risk.
- **Crescentic/RPGN IgAN:** treat as for other crescentic GN — **pulse methylprednisolone + cyclophosphamide ± plasmapheresis**, then azathioprine maintenance.
- **Adjuncts of uncertain/limited benefit:** omega-3 fish oil; tonsillectomy (popular in Japan, *not* validated in the European VALIGA cohort); MMF (benefit largely in Asian cohorts only).

- **Transplantation** is excellent for ESKD, but **histological recurrence develops in ~30% by 5–10 years**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Glomerular schematic (immunofluorescence):** draw a glomerular lobule and label — *capillary loop, glomerular basement membrane (GBM), podocyte with foot processes, mesangial cell + matrix, granular mesangial IgA + C3 deposits (dominant/codominant), Bowman's capsule*. Caption: "Mesangial polymeric IgA1 deposition."
- **Four-hit pathogenesis flow diagram:** Hit 1 *Galactose-deficient IgA1 (Gd-IgA1)* → Hit 2 *anti-glycan IgG/IgA autoantibody* → Hit 3 *circulating immune complex* → Hit 4 *mesangial deposition → alternative + lectin complement activation → mesangial proliferation & podocyte injury*.

Clinical / Diagnostic significance

- **Distinguish from post-streptococcal GN:** IgAN = short/synpharyngitic latency, **normal complement**, recurrent gross haematuria; PSGN = 1–3 week latency, **low C3**, single episode.
- **Distinguish from IgA vasculitis (HSP):** identical renal histology but with systemic features — palpable purpura (buttocks/legs), arthralgia, abdominal pain/GI bleed; typically <20 years after infection.
- **Exclude secondary IgAN:** chronic liver disease/cirrhosis, coeliac disease, HIV, Crohn disease, ankylosing spondylitis, dermatitis herpetiformis, and **IgA-dominant Staphylococcus-associated GN** (mimics post-infectious GN, often in diabetics).
- **Prognostic markers of progression:** hypertension, **persistent proteinuria >1 g/day** (sustained ≥6 months is the strongest predictor), reduced eGFR at diagnosis, *absence* of macroscopic haematuria, male sex, older age, and high **MEST-C** score (M, S, T, C lesions).

High-yield exam pointers

- IgAN = **Berger disease** = commonest primary GN worldwide; mesangial IgA deposition.
- **Synpharyngitic haematuria** (gross haematuria *with* a URI, 1–2 days) is the hallmark — contrast with post-strep latency.
- **Serum complement (C3/C4) is NORMAL** — a favourite exam discriminator.
- IF: **dominant mesangial IgA + C3, λ > κ, C1q absent**; EM: mesangial dense deposits.
- Pathogenesis = **galactose-deficient IgA1** + anti-glycan IgG, complement via **alternative + lectin** pathways.
- Prognosis scored by the **Oxford MEST-C** classification; **proteinuria >1 g/day = key adverse marker**.
- Treatment ladder: **RAAS blockade + SGLT2i → sparsentan / TRF-budesonide / corticosteroids → cyclophosphamide for crescentic disease**.
- ESKD in **25–40% over 20–25 years**; recurs in ~30% of allografts.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Glomerular Diseases" (IgA nephropathy section).
- **Brenner & Rector's The Kidney** — "Primary Glomerular Disease" (IgA nephropathy: epidemiology, genetics, pathology, MEST-C/Oxford classification, pathogenesis, natural history, treatment trials — STOP-IgAN, TESTING, NEFIGAN, VALIGA).
- **CMDT 2026** — "Kidney Disease" (current management: RAAS blockade, SGLT2 inhibitors, sparsentan/PROTECT, targeted-release budesonide/NefIgArd, iptacopan).

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Intrinsic acute kidney injury (AKI)

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

Definition / Introduction — Acute kidney injury (AKI) is an abrupt fall in glomerular filtration over hours to days (within 7 days), with retention of nitrogenous wastes. By **KDIGO**, AKI = a rise in serum creatinine (SCr) **≥0.3 mg/dL within 48 h**, OR SCr **≥1.5× baseline within 7 days**, OR urine output **<0.5 mL/kg/h for >6 h**. The causes are partitioned into **prerenal, intrinsic, and postrenal**. **Intrinsic AKI** denotes structural damage to the renal parenchyma itself — the tubules, interstitium, glomeruli, or microvasculature — and accounts for up to **50%** of all AKI. Its commonest forms are **acute tubular necrosis (ATN)** from sepsis, ischaemia, and nephrotoxins; unlike prerenal azotaemia it is *not* immediately reversible by restoring perfusion.

Classification — Where Intrinsic AKI Sits

Intrinsic AKI is best catalogued **anatomically** by the dominant compartment injured, although overlap is common (e.g. a glomerular lesion can reduce post-glomerular flow and injure tubules).

Compartment	Representative causes	Share of intrinsic AKI
Tubules (ATN)	Ischaemia, sepsis, nephrotoxins (endogenous + exogenous)	~85%
Interstitium	Acute interstitial nephritis (drugs ~70–75%), infection, infiltration	~10–15%
Glomeruli	Acute glomerulonephritis, vasculitis	~5%
Microvasculature	TTP-HUS, DIC, malignant hypertension, scleroderma crisis, atheroemboli	Variable

- **ATN** is the prototype and the majority of hospitalised intrinsic AKI; prolonged **prerenal** hypoperfusion progresses to ischaemic ATN — the two are a **continuum**.
- Early recognition of glomerular/vasculitic and interstitial causes is critical because they are **treatable** (immunosuppression, plasma exchange, drug withdrawal) and may reverse the AKI.

Etiology of Intrinsic AKI

- **Sepsis-associated AKI** — complicates **>50%** of severe sepsis; GFR can fall *without overt hypotension*. Mechanisms: generalised arterial vasodilation (inducible NO synthase, cytokines), efferent arteriolar vasodilation early, endothelial injury with microvascular leukocyte adhesion/thrombosis, interstitial oedema, mitochondrial dysfunction, and reactive oxygen species (ROS).
- **Ischaemia-associated AKI** — postoperative (cardiac surgery on bypass, aortic cross-clamp), haemorrhage with hypotension, burns (AKI in 25% with >10% BSA), pancreatitis, abdominal compartment syndrome (intra-abdominal pressure >20 mmHg → renal vein compression). The **S3 segment of the proximal tubule** and the **outer medullary thick ascending limb** are most vulnerable (hypoxic medulla, oxidative metabolism).
- **Nephrotoxin-associated AKI** (high renal perfusion + tubular concentration of solutes):

Agent	Mechanism / clinical clue
Iodinated contrast	Direct tubular toxicity + medullary ischaemia; SCr rises 24–48 h, peaks 3–5 d, resolves ~1 wk; risk ↑ in diabetic CKD, myeloma
Aminoglycosides	Cortical accumulation; **non-oliguric** AKI after 5–7 d, even at therapeutic levels; **hypomagnesaemia**
Amphotericin B	Vasoconstriction + membrane pores; polyuria, hypoMg, hypoCa, **type 1 (distal) RTA**, dose-dependent
Cisplatin / carboplatin	Proximal tubular necrosis/apoptosis; dose-limiting; prevent with hydration
Ifosfamide	**Fanconi (type II RTA)**, polyuria, hypokalaemia
Acyclovir, methotrexate, indinavir, sulfadiazine	**Intratubular crystal** obstruction
Calcineurin inhibitors	Dose-dependent vasoconstriction; type 4 RTA
PPIs, NSAIDs, β-lactams, rifampin, checkpoint inhibitors	**Acute interstitial nephritis**
Endogenous: myoglobin (rhabdomyolysis), haemoglobin	Pigment nephropathy — vasoconstriction, direct toxicity, cast obstruction with **Tamm-Horsfall protein** in acidic urine
Endogenous: uric acid (tumour lysis), myeloma light chains	Intratubular precipitation/casts; uric acid often >15 mg/dL

- **Glomerular / vascular**: post-streptococcal GN, anti-GBM disease, ANCA vasculitis, lupus nephritis, TTP-HUS, malignant hypertension, scleroderma renal crisis, cholesterol **atheroemboli** (livedo reticularis, eosinophilia, hypocomplementaemia, eosinophiluria).

Pathophysiology of Ischaemic / Septic ATN

The healthy kidney takes **20% of cardiac output** yet the medulla is one of the most hypoxic regions of the body. Injury results from **interacting microvascular and tubular events** (Bonventre):

- **Microvascular** — sustained pre-glomerular (afferent) vasoconstriction in response to **endothelin, adenosine, angiotensin II, thromboxane A_2, and sympathetic activity**, with reduced

vasodilators (NO, PGE_2); enhanced **tubuloglomerular feedback** (injured proximal tubule delivers more solute to the macula densa); leukocyte–endothelial adhesion and congestion of the outer medulla.

- **Tubular** — ATP depletion → loss of apical brush border, **cytoskeletal (F-actin) breakdown**, and **redistribution of Na^+/K^+-ATPase from the basolateral to the apical membrane** (loss of cell polarity → impaired vectorial Na^+ reabsorption → the **high FeNa** of ATN); loss of tight junctions causes **backleak** of filtrate; sloughed cells + Tamm-Horsfall protein form **muddy-brown granular casts** that cause **intratubular obstruction**; cell death by **apoptosis and necrosis**. Frank necrosis is actually inconspicuous and restricted to the outer medulla — hence "ATN" is partly a misnomer.

Clinical phases (Brenner four-phase model; CMDT groups them as three):

- **Initiation** — the ischaemic/toxic insult; GFR falls, potentially reversible.
- **Extension** — continued hypoxia + inflammation + endothelial injury in the corticomedullary junction.
- **Maintenance** — established injury; GFR nadir; oliguric or non-oliguric; lasts **~1–3 weeks**. Complications (hyperkalaemia, acidosis, volume overload, uraemia) cluster here.
- **Recovery** — tubular regeneration; often a **polyuric/diuretic phase** from osmotic diuresis of retained solutes and delayed tubular reabsorption.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Anatomic classification box-diagram** (Fig. 321-1/321-3 style): three columns **Prerenal | Intrinsic | Postrenal**; under Intrinsic, four labelled boxes — **Tubules (ATN — ischaemic, septic, toxic)**, **Interstitium (allergic AIN)**, **Glomeruli/Small vessels (GN, vasculitis, TTP-HUS)**, **Large vessels (renal artery/vein)**. Label endogenous vs exogenous nephrotoxins.
- **Pathophysiology of ischaemic ATN** (Fig. 321-4): two interacting arms — **Microvascular** (label: vasoconstriction — endothelin, angiotensin II, thromboxane A_2; ↓NO/PGE_2; leukocyte–endothelial adhesion) and **Tubular** (label: ATP depletion, cytoskeletal breakdown, loss of polarity / Na^+-K^+-ATPase mislocation, apoptosis & necrosis, desquamation → **tubular obstruction + backleak**) → both converge on ↓ **GFR**.

Clinical / Diagnostic significance

- **Differentiate prerenal vs intrinsic (ATN)** — the cornerstone diagnostic step:

Index	Prerenal azotaemia	Intrinsic ATN
BUN : creatinine	>20 : 1	<20 : 1
Urine Na^+ (mmol/L)	<20	>20
FeNa (oliguric)	<1%	>1% (often >2%)
Urine osmolality (mOsm/kg)	>500	250–300
Sediment	Bland / hyaline casts	**Muddy-brown granular & RTE-cell casts**

- **Caveats**: FeNa may be **<1%** in sepsis (early), contrast, rhabdomyolysis, and pigment nephropathy, and is uninterpretable on diuretics or in CKD. **Fractional excretion of urea (FeUrea <35%)** helps when diuretics are used.
- **Urine sediment as a map** — RBC casts → GN/vasculitis; WBC casts → interstitial nephritis/pyelonephritis; oxalate crystals → ethylene glycol; uric acid crystals → tumour lysis.
- **Novel biomarkers** of tubular injury (rise earlier than SCr): **NGAL**, **KIM-1**, **suPAR**, and the FDA-cleared cell-cycle-arrest pair **TIMP-2 × IGFBP7** (NephroCheck) for risk-stratifying critically ill patients. The **furosemide stress test** (1.0–1.5 mg/kg; urine <200 mL over 2 h) predicts progression and need for dialysis.
- **Complications**: hyperkalaemia (worst in rhabdomyolysis/haemolysis/tumour lysis), high-anion-gap metabolic acidosis, hyperphosphataemia/hypocalcaemia, volume overload/pulmonary oedema, uraemia, anaemia and uraemic platelet dysfunction.
- **Management**: optimise haemodynamics (euvolaemia, **MAP >65 mmHg**, crystalloids over starch), **stop nephrotoxins**, renally dose drugs, treat hyperkalaemia/acidosis, nutrition **20–30 kcal/kg/day**. No proven specific drug reverses established ATN — **dopamine, fenoldopam, ANP, diuretics do not improve recovery**; diuretics only for volume control. Cause-specific: rhabdomyolysis → aggressive IV fluids (up to ~10 L/day) ± alkalinisation; tumour lysis → fluids + **rasburicase/allopurinol**; vasculitis/GN → immunosuppression ± plasma exchange; scleroderma crisis → **ACE inhibitors**; TTP → plasma exchange; atypical HUS → complement blockade.
- **Dialysis — "AEIOU"**: **A**cidosis, **E**lectrolyte (refractory hyperkalaemia), **I**ntoxications, **O**verload (volume) unresponsive to diuretics, **U**raemic complications (encephalopathy, pericarditis, bleeding). Earlier vs later initiation shows no survival benefit (STARRT-AKI).

High-yield exam pointers

- **Intrinsic AKI ≈ 50% of AKI; ATN = 85% of intrinsic AKI**; AIN 10–15%; GN ~5%.
- **ATN triad of causes = ischaemia, sepsis, nephrotoxins**; prerenal azotaemia is the precursor of ischaemic ATN.
- **S3 proximal tubule + outer-medullary TAL** are the most ischaemia-vulnerable nephron segments.
- **High FeNa in ATN** is explained by **Na^+/K^+-ATPase mislocation** to the apical membrane + backleak.
- **Muddy-brown granular casts + RTE-cell casts** = ATN signature; their presence is highly predictive but absent in >20%.
- **Aminoglycoside** = non-oliguric AKI at day 5–7 with **hypomagnesaemia**; **contrast** = SCr peak day 3–5; **amphotericin** = distal RTA + hypoMg/hypoCa.
- Phases of ATN = **initiation → extension → maintenance (1–3 wk) → recovery (polyuric)**.
- **Mortality** of AKI in hospital 20–50%, up to **70%** in ICU patients requiring dialysis; AKI predisposes to subsequent CKD.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Kidney Injury" (KDIGO definition/staging, prerenal–intrinsic–postrenal classification, sepsis/ischaemia/nephrotoxin mechanisms, urine sediment & FeNa, biomarkers, management, dialysis).
- **Brenner & Rector's The Kidney** — "Pathophysiology of Acute Kidney Injury" (S1/S2/S3 segment injury, cytoskeletal/F-actin breakdown, Na^+-K^+-ATPase redistribution → high FeNa, backleak, muddy-brown cast formation, extension phase) and "Prevention and Management of Acute Kidney Injury".
- **CMDT 2026** — "Kidney Disease / Acute Tubular Necrosis" (urinary indices table, ATN clinical phases, "AEIOU" dialysis indications, contrast-AKI prophylaxis, prognosis).

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Lupus nephritis

Asked in: Paper IV 17 Apr 2026 · Paper III 09/2025 · Paper IV Dec 2023 · Paper III Nov 2020 · Paper IV Jul 2020 (5×) — RGUHS MD General Medicine

Definition / Introduction — Lupus nephritis (LN) is immune-complex–mediated glomerulonephritis occurring as a complication of **systemic lupus erythematosus (SLE)**, the human prototype of chronic immune-complex glomerular disease. It results from glomerular deposition (and *in situ* formation) of immune complexes — principally **DNA/anti-dsDNA** — with complement activation, leukocyte infiltration and cytokine release. Clinically apparent renal disease is present in ~25–50% of patients at SLE onset and develops in up to 60% during the course; it is a major determinant of morbidity and mortality, and ~5–20% progress to **end-stage kidney disease (ESKD)**.

Pathogenesis

- **Loss of self-tolerance:** defective clearance of apoptotic material, polyclonal B-cell activation and defective B-/T-cell tolerance generate autoantibodies to **nucleosomes, dsDNA, histones and ribonucleoproteins**.
- **Immune-complex deposition:** circulating and *in situ*-formed complexes localise in the **mesangium, subendothelium and/or subepithelium** (site determines histologic class and clinical picture).
- **Effector amplification: complement cascade** activation (classical pathway), Fc-receptor–mediated leukocyte recruitment, procoagulant activation and cytokine release; **type I interferon (IFN-α)** signature is prominent.
- **Neutrophil extracellular traps (NETs):** poorly degraded in SLE — a source of autoantigen and IFN-α induction by plasmacytoid dendritic cells.
- **Genetic/host factors:** HLA-DR3/DR13, homozygous **C1q/C2/C4 deficiency**, Fcγ-receptor and **APOL1** risk alleles (markedly raise ESKD risk in patients of African descent); female:male ≈ 10:1, peak onset 15–45 yr.

- **Modifiers:** antiphospholipid antibodies (thrombotic microangiopathy), ANCA-associated pauci-immune necrotising lesions, and a podocytopathy (MCD/FSGS/collapsing) pattern.

ISN/RPS classification (2003, modified 2004; 2018 revision)

Biopsy is the cornerstone — it defines class and **guides therapy**. The International Society of Nephrology / Renal Pathology Society (ISN/RPS) system integrates light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM).

Class	Name	Defining histology	Typical clinical picture
I	Minimal mesangial	Normal LM; **mesangial deposits** only on IF/EM	Inactive sediment; normal function
II	Mesangial proliferative	Mesangial hypercellularity (**>3 cells**/mesangial area) + mesangial deposits	Mild; proteinuria <1 g/d; nephrotic syndrome rare
III	Focal	Endocapillary ± extracapillary GN in **<50%** of glomeruli; focal subendothelial deposits ± fibrinoid necrosis	Haematuria, proteinuria, active sediment; ~25–33% nephrotic
IV	Diffuse	Same lesions in **≥50%** of glomeruli; diffuse subendothelial deposits; subdivided **IV-S** (segmental) / **IV-G** (global)*	Most active; high anti-dsDNA, low complement, RBC casts; ~50% nephrotic
V	Membranous	Diffuse **subepithelial** deposits + GBM thickening; may coexist as III+V or IV+V	Nephrotic syndrome; thrombotic risk (RVT, PE)
VI	Advanced sclerosing	**≥90%** globally sclerosed glomeruli, no residual activity	ESKD, hypertension; serologies often normalise

Indices appended: (A) active, (A/C) active+chronic, (C) chronic. *The 2018 revision raised the mesangial cutoff to >3 cells, refined crescent definitions, replaced "endocapillary proliferation" with endocapillary hypercellularity, and applies modified NIH activity/chronicity indices** to all classes (eliminating the IV-S/IV-G split).

Histopathology, immunofluorescence and indices

- **LM hallmarks of proliferative LN:** endocapillary hypercellularity, leukocyte infiltration, fibrinoid necrosis, karyorrhexis, **cellular/fibrocellular crescents**; **"wire-loop"** lesions (subendothelial deposits thickening capillary walls); **"hyaline thrombi"** (large intraluminal deposits); **hematoxylin bodies** (ANA-bound nuclear debris).
- **IF — "full-house" staining: IgG + IgA + IgM + C1q + C3** — highly suggestive of LN (IgG near-universal). "Tissue ANA" nuclear staining may be seen.
- **EM:** electron-dense granular deposits; **"fingerprint" substructure** (curvilinear arrays); **tubuloreticular inclusions** (24-nm "interferon footprints" in endothelial cells).
- **Activity index (0–24):** graded 0–3+ on six features — endocapillary hypercellularity, neutrophils/karyorrhexis, wire-loop deposits, **fibrinoid necrosis** and **crescents** (latter two **double-weighted**), interstitial inflammation; identifies *reversible* lesions.

- **Chronicity index (0–12):** glomerulosclerosis, **fibrous crescents**, tubular atrophy, interstitial fibrosis (each 0–3+); identifies *irreversible* damage. High activity (>7) **plus** chronicity (>3) predicts poor long-term renal survival.
- Tubulointerstitial disease, vasculopathy (non-inflammatory necrotising vasculopathy, thrombotic microangiopathy) and lupus podocytopathy carry independent prognostic weight.

Clinical features and investigations

- **Presentation:** proteinuria (most common), microscopic haematuria, **dysmorphic RBCs and RBC casts**, hypertension, oedema, nephrotic syndrome (esp. class IV/V) and varying GFR loss; rapidly progressive GN with crescents.
- **Serology: anti-dsDNA** (high-avidity, complement-fixing IgG) correlates best with renal activity; **hypocomplementaemia (C3, C4) in 70–90%** of acute LN — falling C3/C4 and rising anti-dsDNA often **herald a flare**. Anti-Sm is specific but insensitive; ANA is a sensitive screen.
- **Indication for biopsy:** new/unexplained proteinuria (**UPCR >0.5 g/g**), active sediment or rising creatinine — to establish class, activity/chronicity and guide/withdraw therapy. **Repeat biopsy** is valuable because classes can **transform** and the 6-month biopsy predicts outcome.
- **Monitoring:** serial UA, UPCR, eGFR, C3/C4 and anti-dsDNA; quarterly urinary biomarkers where available.

Management

General principle: vigorous **induction (~6 months)** to attain remission, then prolonged **maintenance (≥3 years)** — per **KDIGO 2024** and **EULAR 2023/24** recommendations.

- **Background for all classes: hydroxychloroquine** (unless contraindicated); **ACE inhibitor / ARB** for class III/IV/V to cut proteinuria and intraglomerular pressure; consider **SGLT2 inhibitor** if eGFR reduced; BP, lipid, bone and infection prophylaxis; **VKA/heparin** if concomitant antiphospholipid nephropathy.
- **Class I / II:** no class-specific immunosuppression; antiproteinuric therapy and monitor for transformation.
- **Class III / IV (proliferative — aggressive Rx): glucocorticoids** (pulse IV methylprednisolone 125–1000 mg/d ×1–3 days for severe disease, then oral GC tapered rapidly to ≤5 mg/day) **PLUS** one of:
  - **Mycophenolate mofetil (MMF) 2–3 g/day** — first-line, especially in **Black/Hispanic** patients;
  - **Low-dose IV cyclophosphamide — Euro-Lupus regimen: 500 mg every 2 weeks ×6 doses** (then AZA/MMF), as effective as and safer than high-dose;
  - **High-dose ("NIH") IV cyclophosphamide 0.5–1 g/m² monthly ×6** — reserved for crescentic/RPGN, fibrinoid necrosis or reduced eGFR;
  - **Triple therapy:** add **belimumab** (anti-BAFF; FDA-approved 2020) or **voclosporin** (calcineurin inhibitor; FDA-approved 2021, given with MMF) for more severe presentations.
- **Class V (membranous):** treat if significant nephrotic-range proteinuria or superimposed proliferative lesions (V+III / V+IV → treat as class IV); CNIs especially effective; ACEi/ARB + anticoagulation prophylaxis for thrombotic risk.

- **Maintenance: MMF (preferred) or azathioprine** for ≥3 years; **AZA preferred in pregnancy** (cyclophosphamide and MMF are contraindicated/teratogenic). Screen **TPMT** before azathioprine.
- **Treatment targets: ≥25% reduction in UPCR by 3 months; ≥50% reduction (to <3 g/day) by 6 months; UPCR <0.5–0.7 g/day by 12–24 months**, with eGFR within 10% of baseline.
- **Refractory/relapsing: rituximab** (anti-CD20), obinutuzumab + MMF (steroid-sparing) or multi-target regimens; **GnRH agonist** before cyclophosphamide to preserve ovarian function.
- **ESKD:** dialysis (lupus activity often quiesces); **transplant** after ~3–12 months of inactive disease — allograft survival comparable to non-lupus recipients, recurrence low.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Glomerulus showing deposit sites by class:** draw a capillary loop + mesangium and label — *mesangial deposits* (class I/II), *subendothelial deposits = "wire-loop"* (class III/IV), *subepithelial deposits + GBM "spikes"* (class V), *fibrinoid necrosis + cellular crescent* (active class III/IV), and *"full-house" IF (IgG, IgA, IgM, C1q, C3)*.
- **Induction–maintenance algorithm:** boxes for *Biopsy → ISN/RPS class*; *Class III/IV → GC + (MMF or low-dose CYC) ± belimumab/voclosporin (induction 6 mo) → MMF/AZA maintenance ≥3 yr*; *Class V → CNI/MMF if nephrotic*; with the adjunct rail labelled *HCQ + ACEi/ARB ± SGLT2i*.

Clinical / Diagnostic significance

- **Biopsy is decisive:** class, activity and chronicity directly determine immunosuppression intensity and prognosis; clinical/serologic activity alone under-stages disease ("silent LN").
- **Serologic surveillance** (anti-dsDNA ↑, C3/C4 ↓) gives early warning of flares before creatinine rises.
- **Prognostic markers of poor outcome:** raised serum creatinine, **crescents/fibrinoid necrosis**, high combined activity+chronicity index, interstitial fibrosis, nephrotic-range proteinuria, hypertension, male sex, African descent/APOL1, and failure to achieve early complete remission.
- **Pregnancy:** plan for ≥6 months remission; AZA, tacrolimus and HCQ are compatible; anti-Ro antibodies risk **neonatal lupus** and congenital heart block.
- **Drug-induced lupus** (procainamide, hydralazine, minocycline, anti-TNF) rarely causes nephritis; **anti-histone** antibodies positive, renal involvement uncommon.

High-yield exam pointers

- **ISN/RPS classes I–VI**; class III **<50%** vs class IV **≥50%** glomeruli; class VI **≥90%** sclerosed.
- **"Full-house" IF = IgG + IgA + IgM + C1q + C3** — pathognomonic clue to LN.
- **Wire-loop** = subendothelial; **spikes/subepithelial** = membranous (class V); **hyaline thrombi**, **hematoxylin bodies**, **tubuloreticular inclusions** ("IFN footprints").
- **Anti-dsDNA + low C3/C4** correlate with renal activity; **hypocomplementaemia in 70–90%** of acute LN.

- **Activity index 0–24** (crescents + fibrinoid necrosis double-weighted); **chronicity index 0–12** (irreversible).
- **Euro-Lupus CYC = 500 mg IV q2wk ×6**; **MMF 2–3 g/day** first-line, preferred in Black/Hispanic patients.
- **Triple therapy** = standard + **belimumab** (2020) or **voclosporin** (2021); **rituximab** for refractory disease.
- **All patients: hydroxychloroquine + ACEi/ARB**; **AZA preferred in pregnancy**; screen **TPMT** before azathioprine.
- **Targets:** UPCR ↓25% at 3 mo, ↓50% (<3 g/d) at 6 mo, **<0.5–0.7 g/d at 12–24 mo**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Glomerular Diseases" (lupus nephritis section, ISN/RPS classification, Table 326-3) and "Systemic Lupus Erythematosus" (EULAR-based treatment algorithm, Fig. 368-5; belimumab/voclosporin).
- **Brenner & Rector's The Kidney** — "Secondary Glomerular Disease" (ISN/RPS 2003 classification with 2018 revision, full-house IF, NIH activity 0–24 / chronicity 0–12 indices, induction/maintenance trial evidence — NIH, Euro-Lupus, ALMS, MAINTAIN).
- **CMDT 2026** — "Kidney Disease" (lupus nephritis; KDIGO 2024 induction/maintenance regimens, obinutuzumab + MMF).

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Medullary sponge kidney

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

Definition / Introduction — Medullary sponge kidney (**MSK**), also called *precalyceal canalicular ectasia* or *renal tubular ectasia* and eponymously *Lenarduzzi–Cacchi–Ricci disease*, is a developmental malformation characterised by ectasia (dilatation) and cystic transformation of the **terminal (papillary) collecting ducts**, strictly confined to the **medullary pyramids**. It is usually a sporadic, benign, often incidentally-discovered condition, but is clinically important because it predisposes to **recurrent calcium nephrolithiasis, nephrocalcinosis, haematuria and urinary tract infection**. It affects roughly **<1%** of the general population yet is found in **~13%** of patients with calcium urolithiasis, and is typically diagnosed in the **third to fourth decade**.

Etiology, genetics and pathogenesis

- **Developmental basis** — thought to arise from disruption of the **ureteric bud–metanephric mesenchyme interface** during nephrogenesis, producing malformation and cystic dilatation of the collecting ducts. Although the lesion is present from birth, its rarity in children suggests an **acquired/progressive** component, with documented progression of tubular ectasia and cyst development in some patients.
- **Inheritance** — classically regarded as **non-hereditary and sporadic**, but **autosomal dominant** inheritance has been demonstrated in several families. Variants of the **GDNF (glial cell–derived neurotrophic factor)** gene cosegregated with disease in five MSK families. A study of family

members of 50 MSK patients identified 59 affected first- and second-degree relatives, supporting **familial clustering with autosomal dominant inheritance, reduced penetrance and variable expressivity**.

- **Tubular/metabolic consequences** — dilated, stagnant precalyceal ducts cause urinary **stasis**, which together with frequent tubular dysfunction promotes crystal nidus formation and infection.

Pathology and disease associations

- Despite the name the kidney does **not** truly resemble a sponge; it is usually **normal-sized or slightly enlarged**. On sectioning the medulla shows dilated ducts containing small calculi — gross specimens give a *"Swiss-cheese"* appearance.
- Ectasia may involve **one or more papillae in one or both kidneys**; lesions are **bilateral in ~70%** of cases (may be asymmetric, occasionally only a single calyx).
- Dilated ducts communicate proximally with normal-calibre collecting tubules and show a relative **constriction at the calyceal junction**; duct diameter is typically **1–3 mm, occasionally 5 mm, rarely up to 7.5 mm**.

Associated condition	Note
Calcium nephrolithiasis	Strongest association; ~13% of calcium-stone formers have MSK
Primary hyperparathyroidism	"Puzzling association"; possibly via calcium leak / hypercalciuria
Hemihypertrophy	Reported developmental association
Ehlers–Danlos syndrome	Several reported cases
ADPKD	Precalyceal canalicular ectasia frequently seen
Congenital hepatic fibrosis / Caroli (ARPKD)	Medullary ductal ectasia of ARPKD may mimic MSK (different prognosis)

Clinical features

- **Often asymptomatic** and may remain undetected for life; frequently an **incidental** radiological finding.
- **Nephrolithiasis** is the commonest presentation — up to **60–70% lifetime stone risk**; stones are **calcium oxalate and calcium phosphate**, forming in the ectatic ducts.
- **Gross or microscopic haematuria** — may be recurrent.
- **Recurrent urinary tract infections** — often the first manifestation; patients (especially women) are more susceptible, and infected stones may need long-term antimicrobial suppression.
- **Tubular dysfunction:**
  - Mild **renal concentrating defect** (impaired urine concentrating ability).
  - **Incomplete distal (type 1) renal tubular acidosis** in **30–40%** — reduced capacity to lower urine pH after an ammonium-chloride load.
  - Occasionally a low maximal potassium-excretory capacity.

- **Metabolic stone risk factors** — chiefly **hypercalciuria** and **hypocitraturia**. Among MSK stone-formers, hypercalciuria is **absorptive in ~59%** and due to a **renal calcium leak in ~18%**.
- **Prognosis is benign** — MSK **seldom progresses to ESKD**; morbidity stems from recurrent stones, infection, nephrocalcinosis and acidosis. A minority have a poorer course from relapsing urolithiasis and pyelonephritis.

Investigations and diagnosis

- **Excretory urography (IVU/IVP)** is the historical **gold standard** — early and delayed films (without ureteric compression and without obstruction) show contrast pooling in the dilated terminal collecting ducts:
  - **Parallel brush-like striations / "paintbrush" appearance** radiating from the calyceal border.
  - With more severe disease, **grape-like or bead-like ("bouquet of flowers") clusters**.
- **Plain film / non-contrast CT** — characteristic **medullary nephrocalcinosis** with calculi **clustered fanning away from the calyx**; CT best demonstrates the calculi.
- **CT urography** (which has largely replaced IVU) is **less sensitive** for the ectasia itself, but shows cystic dilatation of distal collecting tubules with a **striated "papillary brush" pattern** and collecting-system calcification.
- **Ultrasonography — medullary hyperechogenicity / nephrocalcinosis**: suggestive but **not diagnostic**.
- **Metabolic stone work-up** — 24-h urine for calcium, citrate, oxalate, uric acid, volume and pH; serum calcium/PTH to exclude hyperparathyroidism; urinary acidification testing for incomplete dRTA.

Modality	MSK finding
IVU/excretory urography	"Paintbrush" striations / "bouquet of flowers" calyceal blush — **most specific**
Non-contrast CT	Medullary nephrocalcinosis; stones clustered around papillae
CT urography	Striated papillary brush pattern; less sensitive than IVU
Ultrasound	Medullary hyperechogenicity (non-specific)

Differential diagnosis

Entity	Distinguishing feature
Medullary nephrocalcinosis (1° hyperparathyroidism, dRTA, sarcoid, vit-D excess)	Diffuse calcification without ductal ectasia / brush pattern
Renal papillary necrosis	Sloughed papillae, ring/club calyx; analgesics, diabetes, sickle cell
Calyceal diverticulum	Single, communicates with calyx; not diffuse papillary ectasia
ARPKD with medullary ductal ectasia	Childhood, congenital hepatic fibrosis, far worse prognosis

Entity	Distinguishing feature
Autosomal dominant tubulointerstitial / medullary cystic kidney disease	Progressive CKD, corticomedullary cysts, no stone-clustering

Management

- **No specific cure** — management is **supportive**, directed at stone prevention and treating complications; incidental asymptomatic MSK warrants **reassurance** (benign, not life-threatening).
- **High fluid intake** — aim for urine output **≥2.5–3 L/day**.
- **Dietary** — low-salt, low-animal-protein diet to reduce calcium excretion and stone risk.
- **Potassium citrate (oral alkali) — first-line** for any metabolic risk factor (hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria): start **~20 mEq citrate/day in two divided doses**, titrate up by **10 mEq** to achieve citraturia **>450 mg/24 h**, while keeping **24-h urine pH <7.5** (to avoid promoting calcium-phosphate stones). This regimen reduced the stone event rate from **0.58 to 0.10 stones/patient/year** and improved bone density (vertebral T-score −2.82 → −1.98).
- **Thiazide diuretics** — added/reserved for persistent stone-formation or hypercalciuria despite optimal citrate.
- **Infection** — prompt treatment of UTIs; preventive measures (especially in women); long-term suppressive antibiotics if infected stones cannot be cleared. Avoid repeated unnecessary investigation of benign recurrent haematuria.
- **Urological intervention** (ESWL / ureteroscopy) for obstructing or symptomatic stones, as for any stone-former.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled coronal section of the kidney in MSK** — label: *cortex*, *medullary pyramid*, *papilla*, *dilated/ectatic terminal (precalyceal) collecting ducts*, *small calculi within ducts*, *minor calyx*, *normal-calibre proximal collecting tubule with constriction at calyceal junction*, *renal pelvis*.
- **IVU schematic of a single calyx** — label: *"paintbrush" parallel striations radiating from the calyx*, *"bouquet of flowers"/grape-like contrast clusters in ectatic ducts*, *medullary nephrocalcinosis (clustered stones fanning from calyx)*.

Clinical / Diagnostic significance

- Consider MSK in any **young/middle-aged recurrent calcium-stone former** with **bilateral medullary nephrocalcinosis** and **haematuria/recurrent UTI**.
- Always screen for the treatable/contributory associations — **incomplete distal RTA, hypocitraturia, hypercalciuria and primary hyperparathyroidism** — as these guide therapy.
- IVU's **"paintbrush"/"bouquet-of-flowers"** sign remains the single most diagnostic feature; CT urography may miss the ectasia, so a high index of suspicion is needed in the post-IVU era.
- Distinguishing MSK (benign, normal renal function) from **ARPKD-related medullary ductal ectasia** (progressive, hepatic involvement) is prognostically critical.

High-yield exam pointers

- MSK = **ectasia + cystic dilatation of papillary collecting ducts confined to medullary pyramids**; eponym *Cacchi–Ricci (Lenarduzzi–Cacchi–Ricci) disease*.
- **Bilateral in ~70%**; kidneys **normal-sized**; "**Swiss-cheese**" cut surface.
- **~60–70% lifetime risk of stones** (calcium oxalate/phosphate); **F > M** among calcium-stone formers.
- **Incomplete distal RTA in 30–40%**; with **hypocitraturia + hypercalciuria** (mostly absorptive) and a **urinary concentrating defect**.
- Diagnostic imaging — **"paintbrush" striations** and **"bouquet of flowers"** on IVU; **medullary nephrocalcinosis** on CT.
- **GDNF** gene variants; **autosomal dominant, reduced penetrance, variable expressivity** in familial cases; classically sporadic.
- Associations: **primary hyperparathyroidism, hemihypertrophy, Ehlers–Danlos syndrome, ADPKD**.
- Treatment — **fluids ≥2.5–3 L/day + potassium citrate (keep urine pH <7.5) ± thiazide**; **rarely progresses to ESKD**.

SOURCE & COVERAGE

- **Brenner & Rector's The Kidney** — "Cystic Diseases of the Kidney" (Medullary Sponge Kidney section: epidemiology, GDNF/autosomal-dominant genetics, pathology, diagnosis, metabolic abnormalities, potassium-citrate regimen) and "Diagnostic Kidney Imaging" (paintbrush/bouquet IVU signs, medullary nephrocalcinosis); "Urolithiasis" (potassium-citrate stone data).
- **Harrison's Principles of Internal Medicine, 22e** — "Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development" (MSK as developmental collecting-duct dilatation; stones, concentrating defect, UTI; CT urography less sensitive than IVP) and "Approach to the Patient with Renal Disease" (MSK among congenital anomalies/nephrocalcinosis).
- **CMDT 2026** — "Kidney Disease" (MSK: <1% prevalence, ureteric-bud–metanephric mesenchyme aetiology, "Swiss-cheese" appearance, up to 70% nephrolithiasis, type 1 dRTA, supportive treatment with alkali/citrate, thiazide, fluids; benign prognosis).

Coverage note: The corpus covers MSK well (Brenner provides full subspecialty depth). Harrison's dedicated coverage is brief (as flagged in the spec); the depth, genetics (GDNF), imaging eponyms and citrate-regimen detail are drawn from Brenner & Rector and CMDT. The *Lenarduzzi–Cacchi–Ricci* / *Cacchi–Ricci* eponym is documented in the Brenner reference list (Padua Medical School, 1930s).

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Nephrotic syndrome

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

Definition / Introduction — Nephrotic syndrome is a glomerular disorder defined by **heavy proteinuria (>3.0 g/24 h)** together with **hypoalbuminaemia, oedema/anasarca, hypercholesterolaemia and hypertension**, classically accompanied by *minimal (microscopic) haematuria* and an acellular urinary sediment. When large amounts of protein are excreted without the full clinical picture, the term **nephrotic-range proteinuria** is used. It arises from injury to the glomerular filtration barrier (predominantly the **podocyte and its slit-diaphragm**), and may be a *primary* (idiopathic) glomerulopathy or *secondary* to systemic disease. Untreated, persistent heavy proteinuria progressively damages nephrons and lowers GFR — the higher the 24-h protein excretion, the more rapid the decline.

Diagnostic criteria & pathophysiology

- **Nephrotic "pentad"**: heavy proteinuria + hypoalbuminaemia + oedema + hyperlipidaemia (hypercholesterolaemia) + hypertension; haematuria, when present, is minimal/microscopic.
- **Filtration-barrier injury** — loss of the size- and charge-selective barrier (effacement of podocyte foot processes, weakening of slit-pore membranes) allows albumin and larger proteins to escape. In children the loss is predominantly albumin (*selective proteinuria*); in adults it is typically *non-selective*.
- **Oedema** — due to renal **salt and water retention**; intravascular hypoalbuminaemia (low oncotic pressure) contributes. Severe hypoalbuminaemia with intrarenal oedema (*nephrosarca*) can cause a diuretic-responsive fall in GFR that must be distinguished from acute kidney failure due to **hypovolaemia**.
- **Hyperlipidaemia** — hypoalbuminaemia drives hepatic lipoprotein overproduction with reduced catabolism; patients are at increased **cardiovascular risk**.
- **Hypercoagulable state** — urinary loss of anticoagulant proteins produces a thrombotic tendency; **renal vein thrombosis, pulmonary embolism and deep-vein thrombosis** are the major venous complications (highest with membranous nephropathy).
- **Loss of other binding/transport proteins** — e.g. **thyroid-binding globulin** loss alters thyroid function tests; loss of immunoglobulins predisposes to **infection** [standard medicine].

Classification — causes by histology

Category	Lesion / disease	Key features (Harrison 22e)
Primary glomerular	**Minimal change disease (MCD)**	70–90% of childhood, 10–15% of adult nephrotic syndrome; normal light microscopy, IgM ± in mesangium, **foot-process effacement** on EM; steroid-responsive
	Focal segmental glomerulosclerosis (FSGS)	Most common cause of *primary* glomerular disease in ESKD (US); segmental scars at the **corticomedullary junction**; *APOL1* risk variants; collapsing variant with HIV (HIVAN)

Category	Lesion / disease	Key features (Harrison 22e)
	Membranous glomerulonephritis (MGN)	~25% of adult nephrotic syndrome; peak 30–50 y, M:F 2:1; **subepithelial deposits, silver-stain "spikes"**; anti-**PLA2R** IgG4 in 70–80% of primary cases
	Membranoproliferative GN / C3 glomerulopathy	May present nephrotic with low complement
Secondary / systemic	**Diabetic nephropathy**	Single most common cause of CKD worldwide; **Kimmelstiel-Wilson nodules**, GBM thickening, mesangial expansion
	Amyloidosis (AL primary, AA secondary)	**Congo-red** positive fibrils; nephrotic syndrome common; AL → ~20% dialysis, AA → ~40–60% dialysis
	Light-chain deposition disease / MGRS	Plasma-cell dyscrasia; non-fibrillar, **Congo-red negative** light-chain deposits
	Fibrillary–immunotactoid disease; **Fabry's disease**	Fabry: α-Gal A deficiency, *Maltese-cross* lipid bodies, FSGS pattern
	Infection / drug / malignancy / autoimmune (secondary MGN)	HBV, HCV, syphilis, malaria; gold, penicillamine, NSAIDs; solid tumours (breast, lung, colon); SLE (membranous lupus, ISN/RPS class V)

Clinical features & complications

- **Presentation** — peri-orbital and dependent **oedema**, weight gain, frothy urine, ascites, anasarca; often abrupt in MCD.
- **Infections** — increased susceptibility (urinary immunoglobulin loss); spontaneous bacterial **peritonitis** and pneumococcal sepsis are classic in nephrotic children [standard medicine].
- **Thromboembolism** — renal vein thrombosis (esp. MGN), PE, DVT from the hypercoagulable state.
- **Acute kidney injury** — from hypovolaemia/over-diuresis, *nephrosarca*, acute tubular necrosis or interstitial inflammation.
- **Metabolic** — accelerated **atherosclerosis** (dyslipidaemia), protein malnutrition, and altered drug/hormone protein binding.

Investigations / approach

- **Urinalysis** — heavy proteinuria; *bland/acellular* sediment; **oval fat bodies and "Maltese-cross" lipid-laden casts** under polarised light; *selective* (children) vs *non-selective* (adults) proteinuria.
- **Quantify proteinuria** — 24-h urine protein (nephrotic = >3.0 g/24 h; MCD averages ~10 g) or spot **albumin/protein-to-creatinine ratio** (Table 326-1: albuminuria >300 mg/g).
- **Blood** — serum albumin, lipid profile, creatinine/eGFR, fasting glucose/HbA1c, complement (C3/C4), serology (ANA, anti-dsDNA, ANCA, hepatitis B/C, HIV, syphilis), and serum/urine **electrophoresis with free light chains** when paraproteinaemia suspected.
- **Serology that may obviate biopsy** — **anti-PLA2R antibody** positive with normal creatinine and no other cause supports primary MGN.

- **Kidney biopsy** — the diagnostic cornerstone in adults (light + immunofluorescence + electron microscopy). In children, MCD is assumed and **only steroid non-responders are biopsied**. Diabetic nephropathy with typical features and retinopathy usually needs **no biopsy**.

Principles of management

- **General / supportive (all causes)**:
  - **Reduce proteinuria & preserve GFR** — inhibitors of the **renin–angiotensin system (ACEi/ARB)** plus **SGLT2 inhibitors**.
  - **Oedema** — dietary salt restriction and **diuretics**, avoiding intravascular volume depletion.
  - **Dyslipidaemia** — **lipid-lowering (statin)** therapy, given the raised cardiovascular risk.
  - **Thromboprophylaxis/anticoagulation** for venous thrombotic complications; prophylaxis considered in select patients with severe hypoalbuminaemia (esp. MGN).
- **Disease-specific immunosuppression**:
  - **MCD** — **prednisone** first-line; 90–95% of children and 80–90% of adults achieve complete remission (adults respond more slowly; not called steroid-resistant until 4 months). Cyclophosphamide, MMF, **calcineurin inhibitors (CNIs)** or **rituximab** for frequent relapsers/steroid-dependent/steroid-resistant disease.
  - **Primary FSGS** — steroids (remission in only 20–45% over 6–12 months), CNIs as steroid-sparing; *secondary/genetic FSGS* — treat the cause, **no role for immunosuppression**; recurs in ~30% of transplants (plasmapheresis for presumed circulating factor).
  - **Primary MGN** — immunosuppression for persistent proteinuria, risk-stratified by proteinuria/GFR/albumin: **steroids + cyclophosphamide, CNIs, or rituximab**.
  - **Diabetic nephropathy** — glycaemic and BP control, ACEi/ARB, SGLT2i, and the non-steroidal MRA **finerenone**.
  - **Amyloid/paraprotein** — treat the underlying plasma-cell dyscrasia/inflammatory disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Glomerular filtration barrier (normal vs MCD)** — label: *capillary lumen, fenestrated endothelium, glomerular basement membrane (GBM), podocyte with foot processes, slit diaphragm/slit-pore membrane*; show **foot-process effacement (fusion)** in MCD and **subepithelial deposits with "spikes"** in MGN ("Foot process fusion", "Subepithelial deposits", "MEMBRANOUS GLOMERULONEPHRITIS").
- **FSGS schematic (Glomerular Schematic 5)** — label: *Detachment of cell from GBM, Collapsed capillary and scar, Proliferation of subepithelial cells, Afferent arteriole, Efferent arteriole, FOCAL SCLEROSING GLOMERULONEPHRITIS*.

Clinical / Diagnostic significance

- Distinguishing **nephrotic** (bland sediment, heavy proteinuria) from **nephritic** (haematuria, RBC casts, hypertension, azotaemia) syndrome directs the whole work-up.
- **Age stratifies the differential**: child → MCD; adult → MGN/FSGS/diabetes; older adult with paraproteinaemia → amyloid/LCDD/MGRS.

- **Secondary screen is mandatory** — diabetes, SLE, hepatitis B/C, HIV, malignancy and drugs are reversible/treatable causes.
- **Anti-PLA2R** has transformed MGN into a partly serology-based, biopsy-sparing diagnosis and a **biomarker of disease activity/response**.
- Remission of proteinuria is the key prognostic goal: it markedly improves outcome across MCD, FSGS and MGN.

High-yield exam pointers

- Nephrotic syndrome = proteinuria **>3.0 g/24 h** + hypoalbuminaemia + oedema + hyperlipidaemia + hypertension; sediment is **bland**.
- **MCD** = commonest cause in children (70–90%); EM shows **foot-process effacement**; exquisitely **steroid-responsive**.
- **MGN** = commonest *primary* cause in adults (~25%); **anti-PLA2R IgG4**; **subepithelial deposits + silver "spikes"**; highest risk of **renal vein thrombosis**.
- **FSGS** = leading cause of primary glomerular ESKD (US); **APOL1**; collapsing variant in **HIVAN**; biopsy from corticomedullary junction (else misdiagnosed as MCD).
- **Diabetic nephropathy** = most common cause of CKD overall; **Kimmelstiel-Wilson nodules**; usually no biopsy if retinopathy present.
- **Amyloid** = **Congo-red positive**, apple-green birefringence; LCDD is **Congo-red negative**.
- Universal therapy = **RAAS blockade + SGLT2i + statin + diuretic ± anticoagulation**; add disease-specific immunosuppression.
- Complications to write: **infection, thromboembolism (renal vein thrombosis), AKI, dyslipidaemia/CVD, protein malnutrition**.
- Urine clue: **oval fat bodies / Maltese-cross** lipiduria.

SOURCE & COVERAGE

Harrison 22e — Ch 326 "Glomerular Diseases" (Tables 326-1, 326-2, 326-4, 326-5; Glomerular Schematics 5 & 6). **Coverage note:** the chapter is organised by individual glomerulopathy rather than as a single "nephrotic syndrome" review — the unified definition, oedema/hyperlipidaemia mechanisms and the infection/thrombosis complication list above are assembled from scattered passages plus universally accepted standard internal medicine; points marked *[standard medicine]* (immunoglobulin-loss infection susceptibility, detailed lipid mechanism) are not given verbatim in this chapter but are standard and accurate.

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Renal manifestations in SLE

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

Definition / Introduction — Lupus nephritis (LN) is the immune-complex–mediated glomerular injury of SLE and is one of its most common and serious organ complications. Nephritis occurs in ~**35%** of patients with SLE; clinical kidney involvement is present in about **30%** at diagnosis, and the majority develop renal abnormalities during the disease course. It is more severe in non-White patients, who more often progress to **end-stage renal disease (ESRD)** despite therapy. Renal involvement carries major weight in classification (a biopsy showing class III/IV LN alone meets diagnostic criteria) and is the dominant driver of morbidity, mortality and treatment intensity in SLE.

Pathogenesis

- LN results from deposition of **circulating immune complexes** composed primarily of **DNA and anti-DNA**, which activate the **complement cascade** → complement-mediated damage, leukocyte infiltration, activation of procoagulant factors and cytokine release.
- **In-situ immune-complex formation** in the glomerulus also contributes to injury.
- The anatomical site of deposits determines the histological class and clinical picture — deposits may be **mesangial, subendothelial and/or subepithelial**.
  - *Subendothelial/mesangial deposits* (accessible to inflammatory cells) → proliferative, **nephritic** lesions (class III/IV).
  - *Subepithelial deposits* (separated from the circulation by the GBM) → **membranous**, largely non-inflammatory, **nephrotic** lesion (class V).
- **Anti-dsDNA antibodies that fix complement** correlate best with the presence of kidney disease; **hypocomplementemia** (low C3/C4) is present in **70–90%** of acute LN.
- **Antiphospholipid antibodies** can produce **glomerular microthrombi and thrombotic microangiopathy (antiphospholipid nephropathy)**, worsening renal prognosis despite anticoagulation.

Clinical spectrum of renal involvement

- Manifestations parallel the underlying pathology and range from clinically silent to rapidly progressive renal failure.
- **Proteinuria** is the most common sign — sub-nephrotic to **nephrotic-range**.
- **Glomerular (active) urinary sediment** — microscopic **haematuria**, dysmorphic red cells and **red-blood-cell casts**.
- **Hypertension** and varying degrees of reduced GFR / acute kidney injury.
- **Nephrotic syndrome** — characteristic of class V and severe class IV; class V predisposes to **renal vein thrombosis** and other thrombotic complications.
- **Rapidly progressive glomerulonephritis (RPGN)** — when crescents complicate class III/IV.
- Nephritis may occur **with or without extrarenal SLE activity** and is frequently **asymptomatic**, mandating active surveillance.

Histological classification (ISN/RPS, revised 2003–04)

First outlined by the **WHO (1974)** and revised by the **International Society of Nephrology / Renal Pathology Society (ISN/RPS) Study Group in 2003–04** (with a 2018 revision recommendation). It guides therapy and prognosis.

Class	Designation	Key histology	Clinical correlate
I	Minimal mesangial	Normal light microscopy; mesangial deposits on IF/EM	Minimal manifestations; excellent prognosis
II	Mesangial proliferative	Mesangial hypercellularity + matrix expansion	Mild haematuria/proteinuria; nephrotic syndrome rare
III	Focal nephritis (**<50%** glomeruli)	Focal endocapillary ± extracapillary hypercellularity, focal **subendothelial** deposits ± fibrinoid necrosis	Haematuria, proteinuria, ± active sediment/nephrotic; variable course
IV	Diffuse nephritis (**>50%** glomeruli)	Diffuse endocapillary ± extracapillary hypercellularity, diffuse subendothelial deposits; segmental (**IV-S**) or global (**IV-G**); ± crescents ± fibrinoid necrosis	Most severe — high anti-dsDNA, low complement, RBC casts, ~50% nephrotic; worst untreated prognosis (**IV-S worse than IV-G**)
V	Membranous	Thickened GBM with diffuse **subepithelial** deposits; may coexist with III/IV (**mixed membranous + proliferative**)	Nephrotic syndrome (~60%); thrombotic risk; ~20% of LN with significant proteinuria
VI	Advanced sclerosing	Global sclerosis of **>90%** of glomeruli, interstitial fibrosis	ESKD; immunosuppression not useful

- Lesions are **dynamic** — patients can **transform** between classes, so **repeat biopsy** is often required (e.g., non-response or change in trajectory).
- Class III/IV are presented under **acute nephritic syndromes** because of their aggressive proliferative behaviour; class V behaves like a nephrotic/membranous lesion.

Investigations, serology and monitoring

- **Urinalysis** — proteinuria, haematuria, RBC/cellular casts (active sediment).
- **Quantitation** — random **urine protein-to-creatinine ratio (UPCr)** or 24-h urine protein; screen **every 3 months**.
- **Renal function** — serum creatinine, eGFR.
- **Serology** — **anti-dsDNA titre** (rising titre + falling **C3/C4** herald a flare and impending active nephritis).
- **Renal biopsy** — the key investigation; generally prompted by **UPCr >0.5 and/or declining kidney function**. It establishes the **ISN/RPS class**, distinguishes active (treatable) from chronic (sclerotic) lesions, and guides therapy. Note: a biopsy showing class III/IV LN independently satisfies SLE classification criteria.

Management by class

- **General/adjunctive measures (all classes): hydroxychloroquine** (renoprotective, reduces flares); **ACE inhibitor or ARB** for class III/IV/V to reduce proteinuria and glomerular hypertension; an

SGLT2 inhibitor if eGFR is reduced; blood-pressure, lipid and cardiovascular-risk control; **anticoagulation (vitamin K antagonist/heparin)** if antiphospholipid nephropathy is present on biopsy.

- **Class I / II:** little or no specific immunosuppression; excellent prognosis.
- **Class III / IV (± V) — proliferative LN (aggressive therapy):**
  - **Induction (2–6 months):** high-dose glucocorticoids — including **IV methylprednisolone 125–1000 mg/day for 1–3 days** for severe/crescentic disease — **plus** either **IV cyclophosphamide** *or* **mycophenolate mofetil (MMF)**.
  - **Cyclophosphamide regimens: low-dose 500 mg IV every 2 weeks for six doses** (the *Euro-Lupus* regimen — as effective as high dose with better tolerability) or **high-dose monthly pulses for 6 months**; a **GnRH agonist** can be given before each dose to protect against ovarian failure.
  - **MMF 2–3 g/day** is particularly favoured for induction in **Black/Hispanic** patients.
  - **Newer triple therapies (FDA-approved, steroid-sparing): belimumab** (anti-BAFF, 2020) added to MMF or low-dose cyclophosphamide; **voclosporin** (a calcineurin-inhibitor/cyclosporine analogue, 2021) added to MMF + glucocorticoids.
  - **Maintenance:** lower-dose glucocorticoids (taper prednisone to **≤5 mg/day**) plus **MMF or azathioprine**; total immunosuppression (induction + maintenance) generally **≥36 months** (KDIGO).
  - **Refractory disease: rituximab** (anti-CD20) may be considered.
- **Class V — membranous LN:** treat nephrotic syndrome; severe nephrosis, rising creatinine or progressive course warrant steroids + an additional immunosuppressant; RAS blockade reduces proteinuria.
- **Class VI:** advanced sclerosis — manage as CKD/ESKD with **dialysis or transplantation**; kidney transplant after **~6 months of inactive disease** gives allograft survival comparable to other indications.
- **Treatment targets:** ≥25% reduction in UPCr by **3 months**, ≥50% reduction to **<3 g/day** by **6 months**, and **<0.5–0.7 g/day** by **12–24 months**, each with eGFR within 10% of baseline.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Glomerular capillary loop — sites of immune deposits.** Labels: *Capillary lumen, Endothelial cell, Glomerular basement membrane (GBM), Visceral epithelial cell (podocyte), Mesangium, Mesangial deposits (Class I/II), Subendothelial deposits (Class III/IV), Subepithelial deposits (Class V), Crescent in Bowman's space (extracapillary proliferation), Fibrinoid necrosis, Bowman's capsule.*
- **LN management algorithm.** Labels: *Renal biopsy → ISN/RPS class → Class I/II (HCQ + RAS blockade, no specific immunosuppression); Class III/IV ± V (Induction: glucocorticoid + MMF or low-dose IV cyclophosphamide ± belimumab/voclosporin → Maintenance: low-dose steroid + MMF or azathioprine); Pure Class V (nephrotic management); Class VI (dialysis/transplant)* — with the adjunct box *HCQ, ACEi/ARB, SGLT2i, anticoagulation if APS nephropathy.*

Clinical / Diagnostic significance

- LN is a leading determinant of prognosis: **up to 20% reach ESKD** requiring dialysis/transplant, and in the USA **~20% of class IV patients die or develop ESRD within 10 years**; LN markedly raises mortality versus the general population.
- Achieving **remission** (near-normal kidney function with proteinuria reduced to near-normal) dramatically improves renal outcome.
- A **renal biopsy showing class III or IV LN** is the only single item that, by itself, satisfies the SLE classification criteria — underscoring renal disease as a defining feature.
- Both LN and its corticosteroid treatment accelerate **atherosclerosis, hypertension, hyperglycaemia and hyperlipidaemia**, so cardiovascular risk reduction is integral to care.

High-yield exam pointers

- **Nephritis in ~35% of SLE; ~30% have renal disease at diagnosis.**
- **ISN/RPS classes I–VI** — *III = focal (<50%), IV = diffuse (>50%), V = membranous, VI = sclerotic*; **IV-S worse than IV-G.**
- **Subendothelial/mesangial deposits → proliferative/nephritic; subepithelial → membranous/nephrotic.**
- **Anti-dsDNA high + C3/C4 low** = best correlate of active LN; hypocomplementemia in **70–90%.**
- **Renal biopsy** is essential to assign class and guide therapy (prompted by **UPCr >0.5** / falling GFR); screen UPCr **every 3 months**.
- **Proliferative LN (III/IV):** induction = **steroids + MMF or cyclophosphamide**; maintenance = **MMF or azathioprine**.
- **Newer agents: belimumab (2020)** and **voclosporin (2021)** for steroid-sparing triple therapy.
- **Class V** → nephrotic syndrome + **renal vein thrombosis** risk; **antiphospholipid antibodies** → thrombotic microangiopathy with worse prognosis.
- **HCQ, ACEi/ARB and (if low eGFR) SGLT2 inhibitor** in all proliferative/membranous LN.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 326 "Glomerular Diseases"** (lupus nephritis section, Table 326-3 ISN/RPS classification) and **Ch 368 "Systemic Lupus Erythematosus"** (Renal Manifestations; Fig. 368-5 treatment of lupus nephritis). *Coverage note:* the "Euro-Lupus" eponym for the low-dose cyclophosphamide regimen (500 mg q2-weekly × 6) is standard, universally accepted internal medicine added for completeness; Harrison describes the regimen and dose but does not use the eponym.

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Renal osteodystrophy

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

Definition / Introduction — *Renal osteodystrophy* is the spectrum of bone histological abnormalities that complicates chronic kidney disease (CKD), arising from disordered calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23) and vitamin D metabolism. It is the skeletal component of the wider systemic disorder of mineral metabolism in CKD (which also encompasses biochemical derangements and extraskeletal/vascular calcification). The principal complications of abnormal mineral metabolism in CKD occur in the **skeleton** and the **vascular bed**, with occasional soft-tissue involvement, and disorders of bone turnover and of vascular calcification are pathophysiologically linked.

Pathophysiology — the engine of secondary hyperparathyroidism

The high-turnover lesion is driven by a self-amplifying cascade that begins early (changes start as **GFR falls below 60 mL/min**, with phosphate retention and FGF-23 rise possibly antedating measurable GFR decline):

- **Declining GFR → phosphate retention.** Reduced excretion of phosphate is the initiating event.
- **Retained phosphate stimulates** increased synthesis of **FGF-23 by osteocytes**, increased **PTH** synthesis, and growth of **parathyroid gland mass**.
- **Decreased ionized calcium** results from reduced renal **calcitriol** [**$1,25(OH)_2D_3$**] production — itself a consequence of phosphate retention and of elevated **FGF-23**, which both suppresses 1α-hydroxylation and *increases calcitriol degradation*.
- **Low calcitriol** drives hyperparathyroidism in two ways: by causing hypocalcaemia, and by a *direct effect on PTH gene transcription*.
- The normal inhibitory effect of **FGF-23 on PTH** secretion is **Klotho-dependent** and is *attenuated* in CKD, removing a brake on PTH.
- Net result: **secondary hyperparathyroidism**, sustained high bone turnover, and progressive parathyroid hyperplasia. PTH itself acts as a **uremic toxin** (muscle weakness, cardiac muscle fibrosis, constitutional symptoms, and ESA-resistant anaemia from marrow fibrosis).

Classification — histological types of renal bone disease

The major bone disorders are classified by **bone turnover** and **PTH level** (with mineralisation as a third axis); most patients show a *combination*.

Type	Bone turnover / PTH	Underlying mechanism	Hallmark
Osteitis fibrosa cystica	High turnover, **high PTH**	Secondary hyperparathyroidism	Abnormal osteoid, peritrabecular & marrow fibrosis; bone cysts with haemorrhage = ***brown tumours***
Osteomalacia	Low/defective mineralisation	Reduced production & action of **1,25(OH)$_2$D$_3$**	Accumulation of non-mineralised **osteoid**; fractures, bowing
Adynamic bone disease	**Low turnover, low/normal PTH**	Over-suppression of PTH (vitamin D, high-Ca binders/dialysate), chronic inflammation	Reduced bone volume & mineralisation; microfractures unrepaired
Mixed uremic osteodystrophy	Combined	Osteitis fibrosa + osteomalacia coexisting	Features of both

- **Osteitis fibrosa cystica** is the *classic lesion of secondary hyperparathyroidism*: bone pain, fragility, *brown tumours* with compression syndromes, and erythropoiesis-stimulating-agent (ESA) resistance from marrow fibrosis.
- **Adynamic bone disease** is *increasing in prevalence*, especially among **diabetics and older patients**. Complications include increased **fracture**, bone pain, and an association with **vascular and cardiac calcification**; calcium that cannot enter low-turnover bone may deposit in soft tissue as ***tumoral calcinosis***. These patients often have the **most severe musculoskeletal pain** owing to inability to repair normal microfractures.

Extraskeletal manifestations

- **Vascular / valvular calcification:** strong association between **hyperphosphataemia** and cardiovascular mortality. CKD patients show calcification of the **media of coronary arteries** and **heart valves** far exceeding non-CKD patients; magnitude is proportional to age, hyperphosphataemia, and (paradoxically) **low PTH/low turnover**. Hyperphosphataemia induces an **osteoblast-like gene-expression** switch in vascular cells → calcification/ossification; low **fetuin** permits more rapid calcification.
- **Calciphylaxis** (calcific uraemic arteriolopathy): a devastating disorder almost exclusive to advanced CKD. Heralded by painful **livedo reticularis** and subcutaneous nodules that progress to **ischaemic necrosis/ulceration** (legs, thighs, abdomen, breasts), with vascular occlusion plus extensive vascular & soft-tissue calcification. **Warfarin** is a recognised risk factor (it decreases vitamin-K-dependent activation of **matrix GLA protein**, which normally inhibits vascular calcification).
- **Tumoral calcinosis:** large periarticular calcified concretions in severely, chronically hyperphosphataemic, non-adherent dialysis patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vicious-cycle flow diagram of CKD secondary hyperparathyroidism.** Labels: ↓*GFR* → *Phosphate retention* → ↑*FGF-23 (osteocytes)* and ↑*PTH / parathyroid hyperplasia*; ↓*Renal 1α-hydroxylase* → ↓*Calcitriol*; ↓*Ionised calcium*; *Klotho-dependent FGF-23 brake on PTH attenuated*; outputs → *High-turnover bone (osteitis fibrosa cystica)* and *Vascular calcification*.
- **Spectrum bar of renal bone disease.** Single horizontal axis labelled *Bone turnover / PTH*: left end *Low (Adynamic bone disease)* → middle *Normal* → right end *High (Osteitis fibrosa cystica)*; place *Osteomalacia* (mineralisation defect) and *Mixed uremic osteodystrophy* annotated on the bar.

Clinical / Diagnostic significance

- **Biochemistry (serial trends):** serum **phosphate** (hyperphosphataemia, defined in adults as >1.8 mmol/L [5.5 mg/dL]), **calcium**, **intact PTH**, **alkaline phosphatase** (turnover marker), **25-OH vitamin D**; FGF-23 is elevated early. High FGF-23 is an *independent risk factor for left ventricular hypertrophy* and increased mortality in CKD, dialysis and transplant patients.
- **Bone biopsy** with **double tetracycline labelling** (TMV system — turnover, mineralisation, volume) is the definitive method to distinguish high- from low-turnover disease and to confirm adynamic bone or osteomalacia *(standard nephrology practice; see Coverage note)*.
- **Imaging:** radiographs may show subperiosteal resorption, brown tumours, vascular calcification; CT/electron-beam CT quantifies coronary and valvular calcification.
- **Management pearls:** prevention is paramount — *once parathyroid mass is very large the disease is hard to control*. KDOQI guidance targets **intact PTH 2–9 × the upper limit of normal**, because *very low PTH predisposes to adynamic bone disease, fracture and ectopic calcification*. Avoid over-suppression of PTH (excess vitamin D analogue, calcium-based binders, high-calcium dialysate). For anticoagulation in CKD, **avoid warfarin** where feasible to reduce calciphylaxis risk.

Management / Treatment

Strategy	Agents (per Harrison)	Rationale / caution
Lower serum phosphate	Low-phosphate diet; **phosphate binders** with meals — Ca acetate, Ca carbonate (Ca-based); **sevelamer**, **lanthanum** (non-Ca polymers); **tenapanor** (Na^+/H^+ inhibitor reducing GI phosphate absorption)	Ca-based binders risk **hypercalcaemia** & worsen low-turnover/adynamic bone; non-Ca binders avoid this and may attenuate vascular calcification
Suppress PTH (vitamin D)	**Calcitriol**; analogue **paricalcitol**	Direct PTH suppression + raises ionised Ca; calcitriol can cause hyperCa/hyperphosphataemia → paricalcitol suppresses PTH with less hypercalcaemia
Calcimimetics	**Cinacalcet**, **etelcalcetide**	Increase parathyroid sensitivity to extracellular calcium → dose-dependent fall in PTH **and** plasma calcium; help lower calciphylaxis risk

Strategy	Agents (per Harrison)	Rationale / caution
Refractory disease	**Parathyroidectomy**	For severe, autonomous (tertiary) hyperparathyroidism unresponsive to medical therapy *(standard; see Coverage note)*
Calciphylaxis	**Sodium thiosulfate (IV)**, **hyperbaric oxygen**, discontinue **warfarin**	Multimodal; correct mineral derangements; wound care

High-yield exam pointers

- Renal osteodystrophy = **bone-histology arm** of CKD mineral-bone disorder; turnover + PTH axis classifies it.
- **Phosphate retention** is the prime mover → ↑FGF-23 + ↑PTH + ↓calcitriol → **secondary hyperparathyroidism**; begins at **GFR <60 mL/min**.
- **Osteitis fibrosa cystica** (high PTH) ↔ ***brown tumours***; **adynamic bone disease** (low PTH) — rising in diabetics/elderly, over-suppression risk, fracture + calcification.
- **Osteomalacia** = defective mineralisation from low $1,25(OH)_2D_3$ → excess **osteoid**.
- **FGF-23** is Klotho-dependent, raised early, an independent predictor of **LVH** and mortality.
- **Calciphylaxis**: painful livedo reticularis → ischaemic skin necrosis; **warfarin** (anti–matrix-GLA-protein) is a risk factor; treat with **IV sodium thiosulfate**.
- Drugs to recall: binders (Ca acetate/carbonate, **sevelamer**, **lanthanum**, **tenapanor**); vitamin D (**calcitriol**, **paricalcitol**); calcimimetics (**cinacalcet**, **etelcalcetide**).
- Target **intact PTH 2–9× ULN**; avoid both extremes — high PTH → osteitis fibrosa, over-suppressed PTH → adynamic bone.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 322 "Chronic Kidney Disease" (Disorders of Calcium and Phosphate Metabolism; bone manifestations, calciphylaxis, treatment) and Ch 421 "Bone and Mineral Metabolism in Health and Disease" (FGF-23, hyperphosphataemia, osteomalacia, secondary hyperparathyroidism of renal failure). *Coverage note:* The eponymous term *"renal osteodystrophy"* and the KDIGO **"CKD-MBD"** label are not used verbatim in Harrison 22e Ch 322 (which titles the section "Disorders of Calcium and Phosphate Metabolism"); the histological entities, mechanisms, drugs and doses above are all faithful to the provided text. The **TMV bone-biopsy/double-tetracycline-labelling** classification and **parathyroidectomy** for refractory disease are universally accepted standard nephrology not detailed in these two chapters, and are flagged accordingly.

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Renal replacement therapy

Asked in: Paper IV 17 Apr 2026 · Paper IV Nov 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — Renal replacement therapy (RRT) denotes the techniques that substitute for the excretory (and partly the endocrine/metabolic) functions of the kidney when native function is inadequate, whether transiently in acute kidney injury (AKI) or permanently in end-stage kidney disease (ESKD). The three pillars are **haemodialysis (HD)**, **peritoneal dialysis (PD)** and **kidney transplantation**, supplemented in the critically ill by **continuous renal replacement therapy (CRRT)**. Dialysis exploits two physical principles — **diffusion** of solute down a concentration gradient across a semipermeable membrane, and **convection** (solvent drag with ultrafiltrated plasma water) — while transplantation alone restores all renal functions and is the treatment of choice for ESKD.

Indications for RRT

- **Chronic / ESKD (maintenance dialysis):** uraemic symptoms; **hyperkalaemia** unresponsive to conservative measures; persistent **extracellular volume expansion** despite diuretics; **acidosis** refractory to medical therapy; uraemic **bleeding diathesis**; and an eGFR/creatinine clearance **<10 mL/min/1.73 m^2**. There is *no absolute* level of creatinine, BUN, cystatin C or eGFR that mandates dialysis, and no benefit to preemptive initiation at GFR 10–14 over symptom-guided start (IDEAL trial). CMDT: consider initiation as GFR nears **5–10 mL/min/1.73 m^2** with uraemic symptoms.
- **Acute (AKI) — mnemonic "AEIOU":** **A**cid–base (refractory metabolic acidosis); **E**lectrolyte (hyperkalaemia unresponsive to medical therapy); **I**ntoxications (dialysable poisons); volume **O**verload unresponsive to diuretics; **U**raemic complications — encephalopathy, asterixis, pericarditis/rub, seizures, uraemic bleeding. Randomised trials (STARRT-AKI) show **no survival benefit from earlier vs later** initiation; dialysis should not, however, await a life-threatening complication.
- **Nephrology referral** is advised when GFR <30 mL/min/1.73 m^2, rapid decline (>5 mL/min/1.73 m^2/yr) or albuminuria >300 mg/day — to plan access and modality.

Modalities at a glance

Feature	Haemodialysis	Peritoneal dialysis	CRRT (AKI)	Transplantation
Membrane	Synthetic hollow-fibre dialyzer	Patient's own peritoneum	Extracorporeal haemofilter	— (whole organ)
Clearance	Diffusion + convection	Diffusion + osmotic UF	Convective ± diffusive	Physiological
Setting	In-centre (>80% US) or home	Home, self-care	ICU, haemodynamically unstable	Definitive
Tempo	3–4 h × 3/week	Continuous, daily	Continuous (24 h)	Permanent
Key limit	Intradialytic hypotension	Peritonitis	Needs ICU/anticoagulation	Donor shortage, immunosuppression

Haemodialysis

- **Three components:** the **dialyzer** (hollow-fibre, **biocompatible synthetic polysulfone** membrane — replaced older "bioincompatible" cellulose membranes that activated complement); the **dialysate**; and the **blood-delivery system**.
- **Dialysate composition:** potassium **0–4 mmol/L** (very low-K baths increase sudden-death risk), calcium usually **1.25 mmol/L (2.5 mEq/L)**, sodium 135–140 mmol/L (*sodium modelling* may reduce intradialytic hypotension). Water is purified by softening, deionisation and **reverse osmosis** (~120 L exposure per session).
- **Prescription:** heparinised blood pumped at **250–450 mL/min** with dialysate running **counter-current at 500–800 mL/min**; small molecules (urea, 60 Da) cleared far better than larger ones (creatinine, 113 Da).
- **Vascular access (in order of preference — "Fistula First"):** native **arteriovenous fistula** (*Brescia–Cimino*: cephalic vein at wrist anastomosed end-to-side to radial artery) — highest patency, lowest infection, matures in **6–8 weeks**; **AV graft** (interposed PTFE, usable ~2 weeks, fails by intimal hyperplasia/thrombosis); **tunnelled cuffed catheter** (internal jugular preferred; highest infection/thrombosis — a "lifeline" only). Subclavian access is avoided (stenosis risk).
- **Adequacy: urea reduction ratio (URR) >65–70 %** and **Kt/V >1.2** (single-pool) or 1.05 (equilibrated); standard schedule 9–12 h/week in 3 sessions.
- **Acute complications: hypotension** (commonest — excess/rapid ultrafiltration; avoid removal >13 mL/kg/h), muscle cramps, and **dialyzer reactions** — *type A* (IgE-mediated anaphylaxis to ethylene-oxide, within minutes) and *type B* (complement/cytokine-mediated chest & back pain). **Dialysis disequilibrium syndrome** (cerebral oedema from rapid urea/osmolar shifts) may occur with aggressive early sessions — mitigated by short, low-efficiency initial runs.

Peritoneal dialysis

- **Principle:** 1.5–3 L of hypertonic **dextrose** solution dwells in the peritoneal cavity (2–4 h); solute is removed by diffusion and water by **osmotic ultrafiltration**. **Icodextrin**, a non-absorbable glucose polymer, gives sustained ultrafiltration in the long dwell of high transporters.
- **Forms: CAPD** (manual exchanges, 3–5/day with an overnight dwell) and **CCPD/APD** (automated cycler performs exchanges overnight). The **peritoneal equilibration test (PET)** classifies membranes as **low, low-average, high-average, high transporters** — high transporters need short, frequent (cycler) dwells.
- **Access:** soft silicone catheter with **two Dacron cuffs** that scar to anchor and seal against bacterial tracking.
- **Complications: peritonitis** (commonest serious complication) — cloudy effluent + abdominal pain, **dialysate leukocytes >100/mm^3 with >50% neutrophils**; usually **gram-positive cocci (Staphylococcus, skin origin)**, treated with intraperitoneal/oral antibiotics; *Pseudomonas* or fungal peritonitis mandates **catheter removal**. Also tunnel-exit infections, **protein loss/hypoalbuminaemia**, hyperglycaemia, weight gain, hypertriglyceridaemia and late **encapsulating peritoneal sclerosis**. Advantage: continuous potassium/phosphate removal allows a more liberal diet and suits haemodynamically labile patients.

Continuous & hybrid therapies (AKI)

- **CVVH** (purely convective — plasma water forced across the membrane, replaced by crystalloid), **CVVHD** (diffusive, low blood/dialysate flows), **CVVHDF** (combined). **SLED/EDD** ("hybrid", ≤12 h) capture CRRT's gentleness without 24-h staffing.
- Preferred for **haemodynamic instability, cerebral oedema or severe volume overload**; trials show no survival/recovery superiority over intermittent HD, and no benefit of higher dialysis dose.

Kidney transplantation — the definitive RRT

- **Treatment of choice for ESKD**, conferring longer survival and better quality of life than dialysis; first successful transplant Boston **1954** (identical twins). One-year graft survival ~**98% (living)** and **93% (deceased)**; mean graft survival ~**19 vs 12 years**. The graft is placed **extraperitoneally in the iliac fossa** — donor renal artery→external iliac artery, renal vein→external iliac vein, ureter→bladder.
- **Matching:** ABO compatibility plus **HLA** (chromosome 6; class I = A, B, C; class II = DR, DQ, DP) — more A/B/DR mismatches predict poorer survival. A **positive cytotoxic T-cell crossmatch** (preformed donor-specific anti-HLA class I antibody) predicts **hyperacute rejection** and is the *only absolute immunologic contraindication*.
- **Absolute contraindications:** predicted survival <2 years, active malignancy, active infection, non-adherence/psychosocial barriers, active substance abuse.
- **Rejection:** *hyperacute* (preformed antibody, minutes); *acute T-cell-mediated* (Banff-graded interstitial/tubular/vascular infiltrate → IV **methylprednisolone 500–1000 mg/day × 3**, then ATG); *antibody-mediated* (**C4d** in peritubular capillaries + circulating DSA → plasmapheresis, IVIG, rituximab, bortezomib); and chronic (fibrosis/vasculopathy).
- **Immunosuppression:** *Induction* — depleting **antithymocyte globulin (ATG)** or **alemtuzumab (anti-CD52)**; non-depleting **basiliximab (anti-IL-2Rα/CD25)**. *Maintenance* — a **calcineurin inhibitor** (tacrolimus [binds FKBP-12] or cyclosporine [binds cyclophilin] → blocks IL-2 transcription) + an **antimetabolite** (mycophenolate, or azathioprine — check **TPMT**) + **steroids**; alternatives **mTOR inhibitors** (sirolimus/everolimus) and **belatacept** (CTLA-4–Ig, blocks CD80/86–CD28 costimulation). CNI toxicity: nephrotoxicity, hypertension; cyclosporine causes hirsutism & gingival hyperplasia, tacrolimus causes post-transplant diabetes.
- **Post-transplant infection timeline:** <1 month — bacterial wound/UTI, HSV, candidiasis; **1–6 months** — opportunistic **CMV** (D+/R− highest risk; valganciclovir), **Pneumocystis** (TMP-SMX prophylaxis 6 months), **BK polyomavirus nephropathy** (manage by reducing immunosuppression), Listeria, Nocardia; **>6 months** — Aspergillus, zoster, community pathogens. **Malignancy** (~100× general population): **skin/lip cancers** commonest; **EBV-driven PTLD**. Leading causes of recipient death: cardiovascular (~29%), infection (~18%), malignancy (~17%).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Haemodialysis circuit:** label *arterial line from AV fistula → blood pump → heparin infusion → hollow-fibre dialyzer (blood vs counter-current dialysate compartments) → air/leak detector → venous line back to patient*; on the dialysate side label *purified water (reverse osmosis) + acid/bicarbonate concentrate → dialysate inflow → drain*. Mark **diffusion** and **ultrafiltration/convection** across the membrane.
- **Transplant anatomy:** label *graft kidney in right iliac fossa, donor renal artery → external iliac artery, donor renal vein → external iliac vein, donor ureter → recipient bladder*, native kidneys left in situ.

Clinical / Diagnostic significance

- **Modality choice** balances comorbidity, vascular/peritoneal access, lifestyle and resources; outcomes of HD vs PD are broadly similar, so quality-of-life often decides. PD predominates in resource-limited settings (lower cost).
- **Pre-emptive transplantation** (before dialysis) gives the best outcomes; living-donor grafts outperform deceased-donor.
- **Cardiovascular disease** is the leading cause of death in both dialysis and transplant populations; aggressive BP, lipid and volume control are essential.
- Monitoring tools: **URR/Kt/V** for HD adequacy, **PET** for PD membrane typing, **donor-specific antibody + allograft biopsy (Banff)** for rejection.

High-yield exam pointers

- RRT = **HD + PD + CRRT + transplantation**; dialysis works by **diffusion + convection**.
- **AEIOU** = AKI dialysis indications; ESKD dialysis when GFR ~5–10 with uraemia.
- **Brescia–Cimino radiocephalic fistula** = preferred access ("Fistula First"); matures 6–8 weeks; highest patency, lowest infection.
- **HD adequacy:** URR >65–70 %, **Kt/V >1.2**; commonest acute complication = **hypotension**.
- **PD peritonitis:** cloudy effluent, **>100 WBC/mm^3 (>50% neutrophils)**, usually **gram-positive cocci**; *Pseudomonas*/fungal → remove catheter.
- **CRRT** preferred in haemodynamic instability/cerebral oedema; no survival edge over intermittent HD.
- **Positive cytotoxic crossmatch** = only absolute immunologic contraindication (hyperacute rejection).
- Transplant maintenance = **CNI + antimetabolite + steroid**; **C4d** in peritubular capillaries = antibody-mediated rejection.
- Commonest post-transplant malignancy = **skin cancer**; **CMV** and **BK virus** are key opportunists.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Dialysis in the Treatment of Kidney Failure"; "Kidney Transplantation"; "Acute Kidney Injury" (CRRT/SLED modalities); "Interventional Nephrology" (access).
- **Brenner & Rector's The Kidney** — "Hemodialysis" (Kt/V, adequacy, urea kinetics) and "Peritoneal Dialysis" (icodextrin, transporter status, automated PD).
- **CMDT 2026** — "Kidney Disease" (AEIOU indications, ESKD treatment thresholds, access maturation times, prognosis).

Coverage note: "Dialysis disequilibrium syndrome" and the AEIOU framing are universally accepted standard internal medicine, included for completeness; the Harrison/Brenner dialysis chapters describe the underlying osmolar-shift and indication concepts but do not use these exact labels.

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Renal tubular acidosis

Asked in: Paper IV May 2022 · Paper IV Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — Renal tubular acidosis (RTA) is a group of disorders characterised by a **normal anion-gap (hyperchloraemic) metabolic acidosis** caused by impaired renal tubular acidification—either failure of the proximal tubule to reabsorb filtered bicarbonate or failure of the distal nephron to secrete H^+ / generate ammonium—**despite a relatively preserved glomerular filtration rate**. It is recognised biochemically by a hyperchloraemic acidosis with reciprocal fall in [HCO_3^-] and a **positive urine anion gap** (signifying low urinary NH_4^+ of renal origin). The clinically important forms are **proximal (type 2)**, **classic distal (type 1)**, and **hyperkalaemic / generalised distal nephron dysfunction (type 4)** RTA.

Classification (Harrison Table 58-5)

Type	Defect	Serum K^+	Representative causes
Proximal (type 2)	Reduced proximal HCO_3^- reabsorptive threshold (Tm) → bicarbonaturia	**Low**	Acetazolamide, topiramate, ifosfamide; Fanconi syndrome; light-chain (myeloma) injury; inherited *SLC4A4* (basolateral NBCe1, with ocular abnormalities), *NHE3* (AD, short stature)
Distal / classic (type 1)	Impaired distal H^+ secretion / acidification	**Low**	Amphotericin B, ifosfamide; Sjögren's syndrome; SLE; inherited *ATP6V1B1* defect (distal tubule/collecting duct)
Generalised distal nephron dysfunction (type 4)	Aldosterone deficiency or resistance → impaired NH_4^+ generation + impaired K^+/H^+ secretion	**High**	Hyporeninaemic hypoaldosteronism (diabetes, tubulointerstitial disease); mineralocorticoid resistance (PHA I); voltage defect (PHA I recessive, PHA II); drugs

- Within type 4, Harrison subdivides causes into **(a) selective aldosterone deficiency, (b) mineralocorticoid resistance — pseudohypoaldosteronism (PHA) I, autosomal dominant, (c) voltage defect — PHA I autosomal recessive and PHA II, (d) hyporeninaemic hypoaldosteronism, and (e) tubulointerstitial disease.**
- **Normokalaemic renal acidosis** of chronic progressive kidney disease (the "uraemic" non-AG acidosis of CKD stages 3–4) is a separate category requiring oral alkali.

Pathophysiology by type

- **Proximal RTA (type 2):** generalised proximal tubular dysfunction reduces the bicarbonate reabsorptive threshold. At normal plasma [HCO_3^-] there is **bicarbonaturia** with an inappropriately alkaline urine; once plasma [HCO_3^-] falls **below the reduced threshold**, the distal nephron is intact, so the urine can be acidified to **pH <5.5**. It is frequently part of **Fanconi syndrome** — glycosuria, generalised aminoaciduria and phosphaturia. Alkali therapy enhances distal Na^+/HCO_3^- delivery and **renal K^+ secretion**, aggravating hypokalaemia.
- **Distal RTA (type 1):** failure of distal H^+ secretion produces an inability to lower urine pH appropriately. Classic features are **hypokalaemia, non-AG metabolic acidosis, low urinary NH_4^+ excretion (positive urine anion gap), and an inappropriately high urine pH (>5.5)** for the degree of systemic acidosis. **Hypocitraturia and hypercalciuria** are usual, so **nephrolithiasis, nephrocalcinosis and metabolic bone disease** are common.
- **Type 4 (hyperkalaemic) RTA:** aldosterone deficiency or tubular resistance impairs both potassium and acid secretion. **Hyperkalaemia is disproportionate to the reduction in GFR**, and hyperkalaemia itself **suppresses renal ammoniagenesis**, depressing urinary NH_4^+ and net acid excretion. **Hyporeninaemic hypoaldosteronism** typically presents in **older adults with diabetes mellitus or tubulointerstitial disease and stage 3–4 CKD**, with **K^+ 5.2–6.0 mmol/L, hypertension and congestive heart failure**, both acidosis and hyperkalaemia being out of proportion to the GFR. NSAIDs, trimethoprim, pentamidine, ACE inhibitors and ARBs increase the risk, especially in diabetic nephropathy.

Diagnostic approach

- **Confirm a normal anion-gap (hyperchloraemic) acidosis** — reciprocal rise in [Cl^-] with the fall in [HCO_3^-]; calculate AG (correct for albumin) to exclude a high-AG process.
- **Urine anion gap (UAG)** = $([Na^+] + [K^+])_u - [Cl^-]_u$ to estimate urinary NH_4^+:
  - **Negative UAG** → urinary NH_4^+ appropriately high → **extrarenal / gastrointestinal (diarrhoea)** cause.
  - **Positive UAG** → urinary NH_4^+ inappropriately low → **renal (RTA)** origin.
- **Urine pH:** inappropriately **>5.5** in classic distal RTA and during the bicarbonaturic phase of proximal RTA; in proximal RTA the urine acidifies to **<5.5** once plasma [HCO_3^-] falls below threshold; in type 4 the dominant abnormality is **depressed urinary NH_4^+**.
- **Caveat (Harrison):** the UAG correlates poorly with directly measured urine ammonium, so laboratories are encouraged to **measure urine NH_4^+ directly** (enzymatic assay on a 1:200 saline-diluted sample) rather than rely on the UAG.

- **Supportive findings:** proximal — glycosuria, aminoaciduria, phosphaturia (Fanconi); distal — hypokalaemia, hypercalciuria, hypocitraturia, nephrocalcinosis; type 4 — hyperkalaemia disproportionate to GFR, often diabetic/obstructive/tubulointerstitial kidney disease.

Treatment

- **Proximal RTA (type 2):** the **most difficult RTA to fully correct**, because alkali increases urinary bicarbonate **and** potassium loss; **potassium supplementation is usually required**. An oral **sodium + potassium citrate** solution (citric acid 334 mg, sodium citrate 500 mg, potassium citrate 550 mg per 5 mL) is used; large alkali doses are often needed to restore serum [HCO_3^-] (important for normal growth in children).
- **Distal RTA (type 1): correct hypokalaemia first**, then give alkali — **sodium citrate (Shohl's solution)** or **$NaHCO_3$ tablets (650-mg tablet = 7.8 meq)** — to maintain serum [HCO_3^-] at **24–26 meq/L**. Patients respond readily; benefits include **fewer kidney stones, improved bone density, resumption of normal growth, and preservation of kidney function**.
- **Type 4 RTA: correct the metabolic acidosis** (alkali, as for type 1) **and correct the plasma** [K^+]; restoring normokalaemia restores ammoniagenesis and net acid excretion. Hyperkalaemia is managed with the **calcium–potassium cation-exchange polymer patiromer** (8.4-g packets PO twice daily, titrated weekly to plasma K^+, **max 25.2 g/day**) plus a **low-potassium diet** and withdrawal of potassium-retaining drugs; **documented isolated hypoaldosteronism is treated with fludrocortisone** (cautiously, with furosemide if there is oedema/hypertension).
- **CKD acidosis:** oral alkali to keep [HCO_3^-] **>22–24 mmol/L** (**≈1.0–1.5 mmol/kg/day** as $NaHCO_3$ or Shohl's solution); a diet rich in fruit and vegetables also raises plasma [HCO_3^-] and slows CKD progression.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Nephron schematic of acidification** — label: *proximal tubule* (Na^+/H^+ exchanger NHE3, basolateral NBCe1, HCO_3^- reabsorption — site of **type 2**); *distal tubule / α-intercalated cell of collecting duct* (apical **H^+-ATPase**, basolateral Cl^-/HCO_3^- exchanger AE1 — site of **type 1**); *principal cell / aldosterone action* (ENaC, Na^+–K^+/H^+ secretion — site of **type 4**); annotate **urine pH** and **serum K^+** for each.
- **Diagnostic flow box** — label: *Hyperchloraemic non-AG acidosis → Urine anion gap*; *Negative UAG = GI/diarrhoea*; *Positive UAG = RTA → check serum K^+ (low = type 1/2; high = type 4) and urine pH (>5.5 distal).*

Clinical / Diagnostic significance

- **Tubulointerstitial disease** is a major secondary cause: chronic TIN produces **type II RTA from bicarbonaturia (Fanconi) or type IV RTA from impaired ammoniagenesis**; **Sjögren's syndrome** classically causes **distal RTA and nephrogenic diabetes insipidus** (anti-Ro/SS-A, anti-La/SS-B positive); **lupus nephritis** may present with **type IV RTA**; **calcineurin inhibitors** cause hyperkalaemia via **tubular resistance to aldosterone**.

- **Proximal RTA** points to Fanconi syndrome — screen for **multiple myeloma / light-chain cast nephropathy**, drugs (ifosfamide, acetazolamide, topiramate) and heavy-metal (lead) tubulopathy.
- **Distal RTA** must be considered in any patient with **recurrent calcium nephrolithiasis, nephrocalcinosis, hypokalaemic paralysis, or unexplained osteomalacia/rickets**.
- **Type 4 RTA** is the commonest RTA in adult practice — suspect it in a **diabetic with mild CKD and hyperkalaemia disproportionate to GFR**, particularly on ACE inhibitors/ARBs, NSAIDs, trimethoprim, pentamidine or heparin.

High-yield exam pointers

- RTA = **normal anion-gap (hyperchloraemic) metabolic acidosis with positive urine anion gap**.
- **Type 1 & 2 → hypokalaemia; Type 4 → hyperkalaemia.**
- **Distal (type 1):** urine pH **>5.5**, stones/nephrocalcinosis, hypercalciuria + hypocitraturia; causes — **amphotericin B, Sjögren's, SLE, ATP6V1B1**.
- **Proximal (type 2): Fanconi syndrome** (glycosuria, aminoaciduria, phosphaturia); urine can still acidify **<5.5** when plasma HCO_3^- is low; causes — **acetazolamide, topiramate, ifosfamide, myeloma**.
- **Type 4: hyporeninaemic hypoaldosteronism** in elderly diabetics; hyperkalaemia **suppresses ammoniagenesis**.
- **Positive UAG = renal cause; negative UAG = diarrhoea/GI** (but Harrison: measure urine NH_4^+ directly as UAG is unreliable).
- Treatment anchors: **Shohl's solution / $NaHCO_3$ (650 mg = 7.8 meq)**; **K^+ + alkali (citrate)** for type 2; **patiromer + fludrocortisone** for type 4.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 58 "Acidosis and Alkalosis" (non-AG acidoses, Table 58-5 classification, UAG, treatment of types 1/2/4) and Ch 328 "Tubulointerstitial Diseases of the Kidney" (Fanconi/type II and type IV RTA in TIN, Sjögren's, SLE, CNI hyperkalaemia). **Coverage note:** the *SLC4A1 (AE1/band-3)* gene for autosomal-dominant distal RTA, the formal "type 3 (mixed)" designation, and the ammonium chloride / bicarbonate-infusion (fractional excretion of HCO_3^- >10–15% in type 2) provocative tests are standard textbook additions used here for completeness but are not detailed in the two provided chapters; Harrison lists *ATP6V1B1* as the inherited distal-RTA gene.

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Renovascular hypertension

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Renovascular hypertension (RVH) is a rise in systemic arterial pressure *definitely induced by reduced renal perfusion*, most often from occlusive disease of a main or branch renal artery. It is the prototypical **potentially curable ("secondary") cause of hypertension**, because restoration of renal perfusion can reverse the pressor pathways. *Renal artery stenosis (RAS)* denotes the anatomical lesion; RVH is the *functional* consequence — the two are not synonymous, since many incidentally found stenoses are haemodynamically trivial. Renovascular disease is found in up to 25% of autopsies, yet RVH accounts for only ~1–2% of all hypertension.

Aetiology & Classification

- **Two dominant causes** account for the vast majority:
  - **Atherosclerotic RAS (ARAS)** — ~90%; older patients with diffuse atherosclerotic risk factors.
  - **Fibromuscular dysplasia (FMD)** — ~10%; younger women (age 15–50).
- ARAS is *common*: ~6.8% of a community sample over age 65, rising to 18–23% with coronary artery disease and >30% with peripheral/aortic disease. Untreated, ARAS **progresses in ~50% over 5 years**, sometimes to total occlusion.
- Other causes (Brenner *Box 47.1*): renal artery aneurysm, arterial embolus/thrombosis, dissection, arteriovenous fistula, extrinsic compression (e.g. phaeochromocytoma, tumour), aortic coarctation, systemic vasculitis (**Takayasu arteritis**, polyarteritis), atheroembolic disease, and iatrogenic occlusion by an **endovascular aortic stent-graft**.

Feature	Atherosclerotic RAS (ARAS)	Fibromuscular dysplasia (FMD)
Proportion	~90%	~10%
Typical patient	Older, M≈F, ASCVD risk factors, smoker, diabetic	Young/middle-aged **women** (15–50 y)
Lesion site	**Ostial / proximal third** of renal artery	**Mid–distal** artery, branches; often bilateral
Angiographic look	Discrete proximal stenosis, often aortic plaque extension	**"String of beads" / sawtooth** (medial fibroplasia) ± aneurysm
Natural history	Progressive; causes **ischaemic nephropathy**	Rarely threatens GFR; may occlude / form aneurysm
Response to angioplasty	Poor — **medical therapy preferred**	**Often curative** (PTRA)

- **FMD subtypes** (Brenner *Box 47.1*): *medial fibroplasia* (commonest, classic string-of-beads), *perimedial fibroplasia*, *intimal fibroplasia*, and *medial hyperplasia*.

Pathophysiology — the Goldblatt paradigm

- **Goldblatt (1932–34)** showed that clipping a renal artery reliably produces hypertension — the foundation of RAAS discovery.

- A lesion becomes **haemodynamically "critical" only when luminal obstruction reaches ~70–80%**; a translesional aorto-renal pressure gradient of **10–20 mmHg** is needed before measurable renin release occurs.
- Two physiologically distinct models explain the syndrome:

	Two-kidney, one-clip (2K1C) — unilateral RAS, normal contralateral kidney	One-kidney, one-clip (1K1C) — bilateral RAS or stenosis to a solitary kidney
Driving mechanism	**Renin → Angiotensin II–dependent**	**Volume-dependent** (impaired Na^+/water excretion)
Contralateral kidney	Intact → **pressure natriuresis** keeps it volume-deplete → *sustained* renin release from stenotic side	Absent escape → Na^+/water retention, **volume expansion**
Plasma renin activity	**Elevated**	Normal or low
Lateralisation of tests	**Present** (renal-vein renin, captopril renography)	**None**
Effect of RAAS blockade	Lowers BP; **may drop GFR** in stenotic kidney; sharpens test lateralisation	Lowers BP **only after volume depletion**; **may sharply lower GFR**

- **Downstream Angiotensin II effects**: efferent arteriolar vasoconstriction, aldosterone secretion (→ Na^+ retention, hypokalaemia), sympathetic activation, plus chronic **vascular remodelling, LV hypertrophy, endothelin release, oxidative stress and fibrosis**.
- **Three temporal phases** (experimental): **Phase I** — high circulating renin, BP fully reversible by clip removal; **Phase II** — renin returns to normal, BP persists but still clip-reversible; **Phase III** — BP becomes *clip-independent* (structural remodelling, oxidative injury, contralateral microvascular damage) and is no longer cured by revascularisation. This explains why **late revascularisation often fails to normalise BP**.
- **Ischaemic nephropathy**: with advanced ARAS, falling cortical perfusion and tissue hypoxia → tubulointerstitial fibrosis and loss of GFR. ~85% of revascularisation candidates already have **stage 3–5 CKD (eGFR <60)**.

Clinical features — when to suspect RVH

- **Demographic/temporal clues**: onset of hypertension **before age 20–30 or after 50–55 years**; **abrupt-onset** or **rapidly worsening** previously controlled hypertension.
- **Resistant hypertension** — uncontrolled despite ≥3 drugs (one a diuretic).
- **Abdominal / flank (epigastric) bruit**; evidence of atherosclerosis elsewhere (claudication, CAD) — 15–25% of symptomatic lower-limb PAD have RAS.
- **Abrupt rise in serum creatinine (>25–30%)** after starting an **ACE inhibitor / ARB** — a *functional, reversible* loss of GFR from removing efferent vasoconstriction; strongly suggests **bilateral RAS or stenosis to a solitary kidney**.
- **Recurrent "flash" pulmonary oedema** with surges of BP and preserved LV systolic function (*Pickering syndrome*).

- **Unprovoked hypokalaemia** (secondary hyperaldosteronism), proteinuria, and **asymmetric kidney size (>1.5 cm difference)** on ultrasound.
- *Note*: the Cooperative Study (Simon 1972) confirmed that although early age of onset, abdominal bruit, hypokalaemia and grade 3–4 fundi are commoner in RVH, **no single clinical feature reliably discriminates** it from essential hypertension.

Diagnostic evaluation

- **Principle**: screen non-invasively, confirm by angiography — and *only investigate aggressively if a corrective procedure would be undertaken on a positive result*.

Modality	Role / strength	Caveat
Duplex Doppler ultrasonography	Peak systolic velocity **>200 cm/s predicts >60% stenosis**; renal **resistive index** predicts viability; cheap, repeatable	Highly operator- and habitus-dependent
CT angiography (CTA)	Excellent vascular images; best for **accessory vessels** & distal disease; no stent artefact	Iodinated **contrast toxicity**
MR angiography (MRA)	Good images of artery + perirenal aorta	**Gadolinium / nephrogenic systemic fibrosis** risk — avoid if eGFR <30; cannot image stents
Captopril renography (^{99m}Tc-MAG3)	**Strong negative predictive value** — a normal study excludes RVH	Affected by drugs, Na^+, bilateral disease
Intra-arterial (digital subtraction) angiography	**Gold standard**; usually combined with intended intervention	Invasive; atheroembolism, contrast, dissection

- **Plasma renin activity / renal-vein renin sampling** is transient and drug/sodium-sensitive — it does **not** reliably predict response and is now **rarely performed** (high false-positive and false-negative rates).

Management

- **Optimal medical therapy is the cornerstone** for most patients (especially ARAS):
  - **RAAS blockade (ACE inhibitor or ARB)** — most effective antihypertensives in RVH; **monitor creatinine and potassium** after initiation; not absolutely contraindicated in unilateral disease.
  - **Statin**, **antiplatelet (aspirin)**, **smoking cessation**, attainment of goal BP, glycaemic control.
- **Revascularisation** — endovascular stenting (ARAS) or **percutaneous transluminal renal angioplasty (PTRA)**:
  - **FMD** → PTRA is **often curative** — the single most important reason to *identify* FMD.
  - **ARAS** → the randomised trials **ASTRAL (2009), STAR (2009) and CORAL (2014)** showed **no added benefit of stenting over optimal medical therapy** for BP or renal preservation in moderate stenosis.
  - **Reserve intervention** (Harrison *Table 289-2*; AHA 2022) for: refractory hypertension / medical failure; **rapidly declining or recurrent fall in GFR**, including a fall precipitated by

ACEi/ARB; **flash pulmonary oedema** or recurrent unexplained heart failure; high-grade (>70%) stenosis to the whole functioning renal mass; transplant renal-artery stenosis.

- **Procedural risk <5%** with experienced operators: renal artery dissection, capsular perforation, haemorrhage, and **atheroembolic disease** (which can paradoxically accelerate hypertension and renal failure). Renal flow is usually restored, but function recovers in only ~25% of cases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Goldblatt 2K1C vs 1K1C schematic** — Draw two kidneys. *Left (2K1C):* stenosed renal artery → "↓perfusion → ↑Renin → Angiotensin II → Aldosterone → Angiotensin-II-dependent HTN; PRA HIGH; lateralises"; contralateral kidney labelled "pressure natriuresis (volume-deplete)". *Right (1K1C):* bilateral stenoses / solitary kidney → "↓perfusion → Na^+ + water retention → Volume expansion → volume-dependent HTN; PRA normal/low; NO lateralisation".
- **RAAS cascade box** — Labels: *Angiotensinogen* → *(Renin)* → *Angiotensin I* → *(ACE)* → *Angiotensin II* → branches to **Vasoconstriction**, **Aldosterone → Na^+ retention**, **Sympathetic activation**, **LV hypertrophy / vascular remodelling**.

Clinical / Diagnostic significance

- RVH is a **treatable secondary hypertension** — but in the modern era the chief goal has shifted from *curing BP* to **preserving renal function and preventing cardiovascular events**.
- A **>25–30% creatinine rise after ACEi/ARB** is a clinical "stress test" that unmasks bilateral RAS/solitary-kidney stenosis — recognise it early, as it is reversible.
- ARAS is an independent marker of **cardiovascular morbidity and mortality** regardless of whether revascularisation is done.
- **Atheroembolic (cholesterol-crystal) renal disease** is a key differential/complication after angiography or vascular surgery: **livedo reticularis, blue toes, eosinophilia (60–80%), hypocomplementaemia (15%)**, stuttering renal failure, biopsy showing biconvex cholesterol "clefts"; 1-year mortality >38%. Withdraw anticoagulation; no specific therapy.

High-yield exam pointers

- **RVH = functional consequence; RAS = anatomical lesion** — not interchangeable.
- **~90% ARAS (ostial, older men) vs ~10% FMD (string-of-beads, young women)**; FMD responds to PTRA, ARAS usually does not.
- **Critical stenosis = 70–80% lumen loss; gradient 10–20 mmHg** triggers renin release.
- **2K1C = renin/angiotensin-dependent, PRA high, lateralises; 1K1C = volume-dependent, PRA normal/low, no lateralisation.**
- **Captopril renography**: a *normal* scan excludes RVH (high NPV); **DSA = gold standard**.
- **Suspect RVH**: age <30 or >50, resistant HTN, abdominal bruit, flash pulmonary oedema, **creatinine ↑ >25% on ACEi/ARB**, hypokalaemia, asymmetric kidneys.
- **ASTRAL / CORAL / STAR**: stenting **no better than medical therapy** in ARAS — reserve intervention for refractory HTN, flash pulmonary oedema, or rapidly falling GFR.

- Medical bundle = **RAAS blockade + statin + antiplatelet + smoking cessation + BP control.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Renovascular Disease" (Textor) and "Hypertension" (secondary hypertension / renovascular section).
- **Brenner & Rector's The Kidney** — "Renovascular Hypertension and Ischemic Nephropathy" (Goldblatt 2K1C/1K1C models, phases of RVH, critical-stenosis thresholds, lesion classification Box 47.1, Cooperative Study clinical clues).
- **CMDT 2026** — "Systemic Hypertension" (renal vascular hypertension) and "Kidney Disease — Renal Artery Stenosis" (diagnostic criteria, ASTRAL/CORAL evidence, revascularisation indications, AHA 2022 statement).

Coverage note: The eponym "Pickering syndrome" for recurrent flash pulmonary oedema with bilateral RAS is universally accepted standard medicine but is not named in the cited corpus (which uses "flash pulmonary edema"); trial acronyms ASTRAL/CORAL/STAR appear in the corpus on the RVD historical timeline and CMDT's "two large randomized trials" statement.

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Tubulointerstitial diseases of the kidney

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Tubulointerstitial diseases are a group of disorders that **primarily** target the renal tubules and the interstitium, with relative sparing of the glomeruli and renal vessels (distinguishing them from the *secondary* interstitial fibrosis that complicates almost every chronic glomerular or vascular disease). They are conveniently divided into **acute** (acute tubulointerstitial/interstitial nephritis, AIN/ATIN) and **chronic** (CIN/CTIN) forms. They account for roughly **10–20% of acute kidney injury (AKI)** and are an important, frequently unrecognised, cause of chronic kidney disease (CKD), with **interstitial fibrosis and tubular atrophy** as the final common pathway.

Classification (Causes)

Acute tubulointerstitial disorders	Chronic tubulointerstitial disorders
Drug-induced AIN — antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, rifampin, ethambutol, acyclovir), **NSAIDs/COX-2 inhibitors**, **PPIs**/H2-blockers, diuretics (thiazide, loop, triamterene), anticonvulsants (phenytoin, valproate, carbamazepine), allopurinol, mesalazine, **immune checkpoint inhibitors**, lenalidomide	**Toxins/drugs** — analgesics (phenacetin), lithium, heavy metals (lead, cadmium), **aristolochic acid**, calcineurin inhibitors (cyclosporine, tacrolimus)
Infection-associated — *Streptococcus, Staphylococcus, Legionella, Leptospira*; EBV, CMV, hantavirus, polyomavirus (BK), HIV	**Reflux nephropathy** (vesicoureteral reflux); **sickle cell nephropathy**

Acute tubulointerstitial disorders	Chronic tubulointerstitial disorders
Autoimmune — TINU, Sjögren's, SLE, sarcoidosis (granulomatous), **IgG4-related disease**, anti-brush-border (anti-LRP2) disease	**Metabolic** — hypercalcaemia/nephrocalcinosis, hyperuricaemia (gouty), chronic hypokalaemia, hyperoxaluria
Acute obstructive (crystal) — light-chain cast nephropathy, acute urate nephropathy, acute phosphate nephropathy	**Cystic/hereditary** — ADPKD, nephronophthisis, **ADTKD** (medullary cystic kidney disease), medullary sponge kidney
	Other — chronic GN, obstruction, ischaemia, radiation; **CINAC/CKDu** (agricultural communities)

Pathogenesis / Mechanisms of injury

- **Acute** disease results from aggressive inflammatory infiltrates causing interstitial **oedema, tubular cell injury and compromised tubular flow**, or from frank **tubular obstruction** by casts, cellular debris or crystals; capsular distension may produce **flank pain**.
- **Drug-induced ATIN is a T-cell–mediated delayed (Type IV) hypersensitivity reaction** — drugs act as **haptens/pro-haptens**, bind tubular basement membrane (TBM) proteins or generate neoantigens (molecular mimicry). It is most often a **Type IVb** reaction (IL-5 driven, tissue/blood eosinophilia); NSAID-induced disease lacks eosinophils. The infiltrate is **>80% T lymphocytes** ($CD4^+$ and $CD8^+$) with macrophages and eosinophils, plus **tubulitis** (lymphocytes crossing the TBM).
- **Chronic** disease shows interstitial fibrosis, patchy mononuclear infiltrate, widespread **tubular atrophy**, luminal dilation and **TBM thickening**. Mechanisms of fibrosis include chronic **hypoxia** (peritubular capillary rarefaction), proteinuria-induced proximal tubular injury, persistent inflammation and epithelial–mesenchymal transition (TGF-β driven).
- Because the chronic histology is non-specific, **diagnosis relies on history, drug/toxin exposure and imaging** more than biopsy.

Acute Interstitial Nephritis — clinical features, diagnosis, treatment

- First described by **Councilman (1897)** in scarlet fever and diphtheria; today it is most often an **allergic drug reaction**, accounting for ~10–15% of intrinsic AKI. Drugs cause **>70%** of cases (top classes: antibiotics ~49%, PPIs ~14%, NSAIDs ~11%; commonest single drugs — omeprazole, amoxicillin, ciprofloxacin).
- **Classic triad — fever, rash and (peripheral) eosinophilia with oliguric AKI** ~7–10 days after a β-lactam — is the **exception (only ~5–15%)**, and is commonest with β-lactams/sulfonamides. Latency is long and "silent" with **PPIs (~11 weeks)** and **NSAIDs (6–18 months, often with heavy/nephrotic proteinuria ± minimal-change or membranous lesion)**. **Rifampin**-induced AIN is dose-dependent, antibody-mediated and severe on re-exposure.
- **Urinalysis**: sterile **pyuria, WBC casts, microscopic haematuria** and **low-grade tubular proteinuria (<1–2 g/day)**. **Urinary eosinophils are NEITHER sensitive nor specific and are no longer recommended.** Eosinophilia, raised ESR/CRP and IgE are supportive but inconsistent.

- **Kidney biopsy is the gold standard** (interstitial inflammation + tubulitis ± eosinophils ± granuloma). Ancillary: ^{67}Gallium / FDG-PET show enhanced renal uptake; ultrasound shows enlarged echogenic kidneys (non-specific).
- **Treatment — withdraw the offending agent** (often reversible) and give supportive care; **up to one-third require temporary dialysis**. **Glucocorticoids** are added if there is no recovery within ~5–7 days, severe AKI/impending dialysis, or diffuse infiltrate — efficacy falls if started >1–2 weeks after onset. Regimen: **IV methylprednisolone 250–500 mg/day for 1–4 days** or **prednisone ~1 mg/kg (60 mg/day) for 4–6 weeks** with taper. *Absolute* steroid indications: **Sjögren's, sarcoidosis, SLE interstitial nephritis, adult TINU, IgG4-related and granulomatous/idiopathic IN.**
- **Immune-mediated subtypes**: **TINU** (<5% of AIN; female 3:1; median age 15 yr; painful bilateral anterior uveitis ± Fanconi, raised ESR); **Sjögren's** (anti-Ro/La, distal RTA, nephrogenic DI); **sarcoidosis** (non-caseating granulomas, hypercalcaemia — *exclude TB first*); **IgG4-related disease** (IgG4$^+$ plasma cells, *storiform* fibrosis; with autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis); **checkpoint-inhibitor AIN** (kidney affected in ~2% monotherapy, up to 5% dual therapy; onset usually 2–3 months).
- **Crystal/obstructive tubulopathies**: sulfadiazine (*"sheaf-of-wheat"* crystals), indinavir/atazanavir (needle crystals), acyclovir (red-green birefringent needles); **acute urate nephropathy** (tumour-lysis — treat with **rasburicase**/dialysis, prophylactic allopurinol); acute phosphate nephropathy (oral Phosphosoda). **Light-chain cast nephropathy ("myeloma kidney")** — filtered monoclonal light chains (Bence-Jones) aggregate with **Tamm-Horsfall protein** in distal tubules forming obstructing casts with giant-cell reaction; clues are anaemia, bone pain, hypercalcaemia and a **narrow anion gap**.

Chronic Tubulointerstitial Nephritis — key entities

Entity	Key features
Analgesic nephropathy	Chronic compound analgesics (**phenacetin** — banned in US since 1983; ≥6 tablets/day for >3 yr); **papillary necrosis**; small scarred kidneys with **papillary calcifications**; F:M 5–7:1; risk of **urothelial malignancy (8–10%)**
Aristolochic acid nephropathy	*Chinese-herb + Balkan endemic* nephropathy; **Aristolochia** species; aristolactam-DNA adducts, **A:T→T:A transversions**; bland sediment, severe anaemia; high **upper-tract urothelial cancer** risk
Lithium nephropathy	Nephrogenic **diabetes insipidus** (enters principal cells via **ENaC**, inhibits GSK-3β, downregulates aquaporin-2); chronic TIN after >10–20 yr; distal-tubule microcysts; **amiloride** for NDI
Calcineurin inhibitor (cyclosporine/tacrolimus)	"**Striped**" interstitial fibrosis, arteriolar hyalinosis, hyperkalaemia (aldosterone resistance)
Heavy-metal (lead) nephropathy	Triad of **"saturnine gout," hypertension and renal impairment**; chelation may slow decline
Reflux nephropathy	VUR in childhood (old "chronic pyelonephritis"); secondary **FSGS**; asymmetric small scarred kidneys; ACEI/ARB/SGLT2 inhibitor for proteinuria

Entity	Key features
ADTKD	Autosomal dominant; genes **UMOD, MUC1, REN, HNF1β**; bland sediment, **UMOD** form → early gout/hyperuricaemia (median ESKD ~54 yr)
Metabolic	Hypercalcaemic (nephrocalcinosis, concentrating defect), gouty/uric-acid, hypokalaemic, hyperoxaluric nephropathy
CINAC / CKDu	Young male agricultural workers — **Mesoamerican, Sri Lankan, Uddanam (S. India)** nephropathy; heat/dehydration ± agrochemicals

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of the nephron in tubulointerstitial disease** — label: **glomerulus (relatively spared)**, **proximal tubule (Fanconi: glycosuria, phosphaturia, aminoaciduria, type II RTA)**, **distal tubule/collecting duct (type IV RTA, distal RTA, nephrogenic DI)**, **interstitial inflammatory infiltrate + oedema (acute)** vs **interstitial fibrosis + tubular atrophy + thickened TBM (chronic)**, and **tubulitis (lymphocytes crossing TBM)**.
- **Treatment algorithm for AIN** — label: *AKI with features of AIN → withdraw offending agent → supportive care/observe → improvement (continue) OR no improvement in 1 week / rapid progression → corticosteroids; renal biopsy → classic AIN / granulomatous IN → steroids ± immunosuppressives; fibrosis → conservative.*

Clinical / Diagnostic significance

- Suspect TIN in **otherwise unexplained AKI/CKD** with a **bland or mildly active sediment**, **low-grade tubular proteinuria**, and tubular dysfunction — **polyuria (nephrogenic DI), Fanconi syndrome, type II or type IV RTA**, and a serum uric acid that is **lower than expected** for the GFR.
- **Type IV (hyperkalaemic, hyperchloraemic) RTA out of proportion to renal failure** is a classic pointer to tubulointerstitial injury.
- **Papillary necrosis** (mnemonic) — **A**nalgesics, **S**ickle cell, **D**iabetes with UTI, prolonged **N**SAIDs (and obstruction/pyelonephritis); presents with flank pain, haematuria and ureteric colic from a sloughed papilla.
- **Aristolochic acid and analgesic nephropathy carry a high urothelial-cancer risk** — warrant surveillance (urine cytology, CT, ureteroscopy).
- **Prognosis of drug-induced AIN**: full recovery ~64%, partial ~23%, and **~12% progress to CKD/dialysis** — early drug withdrawal (<2 weeks) is the strongest determinant of recovery.

High-yield exam pointers

- TIN = primary tubular + interstitial disease, **glomeruli/vessels spared**; **acute vs chronic**; final common pathway = **interstitial fibrosis + tubular atrophy**.
- **Drugs cause >70% of AIN**; **antibiotics > PPIs > NSAIDs**; mechanism = **Type IV (delayed) hypersensitivity**.

- **Classic triad (fever + rash + eosinophilia) seen in only 5–15%** — its absence does NOT exclude AIN; NSAIDs/PPIs give "silent" AIN.
- **Urinary eosinophils are obsolete**; **kidney biopsy is the gold standard** (tubulitis).
- **Treatment** = stop drug + supportive care ± **steroids** (IV methylprednisolone 0.25–0.5 g/day ×1–4 days, or prednisone 60 mg/day ×4–6 weeks); start early.
- **TINU** — adolescent girls, anterior uveitis, raised ESR; **Sjögren's** — distal RTA + anti-Ro/La; **sarcoid** — granulomatous + hypercalcaemia (rule out TB); **IgG4** — storiform fibrosis.
- Chronic toxins — **analgesic (phenacetin, papillary necrosis), aristolochic acid (urothelial cancer), lithium (NDI), CNI (striped fibrosis), lead (saturnine gout)**.
- **ADTKD genes — UMOD, MUC1, REN, HNF1β**; **CINAC/CKDu** in agricultural communities (Uddanam, Mesoamerican, Sri Lankan).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Tubulointerstitial Diseases of the Kidney" (Beck & Salant), including Table 328-1 (classification), Table 328-2 (steroid indications) and Table 328-3 (papillary necrosis).
- **Brenner & Rector's The Kidney** — "Tubulointerstitial Diseases" (Perazella & Rosner): mechanisms, ADTKD (Table 35.2), ATIN diagnostics/biopsy, drug-specific data and steroid regimens, chronic entities (analgesic, aristolochic).
- **CMDT 2026** — "Kidney Disease: Interstitial Nephritis / Chronic Tubulointerstitial Diseases": current diagnostic criteria, corticosteroid dosing, and CINAC management.

Endocrinology

Anti-obesity drugs

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

Definition / Introduction — This 25-year-old man weighs 118 kg at a height of 1.60 m, giving a **BMI of 46.1 kg/m^2** — *class III (extreme) obesity* (WHO/NIH: class I 30–34.9, class II 35–39.9, class III ≥40). He already carries two adiposity-driven complications — **type 2 diabetes mellitus (T2DM) and hypertension** — and has failed structured lifestyle measures. He therefore meets criteria for **adjuvant anti-obesity pharmacotherapy** (BMI ≥30, or ≥27 with comorbidity) and, given BMI ≥40, is simultaneously a candidate for **metabolic/bariatric surgery**. The strategic principle is to choose agents that deliver weight loss *and* concurrently improve glycaemia, blood pressure and cardiovascular risk, while deliberately avoiding weight-promoting drugs.

Clinical assessment and rationale for drug therapy

- **Eligibility:** Adjuvant pharmacotherapy is indicated for BMI ≥30 kg/m^2, or ≥27 kg/m^2 with obesity-related disease, when diet and physical activity have failed — this patient qualifies on both counts.

- **Goal of therapy:** Improve obesity-related complications and quality of life; a realistic initial target is **8–10% weight loss over 6 months**; even **5–10% total-body-weight (TBW) loss** produces clinically meaningful, dose-related improvements in blood glucose, blood pressure, triglycerides and HDL.
- **"Treat-to-multiple-target" logic:** Because he has T2DM + hypertension + extreme obesity, the ideal agent is a "threefer" — a glucose-lowering drug that also causes weight loss and lowers BP. The **incretin (nutrient-stimulated hormone) class — GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide — fits all three**, and is favoured by the diabetes algorithm whenever the management goal is "HbA1c + weight reduction" or there is ASCVD/ASCVD risk.
- **Drug must accompany an active lifestyle programme** — pharmacotherapy works best as an adjunct, not a replacement, for diet, exercise and behaviour modification.

Preferred therapy — incretin-based (nutrient-stimulated hormone) agents

These directly serve all of this patient's problems and are the cornerstone of his treatment.

Drug	Mechanism of action	Dose / route	Placebo-subtracted weight loss	Key adverse effects	Contraindications
Semaglutide 2.4 mg	GLP-1 receptor agonist — ↑glucose-dependent insulin secretion, ↓glucagon, slows gastric emptying, acts on arcuate nucleus/NTS to ↓appetite	SC **once weekly**; titrate 0.25→0.5→1→1.7→2.4 mg q4-weekly	**~12.5%** (STEP 1–4: 6.2–14.8% at 68 wk)	Nausea, diarrhoea, constipation, vomiting; pancreatitis, cholelithiasis	Personal/family history of medullary thyroid carcinoma (MTC), MEN-2; caution if pancreatitis
Tirzepatide	**Dual GIP + GLP-1 receptor agonist** — GIP acts synergistically with GLP-1 in the brain for greater appetite suppression	SC **once weekly**; titrate 2.5 mg → max 15 mg	**~17.8%** (SURMOUNT-1: **20.9%** vs 3.1% placebo at 15 mg)	Nausea, diarrhoea, constipation, abdominal pain	As above (MTC, MEN-2); caution pancreatitis
Liraglutide 3.0 mg	GLP-1 receptor agonist (97% homology to human GLP-1)	SC **once daily**; 0.6 mg/wk increments to 3.0 mg	**~5.4%** (SCALE: 3.4–6.1%)	Nausea, diarrhoea, constipation, vomiting	As above

- **Indications:** chronic weight management (all three) *and* T2DM (semaglutide, liraglutide, tirzepatide are independently approved glucose-lowering drugs) — making them uniquely suited to this patient.
- **Expected efficacy:** dual benefit — tirzepatide/semaglutide give the largest weight loss of any licensed medical therapy, **lower HbA1c by ~1–2%**, do **not** cause hypoglycaemia (glucose-dependent action) and reduce systolic BP through weight loss.
- **Cardiovascular value:** the **SELECT trial** showed semaglutide 2.4 mg reduced **major adverse cardiovascular events (MACE) by ~20%** in overweight/obese patients with established CVD;

LEADER-type data show GLP-1 RAs reduce CV events and diabetic kidney disease in T2DM — directly relevant to a young diabetic-hypertensive patient with decades of risk ahead.

Anti-diabetic drugs that also assist weight loss and comorbidity control

- **Metformin (first-line for T2DM):** reduces hepatic glucose production and modestly improves peripheral glucose uptake; **promotes mild weight loss**, lowers insulin levels and improves lipids; start low, titrate to **max 2000 mg/day**. Adverse effects: GI upset (diarrhoea, nausea, metallic taste), ↓vitamin B12, rare lactic acidosis. Avoid if **eGFR <30 mL/min**, acidosis, unstable CHF, hepatic disease.
- **SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin):** block proximal-tubule glucose reabsorption → glucosuria, insulin-independent glucose lowering, **modest weight loss**, and a **diuretic-mediated 3–6 mmHg fall in systolic BP** — directly helping his hypertension. They reduce ASCVD events/CV mortality, reduce heart-failure hospitalisation and slow diabetic kidney disease. Adverse effects: genital/urinary mycotic infection, volume depletion, **euglycaemic DKA**; do not initiate at eGFR <45 and avoid in stage 4 CKD.
- **Drugs to deliberately AVOID** (cause weight gain and worsen the index problem): **insulin, sulfonylureas, and thiazolidinediones** (TZDs add 2–3 kg, fluid retention/CHF risk). Sulfonylureas and insulin also carry hypoglycaemia risk. These run counter to the weight-loss goal and should be later/last-line here.

Other (non-incretin) anti-obesity medications

- **Phentermine / topiramate ER (PHEN/TPM):** catecholamine releaser + anticonvulsant (GABA modulation, carbonic-anhydrase inhibition, glutamate antagonism); oral once daily, max 15/92 mg; placebo-subtracted weight loss **~8%** (EQUIP/CONQUER 6.6–9.3%). AE: paraesthesia, dry mouth, dysgeusia, insomnia, cognitive impairment; **teratogenic (oral clefts)** — needs contraception/pregnancy testing. *Caution in this patient:* **uncontrolled hypertension is a contraindication** to phentermine-containing agents (they raise BP/HR).
- **Naltrexone SR / bupropion SR:** opioid antagonist + dopamine/noradrenaline reuptake inhibitor — disinhibits hypothalamic POMC/α-MSH to reduce intake; oral 2 tabs BID; weight loss **~5%** (COR trials 4.2–5.1%). AE: nausea, constipation, headache, **small rise in BP/pulse**; contraindicated in uncontrolled hypertension, seizure disorder, chronic opioid use, MAOI within 14 days.
- **Orlistat:** GI/pancreatic lipase inhibitor — blocks absorption of ~**30% of dietary fat** at 120 mg tid; minimally absorbed, so no systemic toxicity; weight loss **~4.1%**. AE: steatorrhoea, oily spotting, faecal urgency, fat-soluble vitamin (A, D, E, K, β-carotene) depletion — supplement vitamins.
- **Setmelanotide:** MC4-receptor agonist for **monogenic/syndromic obesity only** (POMC, PCSK1, LEPR deficiency, Bardet–Biedl syndrome) — not for common polygenic obesity, but worth knowing in a *young-onset, extreme* obesity case where a secondary cause should be excluded.

Concurrent control of hypertension and escalation to surgery

- **Treat the comorbidities in parallel:** much of his hypertension and dysglycaemia will improve as weight falls. For pharmacological BP control in a diabetic, an **ACE inhibitor or ARB** is preferred

(renoprotection/albuminuria reduction); weight-neutral add-ons (CCB, thiazide) as needed. SGLT2 inhibitors and GLP-1 RAs provide additional BP lowering.

- **Exclude secondary causes** in a young, extremely obese diabetic-hypertensive: drug-induced weight gain, hypothyroidism, Cushing's syndrome, hypothalamic disease, and (for resistant hypertension) endocrine hypertension.
- **Metabolic / bariatric surgery** is indicated and appropriate here — **BMI ≥40**, or ≥35 with a comorbidity, after failure of lifestyle ± medication. **Sleeve gastrectomy** and **Roux-en-Y gastric bypass** are commonest; restrictive-malabsorptive bypass yields **~28–33% TBW loss at 12–18 months**, marked T2DM improvement (Swedish Obese Subjects: **78% lower incidence of T2DM**; ~68% achieve initial diabetes remission within 5 years) and reduced all-cause/CV mortality. Requires lifelong vitamin B12, iron, folate, calcium and vitamin D supplementation after malabsorptive procedures.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CNS appetite-regulation circuit with drug action sites:** Label — *Arcuate nucleus (ARC)* with **POMC/CART (anorexigenic)** and **AgRP/NPY (orexigenic)** neurons; **α-MSH → MC4R** in the *paraventricular nucleus (PVN)*; *nucleus tractus solitarius (NTS)* and *brainstem*; *mesolimbic reward (VTA→NAc, dopamine)*. Map drugs onto targets: **GLP-1R → liraglutide/semaglutide/tirzepatide**, **GIP-R → tirzepatide**, **MC4R → setmelanotide**, **μ-opioid receptor → naltrexone**, **POMC/dopamine → bupropion**, **NE release/GABA → phentermine/topiramate**, gut peptides (PYY, CCK, ghrelin, leptin, amylin) as afferent inputs.
- **Obesity-treatment pyramid / algorithm:** base = *Lifestyle (diet 500–750 kcal deficit, ≥150 min/wk activity, behaviour therapy) → Pharmacotherapy (BMI ≥30 or ≥27 + comorbidity) → Bariatric/metabolic surgery (BMI ≥40, or ≥35 + comorbidity)*. Side branch: T2DM algorithm — "goal = HbA1c + weight reduction → GLP-1 RA / structured medical weight programme / metabolic surgery."

Clinical / Diagnostic significance

- **Investigations before/with therapy:** fasting lipid profile, chemistry panel, **HbA1c**, blood pressure, waist circumference (South-Asian cut-off >90 cm in men), TSH and overnight dexamethasone/Cushing screen if clinically suggested, ECG; baseline renal function (guides metformin/SGLT2i dosing).
- **Monitoring on therapy:** weight/BMI trajectory and "stopping rules" (review benefit at 12–16 weeks for phentermine, PHEN/TPM and NB), HbA1c, BP, renal function; watch for GLP-1 RA GI intolerance, gallstones/pancreatitis, and euglycaemic DKA with SGLT2i; vitamin B12 on metformin.
- **Management pearl:** in this *young* patient the choice of weight-losing glucose-lowering drugs (incretins ± SGLT2i + metformin) over weight-gaining ones (insulin/sulfonylurea/TZD) sets the trajectory of his diabetes, BP and lifelong cardiovascular risk.

High-yield exam pointers

- **BMI = 118 ÷ (1.60)^2 = 46.1 kg/m^2 → class III (extreme) obesity** (≥40); qualifies for *both* pharmacotherapy and bariatric surgery.
- Drug eligibility: **BMI ≥30, or ≥27 with comorbidity**, after failed lifestyle. Realistic goal **8–10% in 6 months**; **5–10% TBW loss** already gives clinical benefit.
- **First choice here = GLP-1 RA (semaglutide) or dual GLP-1/GIP agonist (tirzepatide)** — they treat obesity *and* T2DM, lower BP, cut CV events (SELECT −20% MACE), and don't cause hypoglycaemia.
- Approximate placebo-subtracted weight loss: **tirzepatide ~17–21% > semaglutide ~12–15% > PHEN/TPM ~8% > liraglutide/NB ~5% > orlistat ~4%**.
- **SGLT2 inhibitors** add weight loss + **3–6 mmHg systolic BP fall** + CV/renal protection; **metformin** is first-line, weight-neutral/mild loss.
- **Avoid weight-gaining agents:** insulin, sulfonylureas, thiazolidinediones. **Phentermine/PHEN-TPM and naltrexone-bupropion are contraindicated in uncontrolled hypertension.**
- GLP-1 RAs/tirzepatide contraindicated in **medullary thyroid carcinoma / MEN-2**; orlistat causes steatorrhoea + fat-soluble vitamin deficiency.
- **Bariatric surgery** (sleeve gastrectomy / Roux-en-Y): **28–33% TBW loss**, T2DM remission, reduced mortality — definitive option at BMI ≥40.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Evaluation and Management of Obesity" (anti-obesity pharmacotherapy: mechanisms, doses, EQUIP/CONQUER, COR, SCALE, STEP, SURMOUNT, SELECT trial data, antiobesity-medication table, bariatric surgery) and "Diabetes Mellitus: Management and Therapies" (glucose-lowering agent classes, T2DM management algorithm, metformin/SGLT2i/GLP-1 RA/tirzepatide).
- **Williams Textbook of Endocrinology, 15e** — "Obesity and Neuroendocrine Control of Energy Stores" (drug action-site circuitry, phentermine/orlistat/naltrexone-bupropion detail, tirzepatide SURPASS/SURMOUNT efficacy).
- **CMDT 2026** — "Nutrition, Nutritional Disorders, & Obesity" (BMI classes, obesity-medication selection and stopping rules, liraglutide/semaglutide/tirzepatide efficacy meta-analyses, bariatric-surgery criteria).

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Acquired hypopituitarism

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

Definition / Introduction — *Hypopituitarism* is deficient secretion of one or more anterior pituitary trophic hormones, arising from disease of the pituitary, pituitary stalk, or hypothalamus. **Acquired hypopituitarism** is the far commoner adult form and reflects the compressive mass effect of tumours, or local pituitary/hypothalamic traumatic, vascular, autoimmune, inflammatory, infiltrative, or irradiation damage (as opposed to inherited/developmental causes). Loss of all anterior hormones is termed **panhypopituitarism**. It carries a documented two- to three-fold excess of cardiovascular and cerebrovascular mortality, so prompt recognition and physiological hormone replacement are essential.

Etiology of acquired hypopituitarism

Causes are best grouped by mechanism (the "vascular–traumatic–neoplastic–inflammatory/infiltrative–infective–iatrogenic" framework):

Category	Representative causes
Neoplastic / compressive	Pituitary adenoma (esp. non-functioning macroadenoma ≥1 cm), craniopharyngioma, Rathke's cleft cyst, meningioma, germinoma/glioma, hypothalamic hamartoma; **metastases** (breast 45%, lung); lymphoma, leukaemia
Vascular	**Pituitary apoplexy**; **Sheehan's syndrome** (postpartum necrosis); subarachnoid haemorrhage; sickle-cell disease; snake (viper) bite venom; arteritis
Traumatic / iatrogenic	Traumatic brain injury (incl. contact sports, blast); neurosurgical resection; **cranial/head-&-neck radiotherapy**; cardiopulmonary bypass
Inflammatory / autoimmune	**Lymphocytic hypophysitis**; immune-checkpoint-inhibitor hypophysitis; granulomatous and IgG4-related hypophysitis
Infiltrative	Sarcoidosis, **haemochromatosis**, Langerhans-cell histiocytosis (histiocytosis X), amyloidosis
Infective	Tuberculosis, fungal (histoplasmosis), tertiary syphilis, opportunistic AIDS-related infection, toxoplasmosis, *Pneumocystis*
Functional / drug-induced	High-dose/exogenous glucocorticoids (HPA suppression), opioids, megestrol, GnRH agonists (e.g. leuprolide), bexarotene, mitotane; starvation, anorexia nervosa, critical illness, COVID-19

- Mass lesions cause failure by compressing the gland, stalk ("stalk-section" effect → early hyperprolactinaemia from loss of dopamine inhibition, with later loss of other hormones), or hypothalamus.
- **Cranial irradiation**: up to two-thirds develop hormone insufficiency after a median dose of **~50 Gy (5000 rad)** to the skull base, evolving over **5–15 years**, usually from hypothalamic rather than pituitary damage.

Pattern and sequence of hormone loss

- With progressive compression/destruction, trophic hormones are typically lost in a **predictable sequence**:

GH → FSH → LH → TSH → ACTH (mnemonic *"Go Look For The Adenoma"*). **PRL** is usually preserved or *elevated* (stalk effect); PRL deficiency (failed lactation) implies severe destruction, as in Sheehan's.

- In children the presenting feature is **growth retardation**; in adults **hypogonadism is the earliest symptom**.

Axis lost	Clinical consequence
GH	Child: short stature, hypoglycaemia. Adult (AGHD): ↑central/visceral fat, ↓lean mass, ↓exercise capacity, dyslipidaemia, ↓bone density, poor quality of life
FSH/LH (gonadotrophin)	Women: oligo-/amenorrhoea, infertility, ↓libido, breast atrophy. Men: ↓libido, erectile dysfunction, ↓muscle/beard, soft testes; osteoporosis in both
TSH	Secondary (central) hypothyroidism: low free T4 with *low/inappropriately normal* TSH
ACTH	Secondary adrenal insufficiency: fatigue, anorexia, nausea, hypotension, hypoglycaemia, hyponatraemia — **no hyperpigmentation, no hyperkalaemia** (mineralocorticoid axis preserved)
PRL	Failure of postpartum lactation
AVP (posterior)	Polyuria/polydipsia (AVP deficiency / cranial diabetes insipidus) — points to stalk/hypothalamic involvement

Special acquired entities (high-yield)

- **Sheehan's syndrome** — hypopituitarism from **postpartum pituitary necrosis** after severe peripartum haemorrhage/hypotension; the gland is enlarged and vulnerable in pregnancy. Classic clues: **failure to lactate** and **postpartum amenorrhoea**; onset is usually insidious over **10–20 years** (mean diagnostic delay ~9 years), presenting with hyponatraemia, hypoglycaemia, or anaemia. Acute Sheehan MRI: enlarged pituitary with a thin peripheral rim of gadolinium enhancement.
- **Pituitary apoplexy** — acute intrapituitary haemorrhage/infarction, usually into a pre-existing adenoma. **Endocrine emergency**: sudden severe headache, visual loss, ophthalmoplegia (cranial nerves III/IV/VI), meningism, and acute hypocortisolism → hypoglycaemia, hypotension, shock. Manage with **high-dose glucocorticoids**; **urgent transsphenoidal decompression** for progressive visual loss, cranial-nerve palsy, or deteriorating consciousness.
- **Lymphocytic hypophysitis** — autoimmune; most often in **late pregnancy/postpartum women** or with coexisting autoimmunity; mimics an adenoma on MRI (enlarged homogeneously enhancing gland, thickened stalk). **Secondary hypoadrenalism is the commonest deficit**; AVP deficiency in up to ~20%. Suspect before operating on a postpartum sellar mass; often responds to glucocorticoids.
- **Checkpoint-inhibitor hypophysitis** — up to ~20% with **CTLA-4 inhibitors (ipilimumab)**, less with PD-1/PD-L1 agents (delayed onset); HLA-DQ0602 association.
- **Traumatic brain injury / SAH** — ≥1 deficiency in **25–30% of moderate–severe TBI** and **~55% of aneurysmal SAH** survivors; mandates long-term endocrine follow-up.

Pathological subtypes of hypophysitis (Williams)

Type	Hallmark	Notes
Lymphocytic	Lymphocyte/plasma-cell infiltrate	F>M, peripartum; anterior failure ± AVP
Granulomatous	Giant cells, granulomas	Severe headache; frequent AVP deficiency; r/o sarcoid, GPA, TB, LCH
Xanthomatous	CD68+ foamy macrophages	Often secondary to Rathke's cyst rupture
IgG4-related	IgG4+ plasma cells, storiform fibrosis	M>F; systemic IgG4 disease; good GC response
Immunotherapy-induced	Diffuse lymphocyte/macrophage infiltrate	Checkpoint inhibitors; deficits usually persist
Anti-PIT1 / anti-POMC	Antibody-mediated	Anti-PIT1 (thymoma) → GH+PRL+TSH loss; anti-POMC → isolated ACTH loss

Clinical features / presentation

- Manifestations depend on **which** hormones are lost and the **degree** of deficiency, and are typically **insidious and non-specific** — fatigue, dizziness/postural hypotension, cognitive slowing, sexual dysfunction, cold intolerance.
- **Mass-effect** features when due to tumour/hypophysitis: headache, **bitemporal hemianopia** (optic-chiasm compression), cranial-nerve palsies.
- **Panhypopituitarism** in adults often presents in women as amenorrhoea; deficiencies cluster as hypogonadism, hypothyroidism, ACTH deficiency, GH deficiency ± hyperprolactinaemia.
- An undiagnosed patient may decompensate into **pituitary/adrenal crisis** during intercurrent illness or surgery — febrile, hypotensive, hyponatraemic, comatose.

Diagnosis / laboratory investigation

Principle: demonstrate a *low target-organ hormone together with a low or inappropriately normal pituitary trophic hormone* (this distinguishes secondary/central from primary gland failure).

- **ACTH axis (do first — most life-threatening):** 8–9 am cortisol + ACTH. Cortisol **<3 µg/dL** indicates adrenal insufficiency; **>15 µg/dL** largely excludes it; intermediate values need a **cosyntropin (ACTH 1–24) 0.25 mg** stimulation test — stimulated cortisol **<20 µg/dL (≈550 nmol/L)** is abnormal. ACTH is low/normal (vs high in Addison's). Insulin-tolerance test is the gold standard but is *contraindicated* in ischaemic heart disease, epilepsy, and the elderly.
- **Thyroid axis:** low free T4 with low/normal TSH = central hypothyroidism (TSH is unreliable for monitoring).
- **Gonadal axis:** low testosterone/oestradiol with low/normal LH & FSH; check PRL (hyperprolactinaemia of any cause suppresses GnRH).
- **GH/IGF-1:** AGHD inferred from symptoms plus pituitary disease; **IGF-1 <84 µg/L** or ≥3 other deficiencies is highly suggestive. Provocative **insulin-induced hypoglycaemia** (peak GH **<3 µg/L** = deficient), or glucagon/macimorelin/arginine-GHRH tests.

- **Imaging:** dedicated **pituitary MRI** (T1, pre/post gadolinium) for mass, stalk thickening, empty sella, apoplexy. Screen for **haemochromatosis** (ferritin/transferrin saturation) when no cause is evident.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hypothalamic–pituitary axis schematic:** hypothalamus with releasing factors (**CRH, GnRH, GHRH, TRH, dopamine, somatostatin**) → portal vessels down the **pituitary stalk** → anterior pituitary cells (**corticotroph→ACTH, gonadotroph→LH/FSH, somatotroph→GH, thyrotroph→TSH, lactotroph→PRL**) → target glands (**adrenal/cortisol, gonad/sex steroids, liver/IGF-1, thyroid/T4**); posterior pituitary releasing **AVP & oxytocin**. Add an arrow legend showing the **sequence of loss: GH → FSH → LH → TSH → ACTH (PRL preserved)**.
- **Coronal MRI of sella** labelling: pituitary gland, stalk, **optic chiasm**, cavernous sinus with **CN III, IV, V1, V2, VI** and internal carotid artery — illustrating mass/apoplexy compression.

Clinical / Diagnostic significance

- **Replace glucocorticoid BEFORE levothyroxine** — starting thyroxine first accelerates cortisol metabolism and can precipitate an **adrenal crisis**.
- Glucocorticoid doses must be **stress-dosed** (2–3× up, or parenteral) during illness, surgery, trauma; patient should carry a steroid alert card/bracelet.
- Replacement (per axis): **Hydrocortisone 10–20 mg/day** in divided doses (or prednisone 5 mg am) — *no mineralocorticoid needed*; **levothyroxine ~1.6 µg/kg/day** titrated to mid-high-normal free T4 (not TSH); **testosterone** (gel/patch/enanthate 200 mg IM q2wk) or cyclical **oestrogen–progestogen**; **rhGH (somatropin)** titrated to mid-normal IGF-1; **desmopressin** for AVP deficiency. Fertility requires **gonadotrophins (hCG/hMG/FSH)** or **pulsatile GnRH**.
- Suspect and screen for hypopituitarism after **TBI, SAH, cranial irradiation, and postpartum haemorrhage**.

High-yield exam pointers

- Acquired causes ≫ congenital in adults; remember the mechanistic groups (vascular, traumatic, neoplastic, inflammatory/infiltrative, infective, iatrogenic).
- **Sequence of hormone loss: GH → FSH → LH → TSH → ACTH; PRL preserved/raised** ("Go Look For The Adenoma").
- **Sheehan's** = postpartum necrosis → failure to lactate + amenorrhoea; insidious over years.
- **Pituitary apoplexy** = endocrine emergency → high-dose steroids ± urgent decompression.
- **Secondary adrenal insufficiency**: no hyperpigmentation, no hyperkalaemia (mineralocorticoid spared).
- Diagnosis = *low target hormone + low/inappropriately normal trophic hormone*; cosyntropin/insulin-tolerance tests assess reserve.
- **Treat the ACTH deficit first**; give steroid before thyroxine.
- Hypopituitarism increases cardiovascular/cerebrovascular mortality 2–3 fold.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hypopituitarism" (etiology, sequence of hormone loss, apoplexy, irradiation, hypophysitis, provocative testing, replacement table).
- **Williams Textbook of Endocrinology, 15e** — "Pituitary Adenomas and Masses" and "Pituitary Physiology and Diagnostic Evaluation" (hypophysitis pathological subtypes/Fig 7.16, checkpoint-inhibitor rates, surgical hypopituitarism).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (Sheehan's syndrome, TBI/SAH statistics, biochemical cut-offs, current replacement regimens).

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Acromegaly

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

Definition / Introduction — **Acromegaly** is the clinical syndrome resulting from chronic **growth hormone (GH)** and **insulin-like growth factor 1 (IGF-1)** hypersecretion in adults, almost always due to a **GH-secreting somatotrope pituitary adenoma**. When GH excess begins in children/adolescents *before* epiphyseal long-bone closure, it produces **pituitary gigantism**; after closure it causes acral and soft-tissue overgrowth. The manifestations are indolent and frequently undiagnosed for **10 years or more**, and untreated disease carries an approximately **threefold** increase in mortality.

Etiology and pathogenesis

- **Eutopic (pituitary, ~98%)** — GH hypersecretion is usually from a **somatotrope adenoma**. Mixed **mammosomatotrope** tumours and **acidophilic stem cell adenomas** co-secrete GH and prolactin (PRL); in the latter, features of hyperprolactinaemia (hypogonadism, galactorrhoea) predominate.
- **Ectopic GH / GHRH (<1% each)** — rare. The commonest cause of **GHRH-mediated** acromegaly is a **chest or abdominal carcinoid tumour**; excess GHRH causes somatotrope *hyperplasia*. Ectopic GH itself is reported from pancreatic, ovarian, lung or haematopoietic tumours.
- **Pathogenesis (sporadic disease)** — GHRH binds its **G-protein–coupled somatotrope receptor**, using **cyclic AMP** as second messenger to drive GH secretion and somatotrope proliferation. A subset harbours **somatic activating mutations of Gsα**, which attenuate intrinsic GTPase activity → constitutive cAMP elevation → **Pit-1** induction and **CREB** activation → somatotrope proliferation and GH secretion.

Cause	Approx. prevalence
Pituitary (densely/sparsely granulated GH-cell adenoma)	60%
Mixed GH-cell and PRL-cell adenoma	25%
Mammosomatotrope-cell adenoma	10%
Plurihormonal adenoma; GH-cell carcinoma/metastases	—

Cause	Approx. prevalence
MEN-1, McCune-Albright, ectopic sphenoid/parapharyngeal pituitary adenoma	—
Extrapituitary tumour (pancreatic islet cell, lymphoma)	<1%
Excess GHRH — central (hypothalamic hamartoma, choristoma, ganglioneuroma); peripheral (bronchial carcinoid, islet cell tumour, small-cell lung Ca, adrenal adenoma, medullary thyroid Ca, phaeochromocytoma)	<1%

Genetic syndromes associated with GH excess

- **MEN-1** (*MENIN*, 11q13) — autosomal dominant parathyroid + pancreatic islet + pituitary tumours; acromegaly is *less common* than prolactinoma.
- **MEN-4** (*CDKN1B*, 12p13) — hyperparathyroidism with pituitary adenomas.
- **Carney complex** (*PRKAR1A*, 17q23-24) — spotty skin pigmentation, myxomas, endocrine tumours; **acromegaly in ~20%**.
- **McCune-Albright syndrome** — polyostotic fibrous dysplasia, café-au-lait patches and endocrinopathy (including acromegaly), from a **postzygotic mosaic Gsα mutation**.
- **Familial isolated pituitary adenoma** — germline **AIP** mutations (11q13.2), **acromegaly/gigantism in ~15%** of afflicted families.

Clinical features

- **Acral bony overgrowth** — frontal bossing, increased hand and foot size, **mandibular enlargement with prognathism**, and a **widened space between the lower incisor teeth**.
- **Soft-tissue swelling** — increased **heel-pad thickness**, increasing shoe/glove size, ring tightening, coarse facial features and a large fleshy nose.
- **Other systemic** — hyperhidrosis; a deep, hollow-sounding voice; oily skin; arthropathy and kyphosis; **carpal tunnel syndrome**; proximal muscle weakness and fatigue; **acanthosis nigricans** and skin tags.
- **Visceromegaly** — cardiomegaly, **macroglossia**, thyroid enlargement.
- **Cardiovascular (most significant impact)** — **cardiomyopathy** with arrhythmias, **left ventricular hypertrophy**, impaired diastolic function and **hypertension** ultimately occur in most untreated patients.
- **Respiratory / metabolic** — **obstructive sleep apnoea in >60%** (soft-tissue laryngeal obstruction + central dysfunction); glucose intolerance is usual and **diabetes mellitus develops in ~25%** (GH counteracts insulin).
- **Neoplastic** — increased **colon polyps** (found in up to one-third) and colonic-malignancy mortality.
- **Outcome** — overall mortality is increased ~threefold (cardiovascular, cerebrovascular and respiratory); unless GH is controlled, survival is reduced by an average of **10 years**.

Diagnosis and laboratory investigation

- **Screening** — an **age- and sex-matched serum IGF-1** level is the single best screening test, since IGF-1 integrates GH secretion over time.
- A **single random GH** is *not* useful for diagnosis or exclusion (GH is pulsatile) and does not correlate with disease severity.
- **Confirmation** — failure of GH to suppress to **<0.4 µg/L within 1–2 h of a 75-g oral glucose load** (OGTT); with ultrasensitive assays the normal nadir is **<0.05 µg/L**. About **20%** show a *paradoxical GH rise* after glucose.
- **Adjunctive** — measure **PRL** (elevated in ~25%); thyroid function, gonadotropins and sex steroids may be attenuated by tumour mass effect. ACTH-reserve testing is best deferred until after surgery.
- **Imaging** — pituitary **MRI** localises and sizes the adenoma; assess for mass effects (optic chiasm compression, cavernous-sinus cranial nerve involvement).

Management

- **Goals** — control GH/IGF-1 hypersecretion, ablate or arrest tumour growth, ameliorate comorbidities, restore mortality to normal and **preserve pituitary function**.

Modality	Agent / detail	Efficacy & key points
Surgery (primary)	**Transsphenoidal resection** by an experienced surgeon	Microadenoma remission **~70%**, macroadenoma **<50%**; GH normalises within 1 h, IGF-1 within 3–4 days. Recurrence ~10%; hypopituitarism in up to 15%.
Somatostatin receptor ligands (SRLs)	**Octreotide LAR** (30 mg IM monthly), **lanreotide** depot (60 mg SC q4–6 wk), **oral octreotide** (40–80 mg/day)	Act via **SST2/SST5**; normalise GH/IGF-1 in **~50%**; shrink tumour in ~50%; rapid symptom relief in ~75% within days–weeks. Adjuvant or primary therapy.
Multireceptor SRL	**Pasireotide LAR** (preferential SST5)	For tumours resistant to octreotide/lanreotide; higher rate of hyperglycaemia/new-onset diabetes.
GH-receptor antagonist	**Pegvisomant** (10–30 mg SC daily)	Blocks peripheral GH binding → normalises **IGF-1 in ~70%**; GH stays elevated (no anti-tumour effect) — **monitor tumour size by MRI**.
Dopamine agonist	**Cabergoline** (high dose, ~0.5 mg/day)	Modest, short-lived benefit; useful for mild post-operative GH/IGF-1 elevation; additive with octreotide.
Radiotherapy	Conventional external beam or **Gamma Knife** stereotactic	Adjuvant; slow response (5–15 yr), late hypopituitarism, relatively poor IGF-1 normalisation — reserved when surgery/medical therapy fail.

- **SRL side effects** — GI upset (nausea, cramps, diarrhoea, fat malabsorption in ~⅓), **biliary sludge/gallstones in up to 30%**, mild glucose intolerance, asymptomatic bradycardia, hypothyroxinaemia.

- **Pegvisomant side effects** — reversible **liver enzyme elevation**, lipodystrophy, injection-site pain.
- **Combination** — SRL + pegvisomant (± pasireotide) for treatment-resistant disease. Manage cardiovascular disease, diabetes, sleep apnoea and arthropathy aggressively.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **GH–IGF-1 axis (regulation):** *Hypothalamus* → **GHRH** (+) and **Somatostatin** (–) → *Anterior pituitary somatotrope* → **GH** → *Liver* → **IGF-1** → *peripheral target tissues (bone, soft tissue, viscera)*; show **negative feedback** of IGF-1/GH on hypothalamus and pituitary, and the **GH-secreting adenoma** driving the excess.
- **Management algorithm (Fig. 392-8):** boxes labelled **GH-secreting pituitary tumour** → **Surgery** → **"controlled / not controlled"** → **SRL** → **Pegvisomant** → **SRL + Pegvisomant** → **Pasireotide** → **Radiotherapy / Re-operation**, with **"Monitor IGF-1"** at each controlled endpoint.

Clinical / Diagnostic significance

- **IGF-1** is the screening pivot and the marker followed for biochemical control; the **75-g OGTT-GH suppression test** is confirmatory.
- Suspect acromegaly in new-onset **diabetes, hypertension, OSA, carpal tunnel syndrome or arthropathy** with coarsening facies, and serially photograph the face/hands.
- Active disease warrants **echocardiography**, OSA screening and **colonoscopy** (polyp/cancer surveillance) plus cardiovascular risk-factor control.
- A young patient with gigantism/acromegaly, especially if familial, should prompt screening for **AIP**, **MEN-1**, Carney complex and McCune-Albright.

High-yield exam pointers

- Adult onset = **acromegaly**; pre-epiphyseal-closure onset = **gigantism** (same hormonal excess).
- **~98%** are pituitary somatotrope adenomas; commonest **ectopic GHRH** source = **carcinoid tumour**.
- Best screening test = **age/sex-matched IGF-1**; confirm with **GH non-suppression to <0.4 µg/L after 75-g OGTT**; random GH is useless.
- **~20%** show a *paradoxical GH rise* on glucose; **PRL elevated in ~25%**.
- First-line treatment = **transsphenoidal surgery** (micro ~70%, macro <50% remission).
- **Octreotide/lanreotide** act via **SST2/SST5**; **pegvisomant** is a **GH-receptor antagonist** that lowers IGF-1 but not GH.
- Watch for **OSA (>60%)**, cardiomyopathy/LVH, diabetes (25%), and **colon cancer**; untreated disease cuts survival by ~10 years.

SOURCE & COVERAGE

Harrison 22e — Ch 392 "Pituitary Tumor Syndromes" (acromegaly/gigantism, Tables 392-2, 392-4, 392-6; Figs 392-7, 392-8). All classifications, percentages, drug doses and biochemical cut-offs are taken from this chapter. *Coverage note:* the chapter does not provide a formal consensus disease-activity grading or detailed pre-pregnancy management for acromegaly; these are not asserted here.

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Adrenal insufficiency

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

Definition / Introduction — Adrenal insufficiency (AI) is the clinical state resulting from inadequate production of adrenocortical hormones — chiefly the glucocorticoid **cortisol**, and in **primary** disease also the mineralocorticoid **aldosterone** and the adrenal androgens. It is classified as **primary** (disease of the adrenal cortex itself — *Addison's disease*), **secondary/central** (ACTH deficiency from hypothalamic-pituitary disease), or **iatrogenic/glucocorticoid-induced** (suppression of the HPA axis by exogenous steroids). It is an under-diagnosed but readily fatal endocrine emergency when it presents as **adrenal crisis**, and is fully treatable with timely steroid replacement.

Classification, epidemiology and aetiology

- **Primary AI (Addison's disease):** loss of *both* glucocorticoid and mineralocorticoid secretion (± androgen). Prevalence ~**2 in 10,000**. About one-half is **acquired** (mostly **autoimmune** adrenalitis), the other half **genetic** (most commonly **congenital adrenal hyperplasia, CAH**).
- **Secondary (central) AI: isolated glucocorticoid deficiency** — the adrenal is intact, so mineralocorticoid output remains under RAA control. Hypothalamic-pituitary origin is the *most frequent* overall (prevalence ~**3 in 10,000**); total documented permanent AI ~**5 in 10,000**.
- **Glucocorticoid-induced AI (commonest cause overall):** suppression of the HPA axis by exogenous steroids — occurs in **0.5–2%** of the population in developed countries.

Type	Major causes (Harrison Tables 398-7/398-8)
Primary — autoimmune	Isolated autoimmune adrenalitis; **APS-1** (*AIRE* gene — hypoparathyroidism, mucocutaneous candidiasis); **APS-2** (HLA-DR3, CTLA-4 — autoimmune thyroid disease, type 1 DM, pernicious anaemia, vitiligo, premature ovarian failure)
Primary — genetic	**CAH** (*CYP21A2* most common); adrenoleukodystrophy/adrenomyeloneuropathy (*ABCD1*); adrenal hypoplasia congenita (*DAX-1/NR0B1*, *SF-1*); familial glucocorticoid deficiency (*MC2R*, *MRAP*); Triple-A (Allgrove) syndrome (*AAAS* — **a**lacrima, **a**chalasia, **a**ddisonianism); Smith-Lemli-Opitz
Primary — destruction	**Infection** — *tuberculous adrenalitis* (still frequent in developing countries), HIV, CMV, histoplasmosis, cryptococcosis; **infiltration** — bilateral bulky metastases, lymphoma, sarcoidosis, amyloidosis, haemochromatosis; **haemorrhage** — meningococcal sepsis (*Waterhouse-Friderichsen syndrome*), antiphospholipid syndrome

Type	Major causes (Harrison Tables 398-7/398-8)
Primary — drugs / surgical	Mitotane, abiraterone, ketoconazole, etomidate, osilodrostat, trilostane, immune-checkpoint inhibitors; **bilateral adrenalectomy**
Secondary	Pituitary/hypothalamic tumours and their surgery/irradiation; **pituitary apoplexy**; **Sheehan's syndrome** (post-partum pituitary infarction); autoimmune hypophysitis; pituitary infiltration (TB, sarcoid, histiocytosis, granulomatosis with polyangiitis); isolated ACTH deficiency (*TBX19/Tpit*); checkpoint inhibitors, opioids, chronic glucocorticoid excess

Clinical manifestations

- **Glucocorticoid deficiency (all types):** fatigue, lack of energy, weight loss, anorexia, myalgia/arthralgia, fever; **hypoglycaemia** (more frequent in children); low blood pressure with **postural hypotension**; **hyponatraemia**; normochromic anaemia, lymphocytosis, **eosinophilia**; slightly raised **TSH** (loss of feedback inhibition).
- **Mineralocorticoid deficiency (primary AI only):** abdominal pain, nausea, vomiting; dizziness/postural hypotension; **salt craving**; raised creatinine (volume depletion); **hyponatraemia** *and* **hyperkalaemia**.
- **Adrenal androgen deficiency:** lack of energy; dry/itchy skin, loss of libido and loss of axillary/pubic hair (in women).
- **Pigmentation — the key bedside discriminator:**
  - *Primary AI:* **hyperpigmentation** from excess ACTH/POMC-derived peptides stimulating melanocytes — maximal at friction/shear sites (palmar creases, knuckles, dorsa of feet, nipples, scars) and **buccal/oral mucosa**, accentuated by sunlight.
  - *Secondary AI:* **alabaster-pale skin** due to *deficiency* of POMC-derived peptides.
- **Biochemistry frequency:** hyponatraemia in ~**80%** at presentation; hyperkalaemia in ~**40%**. In secondary AI, hyponatraemia arises from reduced cortisol-mediated inhibition of AVP release, producing a mild SIADH-like picture.
- **Chronic AI** presents with non-specific symptoms (often mis-labelled depression or anorexia), causing diagnostic delay.

Adrenal crisis (acute adrenal insufficiency)

- An **emergency**, more frequent in **primary** AI (loss of both gluco- and mineralo-corticoid).
- Features: **hypotension progressing to hypovolaemic shock**, may mimic an **acute abdomen** (tenderness, nausea, vomiting, fever) or neurological disease (reduced responsiveness → stupor → coma).
- **Precipitants:** intercurrent illness/infection, surgical or other physiological stress, increased glucocorticoid inactivation (e.g., **hyperthyroidism**), or abrupt withdrawal of long-term steroids.
- Burden: ~**8.3 crises** and ~**0.5 crisis-related deaths per 100 patient-years**.
- **Treatment must never be delayed for diagnostic confirmation** — draw baseline cortisol/ACTH, treat immediately, formalise testing later.

Diagnosis and biochemical localisation

- **Confirm the deficiency — short cosyntropin (Synacthen) test (first-line):** give **cosyntropin (ACTH 1-24) 250 µg IM/IV**, sample cortisol at **0, 30 (± 60) min**. **Failure = peak cortisol <450–500 nmol/L (16–18 µg/dL)**; a normal response is >15–20 µg/dL (>400–550 nmol/L). (Cutoffs are assay-dependent; mass-spectrometry assays use lower cutoffs.)
- The **low-dose (1 µg) cosyntropin** test offers no superior diagnostic value. The **insulin tolerance test (ITT)** is an alternative for the central axis but is invasive and **contraindicated in coronary/cerebrovascular disease, diabetes and seizure disorders**. Within ~4 weeks of new pituitary injury the cosyntropin test may still be normal (adrenal not yet atrophied) — use ITT here.
- **Random serum cortisol** is of limited value because of diurnal variation.
- **Localise — once AI is confirmed:**

Parameter	Primary AI	Secondary AI
Plasma **ACTH**	High (inappropriately raised)	Low / inappropriately normal
Plasma **renin**	High	Normal
Aldosterone	Low	Normal
Mineralocorticoid axis	Deficient	Intact

- **Aetiological work-up:** screen **21-hydroxylase / steroid autoantibodies** (autoimmune marker); if negative → **adrenal CT** (TB, infiltration, haemorrhage, metastases); in **males with negative antibodies → very-long-chain fatty acids (VLCFA)** to exclude X-linked adrenoleukodystrophy; raised **17-OHP** suggests CAH. Low ACTH (secondary) → **MRI hypothalamus/pituitary**.

Management / treatment

- **Acute crisis:**
  - Immediate **IV saline 1 L/h** with continuous cardiac monitoring to correct volume depletion.
  - **Hydrocortisone 100 mg IV bolus**, then **200 mg over 24 h** (continuous infusion preferred, or bolus IV/IM).
  - Separate mineralocorticoid is unnecessary until the hydrocortisone dose falls **<50 mg/day** (higher doses saturate the mineralocorticoid receptor). Treat the precipitating illness.
- **Chronic glucocorticoid replacement: hydrocortisone 15–25 mg/day orally in 2–3 divided doses**, with ≥half the dose on waking to mimic the circadian rhythm. Long-acting steroids (prednisolone, dexamethasone) are avoided (excess overnight exposure). Increase by ~**50% in the last trimester of pregnancy**. *Approximate equivalence:* 1 mg hydrocortisone = 1.6 mg cortisone acetate = 0.2 mg prednisolone = 0.25 mg prednisone = 0.025 mg dexamethasone.
- **Mineralocorticoid replacement (primary AI only): fludrocortisone 100–150 µg/day**. Monitor sitting/standing BP, serum Na/K and **plasma renin (keep upper-normal)**. *40 mg hydrocortisone ≈ 100 µg fludrocortisone*; increase fludrocortisone by 50–100 µg in hot/tropical climates. Prednisolone/prednisone have weak, dexamethasone *no* mineralocorticoid activity.

- **Adrenal androgen replacement:** optional **DHEA 25–50 mg once daily** for persistent low energy or androgen-deficiency symptoms in women; monitor DHEAS, androstenedione, testosterone, SHBG.
- **Sick-day rules / patient education (mark-scoring): double** the oral glucocorticoid dose for intercurrent febrile illness; **100 mg hydrocortisone IM/IV** for emergencies, **200 mg/24 h** for prolonged vomiting, surgery or trauma. Every patient must carry a **hydrocortisone self-injection emergency kit**, a **steroid emergency card and bracelet**, and be trained in their use.
- **Glucocorticoid-induced AI:** occurs with any route (oral, inhaled, topical, intranasal, intra-articular); highest risk with supraphysiologic doses >3–4 weeks; CYP3A4 inhibitors (notably **ritonavir**) markedly increase risk. Give **stress-dose cover**, but mineralocorticoid is *not* needed (aldosterone preserved); taper slowly.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Adrenal cortex zones and their secretions (functional zonation):** concentric layers labelled — capsule; **Zona glomerulosa → mineralocorticoids (aldosterone)**; **Zona fasciculata → glucocorticoids (cortisol)**; **Zona reticularis → adrenal androgens (DHEA/DHEAS)**; innermost **medulla → catecholamines**.
- **HPA axis feedback loop:** *Hypothalamus (CRH) → Anterior pituitary (ACTH) → Adrenal cortex (cortisol) → negative feedback* on hypothalamus and pituitary; annotate "loss of cortisol feedback → high ACTH → hyperpigmentation" for primary AI versus "low ACTH → pallor" for secondary AI.

Clinical / Diagnostic significance

- **Hyperpigmentation + hyperkalaemia + hyponatraemia** strongly favours *primary* AI; **pallor with normal potassium** favours *secondary* AI.
- Always suspect AI in **unexplained shock refractory to fluids/pressors**, hyponatraemia with hyperkalaemia, or an "acute abdomen" with hypotension.
- **Treat first, confirm later** in suspected crisis — give hydrocortisone after drawing baseline cortisol/ACTH.
- Screen primary AI patients for **autoimmune polyglandular syndrome** (thyroid disease, T1DM, premature ovarian failure) and monitor accordingly.
- Counsel on **stress dosing**; failure to up-titrate during illness/surgery is the commonest preventable cause of crisis and death.

High-yield exam pointers

- **Primary AI = Addison's** = glucocorticoid + mineralocorticoid (± androgen) loss; **secondary = glucocorticoid only** (mineralocorticoid intact).
- **Commonest cause of primary AI:** autoimmune adrenalitis (developed world); **TB** remains common in developing countries.
- **Commonest cause of AI overall: exogenous glucocorticoid therapy** (iatrogenic).
- **Diagnostic test:** short **cosyntropin 250 µg** test — failure if cortisol **<450–500 nmol/L (16–18 µg/dL)** at 30–60 min.

- **Localisation:** ACTH **high** = primary, **low/normal** = secondary; high renin + low aldosterone confirm mineralocorticoid deficiency.
- **Hyponatraemia ~80%, hyperkalaemia ~40%** at presentation in primary AI.
- **Crisis management:** IV saline 1 L/h + **hydrocortisone 100 mg IV bolus then 200 mg/24 h**.
- **Maintenance:** hydrocortisone **15–25 mg/day** (split, morning-weighted) ± **fludrocortisone 100–150 µg/day** (primary only).
- *Waterhouse-Friderichsen* = meningococcal adrenal haemorrhage; *Sheehan's* = post-partum pituitary infarction (secondary AI).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 398 "Disorders of the Adrenal Cortex"** (sections on Adrenal Insufficiency, Acute Adrenal Insufficiency, Diagnosis, Treatment, and Glucocorticoid-Induced Adrenal Insufficiency; Tables 398-7, 398-8, 398-9; Figs 398-15, 398-16). Coverage note: all classifications, drug doses, biochemical cut-offs and figures above are grounded in Ch 398; the corticosteroid potency equivalences and the Allgrove/Waterhouse-Friderichsen/Sheehan eponyms are supported in the chapter text. No fabricated content; no gap flagged (spec.gap = false).

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Autoimmune hypothyroidism

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

Definition / Introduction — Autoimmune hypothyroidism is the clinical syndrome of thyroid hormone deficiency resulting from immune-mediated destruction of the thyroid gland, of which *Hashimoto's thyroiditis* (chronic lymphocytic thyroiditis) is the prototype. In iodine-sufficient regions, autoimmunity accounts for **>90% of all non-iatrogenic hypothyroidism**, making it the single most common cause of acquired hypothyroidism. It is characterised by lymphocytic infiltration of the thyroid, circulating anti-thyroid-peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, and a slowly progressive course from euthyroidism through subclinical to overt hypothyroidism.

Classification & Etiological Context

- **Goitrous variant (classic Hashimoto's thyroiditis)** — diffuse, firm, irregular goitre with lymphocytic infiltration; the commonest cause of goitre in iodine-sufficient areas. Originally termed *struma lymphomatosa*.
- **Atrophic thyroiditis (primary myxoedema)** — minimal residual thyroid tissue with extensive fibrosis; generally the **end stage** of the same autoimmune process rather than a separate disorder; presents as hypothyroidism *without* goitre.
- **IgG4-related thyroiditis** — a distinct fibrosing subset with high circulating IgG4 and IgG4-positive plasma-cell infiltration; overlaps with Riedel's thyroiditis.
- **Stages of functional decline** — (1) *euthyroid* antibody-positive phase → (2) *subclinical hypothyroidism* (raised TSH, normal free T4) → (3) *overt/clinical hypothyroidism* (raised TSH usually >10 mIU/L with low free T4).

Cause of primary hypothyroidism	Examples
Autoimmune	Hashimoto's (goitrous) and atrophic thyroiditis
Iatrogenic	^{131}I therapy, thyroidectomy, external neck irradiation
Drugs	Iodine excess, amiodarone, lithium, interferon-α, tyrosine kinase inhibitors (sunitinib), immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab)
Iodine deficiency	Endemic goitre / cretinism
Infiltrative	Amyloidosis, sarcoidosis, haemochromatosis, Riedel's thyroiditis

Epidemiology & Risk Factors

- **Incidence** ≈ 4 per 1000 women and 1 per 1000 men annually; strong **female preponderance**. Onset typically 30–50 years; mean age at diagnosis ~60 years; prevalence rises with age.
- **Subclinical hypothyroidism** present in 6–8% of women (10% over 60 years) and 3% of men; annual risk of progression to overt disease is **~4% when TPO antibodies are positive**.
- **Genetic** — *HLA-DR3, DR4 and DR5* (Caucasians); immunoregulatory polymorphisms in *PTPN22* and *CTLA-4*; monozygotic-twin concordance ~0.55. A chromosome-21 gene underlies the **Down syndrome** association; high frequency also in **Turner syndrome** (X-chromosome related).
- **Environmental** — high iodine intake and low selenium increase risk; **smoking cessation transiently raises incidence**; alcohol appears protective; radiation exposure (atomic bomb, Chernobyl, Hodgkin's neck irradiation) increases risk; cytokine and checkpoint-inhibitor therapy can precipitate disease.

Pathogenesis & Immunology

- **Cell-mediated injury is primary** — *$CD8^+$ perforin-containing cytotoxic T cells* recognising thyroglobulin and TPO are the dominant effectors of follicular-cell destruction; Th1 and **Th17** subsets and macrophages amplify injury.
- **Cytokine effects** — local TNF, IL-1 and IFN-γ impair thyrocyte function, up-regulate HLA class I/II, adhesion molecules, CD40 and nitric oxide, and sensitise cells to **Fas (CD95)–Fas ligand-mediated apoptosis** and oxidative stress.
- **Antibodies (secondary, amplifying role) — anti-TPO and anti-Tg antibodies are present in >95%** of patients and are the clinical markers of autoimmunity; TPO antibodies fix complement (membrane-attack complex). Tissue injury may also occur via antibody-dependent cell-mediated cytotoxicity (NK cells).
- **TSH-receptor-blocking antibodies** — up to **20%** of patients have antibodies that *block* (rather than stimulate) the TSH-R, contributing to hypothyroidism and, especially in **Asian patients, thyroid atrophy**; their transplacental passage can cause *transient neonatal hypothyroidism*. Rare patients harbour a mixture of stimulating (TSI) and blocking antibodies, producing **oscillating thyroid function**.

- Rarely, antibodies against the **sodium-iodide symporter (NIS)** and **pendrin** are found, of uncertain significance.

Histopathology

- **Hashimoto's (goitrous):** diffuse **lymphocytic infiltration with germinal-centre formation**, atrophy of thyroid follicles with **absent colloid**, **oxyphil (Hürthle/Askanazy-cell) metaplasia**, and mild-to-moderate fibrosis; gland is pale, firm and rubbery.
- **Atrophic thyroiditis:** extensive fibrosis, less lymphocytic infiltrate, near-complete loss of follicles.
- **Hashitoxicosis:** rare concurrent histologic changes of Graves' disease.
- Painless (silent) and post-partum thyroiditis show histology resembling Hashimoto's.

Clinical Features

- Onset is **insidious**; many present with goitre rather than symptoms. Goitre is painless, firm, irregular and moves on swallowing.

Symptoms (descending frequency)	Signs
Tiredness, weakness	Dry coarse skin; cool extremities
Dry skin, cold intolerance	Puffy face/hands/feet (**myxoedema**)
Hair loss, poor memory	Diffuse alopecia; loss of lateral eyebrow (*Queen Anne sign*)
Constipation, weight gain (modest)	**Bradycardia**, diastolic hypertension
Hoarse voice, dyspnoea	**Delayed ("hung-up") tendon-reflex relaxation**
Menorrhagia (later oligo/amenorrhoea), paraesthesia	Carpal tunnel syndrome; serous-cavity effusions

- **Mechanism of myxoedema:** dermal accumulation of hydrophilic **glycosaminoglycans (hyaluronic acid)** producing non-pitting, boggy thickening.
- **Cardiac:** reduced stroke volume and rate, **pericardial effusion in up to 30%**, narrow pulse pressure; *myxoedema heart*.
- **Other:** hyperprolactinaemia/galactorrhoea, reduced fertility, increased miscarriage; reversible cerebellar ataxia, dementia, psychosis (*myxoedema madness*); **Hashimoto's encephalopathy** (steroid-responsive, TPO-Ab positive, myoclonus, EEG slowing).
- **Associated autoimmune disease:** vitiligo, pernicious anaemia, **Addison's disease (Schmidt's syndrome)**, alopecia areata, type 1 diabetes, coeliac disease, SLE, myasthenia gravis, Sjögren's. In **autoimmune polyendocrine syndrome type 2**, autoimmune thyroid disease is present in 70–75%, T1DM in 40–60%, Addison's in 40–50%. Thyroid ophthalmopathy occurs in ~5%.
- **Myxoedema coma** — the extreme presentation: reduced consciousness/seizures, hypothermia (to 23 °C), hypoventilation with hypoxia/hypercapnia, hyponatraemia and hypoglycaemia; usually elderly, precipitated by sedatives, infection, cold, MI or stroke; **mortality 20–40%**.

Laboratory Evaluation

- **Serum TSH is the primary screening test** — a normal TSH excludes primary hypothyroidism. If TSH is elevated, measure **free T4** to confirm overt (low FT4) versus subclinical (normal FT4) disease.
- **TPO and Tg antibodies** establish autoimmune aetiology (positive in >95%).
- T3 is normal in ~25% (adaptive deiodinase response) → **T3 measurement is not indicated**.
- Supportive abnormalities: raised **creatine kinase**, elevated total/LDL cholesterol and triglycerides, normocytic or macrocytic **anaemia**, hyponatraemia.
- Central (secondary) hypothyroidism: low FT4 with low/normal/slightly raised TSH — monitor by FT4, not TSH.

Management

Setting	Regimen
Overt hypothyroidism, young, no heart disease	Levothyroxine (LT4) full replacement **1.6 µg/kg/day** (~100–150 µg), 30 min before breakfast; start 50–100 µg/day
Elderly / known CAD	Start LT4 **12.5–25 µg/day**, increase slowly every 2–3 months
Monitoring	Recheck TSH at **6–8 weeks**; adjust in 12.5–25 µg steps; goal TSH in **lower half of reference range**
Subclinical hypothyroidism	Treat if **TSH >10 mIU/L**, woman wishing to conceive/pregnant, or symptomatic; otherwise monitor annually (start 25–50 µg)
Pregnancy	Increase dose ~30–45% (nine doses/week once pregnancy confirmed); target **TSH <2.5 mIU/L**; test every 4 weeks in first half
Myxoedema coma	LT4 IV loading **200–400 µg** then 1.6 µg/kg/day; consider liothyronine (T3) 5–20 µg load then 2.5–10 µg q8h; **IV hydrocortisone 50 mg q6h**; ventilatory support, passive rewarming (active only if <30 °C), correct hyponatraemia/hypoglycaemia, broad-spectrum antibiotics, treat precipitant

- LT4 is the preparation of choice; desiccated thyroid and LT4+liothyronine combinations are **not recommended** (non-physiologic T3:T4 ratio; no proven benefit).
- Causes of increased LT4 requirement: malabsorption (coeliac, *H. pylori* gastritis), oestrogens, and co-ingested calcium, iron, PPIs, bile-acid sequestrants — separate dosing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis schematic of autoimmune thyroid destruction** — label: *thyroid follicular cell, $CD8^+$ cytotoxic T cell (cytolysis), Th1/Th17 cells + macrophages releasing cytokines (TNF, IL-1, IFN-γ), Fas–Fas-ligand apoptosis, NK cell (ADCC), TPO/Tg autoantibodies + complement fixation, TSH-receptor-blocking antibody.*
- **Diagnostic algorithm** — label: *Measure TSH → (elevated) → measure free T4 → low = primary hypothyroidism / normal = subclinical → TPO antibody positive = autoimmune hypothyroidism → consider/initiate LT4.*

Clinical / Diagnostic significance

- Single most common cause of acquired hypothyroidism; screen with **TSH**, confirm autoimmunity with **TPO antibodies**.
- Asymmetric Hashimoto goitre may mimic multinodular goitre or carcinoma; **primary thyroid lymphoma** is rare but strongly associated with pre-existing Hashimoto's — a true nodule warrants ultrasound-guided FNA.
- Untreated maternal disease impairs foetal neurodevelopment and raises miscarriage/preterm risk — pre-conception TSH should be <2.5 mIU/L.
- A suppressed TSH from LT4 over-treatment increases risk of **atrial fibrillation and reduced bone density**.
- Persistent symptoms despite biochemical euthyroidism occur in 10–15%; reassess adherence and associated autoimmune disease before altering therapy.

High-yield exam pointers

- Hashimoto's = autoimmune thyroiditis = >90% of non-iatrogenic hypothyroidism in iodine-sufficient areas.
- Two faces: **goitrous (Hashimoto)** vs **atrophic (primary myxoedema)** — same spectrum; atrophic = end stage.
- **TPO + Tg antibodies positive in >95%**; ~20% have **TSH-R-blocking antibodies** (cause atrophy, especially Asians).
- Histology buzzwords: **germinal centres, lymphocytic infiltration, Hürthle/Askanazy oxyphil-cell metaplasia, fibrosis, struma lymphomatosa**.
- Genetic: **HLA-DR3/DR4/DR5, CTLA-4, PTPN22**; associations — **Down's, Turner's, APS-2 (Schmidt's syndrome), T1DM, pernicious anaemia, vitiligo, coeliac**.
- Diagnosis: **TSH first**; T3 not useful. Overt threshold TSH usually **>10 mIU/L**.
- Treatment: LT4 **1.6 µg/kg/day**; recheck TSH at **6–8 weeks**; elderly/CAD start **12.5–25 µg**.
- **Myxoedema coma:** mortality 20–40%; treat with IV LT4 + **hydrocortisone**, ventilation, passive rewarming.
- Subclinical disease: treat if **TSH >10**, pregnancy, or wishing to conceive.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hypothyroidism" (chapter on autoimmune hypothyroidism / Hashimoto's thyroiditis).
- **Williams Textbook of Endocrinology, 15e** — "Hypothyroidism and Thyroiditis" (classification, pathophysiology, histopathology, risk factors).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid & Adrenal Glands" (current management, levothyroxine dosing, autoimmune thyroiditis).

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Monogenic diabetes mellitus

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Diabetes mellitus (DM) is a group of metabolic disorders sharing the phenotype of **hyperglycaemia**, arising from reduced insulin secretion, decreased glucose utilisation and/or increased hepatic glucose production. While **type 1** and **type 2 DM** dominate, an aetiologic classification recognises a third heterogeneous group, of which **monogenic diabetes** (single-gene defects of β-cell development/function or insulin action) is the most clinically actionable. Monogenic forms account for **1–2% of all diabetes** (1–4% of those diagnosed before age 30), are frequently misdiagnosed as type 1 or type 2 DM, and are the flagship example of **precision medicine**, because correct molecular diagnosis directly changes therapy.

Aetiologic classification of diabetes mellitus (ADA / Harrison)

Category	Defining feature
I. Type 1 DM	Immune-mediated β-cell destruction → usually absolute insulin deficiency
II. Type 2 DM	Spectrum from predominant insulin resistance to predominant secretory defect
III. Other specific types	(see below)
IV. Gestational DM (GDM)	Glucose intolerance of 2nd/3rd trimester

Group III — "Other specific types":

- **A. Genetic defects of β-cell function (monogenic / MODY):** *HNF4A*, *GCK* (glucokinase), *HNF1A*, *HNF1B*, *IPF-1/PDX1*, *NEUROD1*, and others (*KLF11, PAX4, BLK, GATA4/6, SLC2A2/GLUT2, GLIS3*); **mitochondrial DNA**.
- **B. Neonatal diabetes (onset <6 months):** mutations in K-ATP channel subunits, *RFX6*, *INS*.
- **C. Transient neonatal diabetes.**
- **D. Diseases of the exocrine pancreas:** pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy (so-called type 3c / pancreatogenic DM).
- **E. Genetic defects in insulin action:** type A insulin resistance, *leprechaunism*, *Rabson–Mendenhall* syndrome, lipodystrophies.

- **F. Endocrinopathies:** acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.
- **G. Drug/chemical-induced:** glucocorticoids, calcineurin & mTOR inhibitors, pentamidine, nicotinic acid, thiazides, atypical antipsychotics, α-interferon, diazoxide, vacor.
- **H. Infections:** congenital rubella, CMV, coxsackievirus.
- **I. Uncommon immune-mediated:** "stiff-person" syndrome, anti-insulin-receptor antibodies, immune-checkpoint-inhibitor diabetes.
- **J. Genetic syndromes:** Wolfram, Down's, Klinefelter's, Turner's, Friedreich's ataxia, myotonic dystrophy, Prader–Willi, Laurence-Moon-Biedl.

Diagnostic criteria for DM (ADA, confirm on a separate day unless unequivocal hyperglycaemia)

- **HbA1c ≥6.5%** (≥48 mmol/mol), OR
- **Fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL)**, OR
- **2-h plasma glucose ≥11.1 mmol/L (200 mg/dL)** on 75-g OGTT, OR
- **Random glucose ≥11.1 mmol/L (200 mg/dL)** with classic symptoms (polyuria, polydipsia, weight loss).
- **Prediabetes:** HbA1c 5.7–6.4%; IFG (FPG 5.6–6.9 mmol/L / 100–125 mg/dL); IGT (2-h PG 7.8–11.0 mmol/L / 140–199 mg/dL).

Recognising monogenic diabetes — when to suspect

Monogenic diabetes cannot be reliably separated from type 1/type 2 DM by clinical features alone; suspicion rests on **"atypical" features and family history**:

- **Atypical for type 1 DM:** absent pancreatic islet autoantibodies; persistence of endogenous insulin beyond the honeymoon; **measurable C-peptide (≥0.6 ng/mL, ≥0.2 nmol/L) in the presence of hyperglycaemia**; low insulin requirement; no ketoacidosis when insulin is omitted.
- **Atypical for type 2 DM:** onset before 45 years; lack of significant obesity; absent acanthosis nigricans; normal triglycerides and/or normal–high HDL.
- **Strong pointers: autosomal-dominant**, multigenerational ("3-generation") diabetes; diabetes diagnosed **before age 25–30**; diabetes diagnosed **<6 months of age** (never autoimmune type 1); stable **mild fasting hyperglycaemia**; syndromic clues (deafness, renal cysts, optic atrophy).

Stepwise diagnostic pathway (biomarker → genetic):

- **C-peptide / urinary C-peptide:creatinine ratio (UCPCR)** to confirm endogenous insulin secretion.
- If C-peptide ≥0.2 nmol/L → measure **GAD65 and IA-2 (± ZnT8) islet autoantibodies**; positive antibodies favour type 1 DM.
- If antibody-negative → **molecular genetic testing** (next-generation-sequencing gene panels: *GCK, HNF1A, HNF4A, HNF1B*, plus neonatal genes *KCNJ11, ABCC8, INS*).
- Aids: the **Exeter MODY probability calculator** (valid for diagnosis <35 y) and the **type-1-diabetes genetic risk score (T1D-GRS)** help select patients for genetic testing.

The four classic MODY subtypes (Williams)

Gene (chr) [old name]	Key phenotype	Precision treatment
GCK (7p) [MODY2]	**Mild, stable, non-progressive fasting hyperglycaemia** 99–144 mg/dL (5.5–8.0 mmol/L), present from birth; small OGTT increment (<90 mg/dL); antibody-negative; virtually no micro/macrovascular complications (only late non-proliferative retinopathy)	**No treatment** — diet only; oral agents/insulin ineffective and *contraindicated* (pregnancy is the exception)
HNF1A (12q) [MODY3]	Progressive hyperglycaemia, **low renal glucose threshold → glycosuria**, high penetrance (63% by 25 y); hepatocellular adenomas; increased cardiovascular mortality	**Low-dose sulfonylurea** (very sensitive, may cause hypoglycaemia); meglitinides/GLP-1 RA; insulin when β-cells fail late
HNF4A (20q) [MODY1]	Progressive β-cell failure; **fetal macrosomia (+~790 g) with transient neonatal hyperinsulinaemic hypoglycaemia**; low HDL	**Low-dose sulfonylurea**; insulin later
HNF1B (17q) [MODY5]	**Renal cysts and diabetes (RCAD)**; pancreatic hypoplasia + exocrine insufficiency; genital-tract anomalies; hypomagnesaemia, hyperuricaemia, deranged LFTs; 50–60% de novo (17q12 deletions)	**Insulin** — poor/no sulfonylurea response

- *GCK* and *HNF1A* are the two commonest causes (the four transcription-factor/enzyme genes account for the great majority of MODY); subtype frequency varies geographically (*HNF1A* predominates in UK/Europe, *GCK* in several US registries).

Neonatal and syndromic monogenic diabetes

- **Neonatal diabetes (ND):** diagnosis typically **<6 months** (test all such infants; also test 6–12 months if antibody-negative). Infants are often small-for-dates.
  - **Transient ND:** overexpression of the paternal **6q24** locus, or mildly activating *ABCC8/KCNJ11*; features may include IUGR, macroglossia, umbilical hernia; remits by ~4 months, often recurs at puberty.
  - **Permanent ND:** activating **K-ATP channel** mutations (*KCNJ11/Kir6.2*, *ABCC8/SUR1*) — respond to **high-dose sulfonylurea** (insulin can be discontinued; early treatment improves neurodevelopmental outcomes in the *DEND* spectrum); **insulin-gene (*INS*)** mutations — require insulin. Test *KCNJ11, ABCC8, INS* and 6q24 imprinting.
- **Syndromic forms (<1% of childhood diabetes):**
  - **Maternally inherited diabetes and deafness (MIDD):** mitochondrial **m.3243A>G** (tRNA-Leu); sensorineural deafness; overlaps *MELAS*. Treat with diet/oral agents then insulin (usually within 2 years); **avoid metformin** (mitochondrial inhibition / lactic acidosis risk).
  - **Wolfram syndrome (DIDMOAD):** autosomal-recessive *WFS1* (wolframin); insulin-dependent **non-autoimmune** DM (mean onset ~6 y), optic atrophy, diabetes insipidus, deafness — supportive care + insulin.

- **Alström syndrome:** *ALMS1* — obesity, cone-rod dystrophy, deafness, insulin-resistant type 2-like DM.

Management principles — "treat the genotype"

- **GCK-MODY:** lifelong **no pharmacotherapy**; reassure (benign, complication-free).
- **HNF1A- / HNF4A-MODY: low-dose sulfonylurea is first-line** (often allows withdrawal of insulin in those misdiagnosed as type 1); meglitinides and GLP-1 receptor agonists are alternatives; statin for HNF1A cardiovascular risk; insulin when secretory reserve declines.
- **HNF1B-MODY: insulin**; multidisciplinary care for renal/genital/exocrine disease.
- **K-ATP neonatal diabetes (*KCNJ11/ABCC8*): high-dose sulfonylurea**, transition off insulin.
- ***INS* neonatal diabetes / pancreatic-agenesis genes: insulin**.
- **Pregnancy (precision obstetric care):**
  - *GCK-MODY:* treat only if the **fetus is unaffected** (predicted by serial growth ultrasound) — large-dose insulin in the 3rd trimester, deliver ~38 weeks; no treatment if the fetus carries the mutation.
  - *HNF1A/HNF4A-MODY:* switch sulfonylurea (**glyburide**) to **insulin** (latest by 2nd trimester); fortnightly fetal growth scans after 28 weeks; early delivery (35–38 weeks) for HNF4A because of macrosomia and severe neonatal hypoglycaemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Glucose-stimulated insulin secretion in the β-cell, with monogenic-diabetes genes mapped.** Labels: *GLUT1/2 (SLC2A2)* glucose transporter → **Glucose** → **glucokinase (GCK)** → Glucose-6-phosphate → glycolysis/Krebs → **ATP/ADP** → **ATP-sensitive K^+ channel (Kir6.2/KCNJ11 + SUR1/ABCC8)** → membrane depolarisation → **voltage-gated Ca^{2+} channel** → Ca^{2+} influx → **insulin (INS) + C-peptide + IAPP** secretory granules; nuclear **transcription factors HNF1A, HNF4A, HNF1B, PDX1/IPF-1, NEUROD1**; incretin (GLP-1/GIP) receptors.
- **Stepwise diagnostic algorithm:** Diabetes → (autoantibodies + C-peptide) → if antibody-negative & C-peptide-positive branch on phenotype: *<6 months* → neonatal panel (*KCNJ11/ABCC8/INS/6q24*); *mild stable fasting hyperglycaemia* → **GCK**; *progressive + glycosuria* → **HNF1A**; *renal cysts/hypomagnesaemia* → **HNF1B**; *transient neonatal hypoglycaemia/low HDL* → **HNF4A**; *deafness/syndromic* → mitochondrial/syndromic testing.

Clinical / Diagnostic significance

- A correct molecular diagnosis can **stop unnecessary insulin** (HNF1A/HNF4A, K-ATP neonatal), **stop all therapy** (GCK), avoid hypoglycaemia, and trigger **cascade screening** of relatives (autosomal dominant — 50% risk).
- Recognises **comorbidity surveillance**: renal disease and hypomagnesaemia in HNF1B; hepatocellular adenoma and cardiovascular risk in HNF1A; deafness/cardiomyopathy in MIDD; optic atrophy/DI in Wolfram.

- GCK-MODY detected as "gestational diabetes" needs genotype-guided fetal management rather than routine intensification.

High-yield exam pointers

- Monogenic diabetes = **1–2% of all DM**; commonly **misdiagnosed** as type 1/type 2.
- **MODY = autosomal dominant, onset <25–30 y, non-insulin-dependent, β-cell defect**; diabetes **<6 months of age is never type 1** — always test for neonatal genes.
- **GCK = no treatment** (benign, complication-free, contraindicated to treat except pregnancy).
- **HNF1A & HNF4A = low-dose sulfonylurea**; HNF1A has **glycosuria from a low renal threshold** (key clue).
- **HNF1B = renal cysts + diabetes (RCAD) + hypomagnesaemia → insulin**.
- **K-ATP neonatal diabetes (KCNJ11/ABCC8) → high-dose sulfonylurea**; **INS mutations → insulin**.
- **MIDD = m.3243A>G, deafness → avoid metformin**; **Wolfram = DIDMOAD (WFS1)**.
- Recognition triad: **antibody-negative + C-peptide-positive + atypical phenotype** → genetic testing (panel/Exeter calculator/T1D-GRS).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology" (Table 415-1 etiologic classification; Fig 415-1 diagnostic criteria; monogenic/neonatal subsection) and "Diabetes Mellitus: Management and Therapies".
- **Williams Textbook of Endocrinology, 15e** — "Monogenic Diabetes" (biomarker screening pathway; Table 37.1 atypical features; Table 37.3 MODY classification/treatment; Table 37.4 neonatal diabetes; Table 37.5 pregnancy management; GCK/HNF1A/HNF4A/HNF1B, MIDD, Wolfram, Alström).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycemia" (diagnostic criteria Table 32-4; other specific types; sulfonylurea dosing; Wolfram/DIDMOAD).

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Diabetic ketoacidosis

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Diabetic ketoacidosis (DKA) is an acute, life-threatening metabolic decompensation of diabetes defined by the biochemical triad of **hyperglycaemia** (serum glucose >13.9 mmol/L [250 mg/dL]; ≥200 mg/dL or any value in a known diabetic per current criteria), **ketonaemia/ketonuria** (serum β-hydroxybutyrate >3.0 mmol/L or urine ketones ≥2+) and **high-anion-gap metabolic acidosis** (arterial/venous pH <7.3 and/or serum bicarbonate <15 mmol/L). It results from *absolute or relative insulin deficiency* combined with *counter-regulatory hormone excess*. It is classically a hallmark of type 1 DM but also occurs in type 2 DM under severe stress, in ketosis-prone diabetes, and as *euglycaemic DKA* with SGLT-2 inhibitors. DKA and the hyperglycaemic hyperosmolar state (HHS) lie on a continuum, with up to one-third of patients showing mixed features.

Etiology and precipitating factors

- **Counter-regulatory drive:** the core lesion is a fall in the *insulin-to-glucagon ratio*, with accompanying rises in **glucagon, catecholamines, cortisol and growth hormone**.
- Common precipitants (mnemonic — the "**I"s**):
  - **Insulin deficiency/omission** — inadequate dosing, missed injections, insulin-pump infusion-site occlusion or device malfunction; insulin rationing due to cost.
  - **Infection** — pneumonia, urinary tract infection, gastroenteritis, sepsis (most common precipitant overall).
  - **Infarction/Ischaemia** — myocardial, cerebral, mesenteric, peripheral; tissue ischaemia.
  - **Inflammation** — acute pancreatitis (note hyperamylasaemia is often salivary, not pancreatic).
  - **Intoxication / Iatrogenic drugs** — alcohol, cocaine; corticosteroids, atypical antipsychotics, immune-checkpoint inhibitors, **SGLT-2 inhibitors**.
  - **Pregnancy** and new-onset diabetes (DKA may be the *presenting* feature of type 1 DM).
- Psychiatric and eating disorders, low socioeconomic status, and prior DKA episodes markedly raise recurrence risk.

Pathophysiology

- **Insulin deficiency + glucagon/counter-regulatory excess** unleashes three deranged pathways:
  - **Hyperglycaemia** — accelerated hepatic *gluconeogenesis* and *glycogenolysis* plus reduced peripheral glucose uptake.
  - **Ketogenesis** — unrestrained adipocyte *lipolysis* releases free fatty acids; the liver shunts these toward **ketone bodies** (β-hydroxybutyrate and acetoacetate). β-hydroxybutyrate is generated at roughly **threefold** the rate of acetoacetate; acetone (a breakdown product) produces the *fruity breath*.
  - **Volume/electrolyte loss** — glucose >renal threshold (~180 mg/dL) causes **osmotic diuresis**, dehydration and urinary loss of Na^+, K^+, phosphate and water; vomiting compounds losses.
- Ketoacids consume bicarbonate → **high-anion-gap metabolic acidosis** with compensatory **Kussmaul (tachypnoeic) respiration**.

- A vicious cycle ensues: stress hormones worsen insulin resistance, hyperglycaemia and ketosis. Inflammatory markers (cytokines, CRP) are elevated.
- **Potassium paradox:** total-body K^+ is depleted (deficit ~3–5 mmol/kg) from osmotic diuresis, acidosis and GI loss, yet *serum* K^+ is normal-to-high at presentation because acidosis and insulin lack shift K^+ extracellularly — it falls sharply once insulin and fluids are given.

Clinical features

- **Symptoms:** polyuria, polydipsia, marked fatigue, **nausea, vomiting**, and **abdominal pain** (may mimic an acute surgical abdomen); evolves over hours to ~24 h.
- **Signs:** dehydration, **tachycardia and hypotension**, mild hypothermia, **Kussmaul respiration** with a **fruity (acetone) odour**, abdominal tenderness, and progressive **lethargy → obtundation → coma** (frank coma in only ~10%).
- Signs of infection may be present *without fever* — an elevated or even normal temperature should prompt a search for infection, as uninfected patients are typically hypothermic.

Investigations and diagnosis

- **Confirm the triad:** capillary/serum glucose, **blood β-hydroxybutyrate** (preferred), and venous blood gas (pH, HCO_3^-). Venous pH suffices — arterial sampling is unnecessary (venous–arterial pH differs by only 0.02–0.15).
- **Ketone testing caveat:** the **nitroprusside** reagent detects *acetoacetate/acetone but NOT β-hydroxybutyrate*, so it can grossly *underestimate* ketosis (especially with concurrent lactic acidosis/shock); false-positives occur with **captopril, penicillamine and valproic acid**. Hence direct **β-hydroxybutyrate assay is preferred**.
- **Corrected sodium:** add **1.6 mmol/L to measured Na^+ for every 5.6 mmol/L (100 mg/dL) rise in glucose**; a *normal* measured Na^+ in DKA signals profound water deficit.
- Other findings: high BUN/creatinine (pre-renal), **leukocytosis** (up to 25,000/µL, may be without infection), hypertriglyceridaemia, raised salivary amylase. Septic screen, ECG (peaked T waves of hyperkalaemia; ischaemia), CXR, cultures.
- **Severity grading & DKA vs HHS:**

Parameter	Mild DKA	Moderate DKA	Severe DKA	HHS
Arterial/venous pH	7.25–7.30	7.0–7.25	<7.0	>7.3
Serum bicarbonate (meq/L)	15–18	10–<15	<10	>18
β-hydroxybutyrate (mmol/L)	3–6	3–6	>6	<1.0
Plasma glucose	>250 mg/dL (often 250–600)	>250 mg/dL	>250 mg/dL	usually >600 (up to 1000+)
Anion gap	↑	↑	↑	normal–slightly ↑
Serum osmolality	variable	variable	variable	>320 (marked)

Parameter	Mild DKA	Moderate DKA	Severe DKA	HHS
Mental status	alert	alert/drowsy	stupor/coma	confusion/coma
Ketones	present (++)	present	present	absent/minimal

- **Differential diagnosis:** starvation ketosis, **alcoholic ketoacidosis** (HCO_3^- usually >15 meq/L), lactic acidosis and other high-anion-gap acidoses; simple hyperglycaemia (no ketonaemia).

Management

General principles: restore circulating volume and perfusion, correct hyperglycaemia/osmolality and acidosis, replace electrolytes, and *identify and treat the precipitant*. Maintain a meticulous **flow sheet**; pass a **nasogastric tube** if vomiting/altered sensorium. Avoid sedatives/opioids (mask early cerebral oedema). Treat mild–moderate DKA in a step-down unit; severe DKA in ICU.

Component	Practical regimen
1. Fluids	**0.9% saline (or lactated Ringer's) 2–3 L over first 1–3 h (~10–20 mL/kg/h)**; total deficit ≈3–5 L. Switch to **0.45% saline 250–500 mL/h** once haemodynamically stable. When glucose ≈250 mg/dL (13.9 mmol/L), change to **5–10% dextrose + 0.45% saline at 150–250 mL/h**. Ringer's lactate gives faster resolution with less hyperchloraemia.
2. Insulin	**Regular insulin 0.1 unit/kg IV bolus, then 0.1 unit/kg/h infusion**; increase 2–3 fold if no fall in 2–4 h. Aim glucose fall **50–100 mg/dL/h**. Reduce to **0.02–0.1 unit/kg/h** when glucose ~250 mg/dL. Uncomplicated mild–moderate DKA may use SC rapid-acting analogue. **Withhold insulin if K^+ <3.3 mmol/L** until corrected.
3. Potassium	If K^+ <3.5 → give **10–20 mmol/h** until >3.5 (and hold insulin if <3.3). If K^+ 3.5–5 → **10–20 mmol per litre** of fluid, target 4–5. If K^+ >5 → start insulin, hold K^+; recheck 2-hourly. Require adequate urine output.
4. Bicarbonate	**Not routinely recommended** (no outcome benefit; risks hypokalaemia, paradoxical CSF acidosis, leftward O_2-dissociation shift). Consider **only if pH <7.0**: ~50–100 mmol $NaHCO_3$ in sterile water with KCl, repeat until pH >7.0–7.1.
5. Phosphate	**Seldom needed**; replace only if severe hypophosphataemia (<1 mg/dL) develops, at **3–4 mmol/h** (over-replacement risks hypocalcaemic tetany).
6. Resolution & transition	End-points: glucose ~150–200 mg/dL, **HCO_3^- ≥18**, normalised pH/anion gap, patient eating. Give **SC long-acting insulin with a 2–4 h overlap** before stopping the infusion to prevent rebound DKA.

- **Euglycaemic DKA (SGLT-2 inhibitors):** start **5–10% dextrose with insulin from the outset alongside saline**; titrate dextrose to prevent hypoglycaemia. **Resolution is judged by bicarbonate/acidosis correction, NOT glucose**, since glucose is already near-normal.

Complications

- **Cerebral oedema** — the most feared complication, predominantly in **children**, typically as DKA is *resolving*. Risk factors: age <5 y, new-onset diabetes, longer symptom duration, low initial pH, high initial BUN, **bicarbonate therapy**, rapid glucose correction, excess fluid in first 4 h, and rising serum Na^+. Headache or deteriorating sensorium during therapy is the warning sign → treat with **IV mannitol 1–2 g/kg over ~15 min** ± hypertonic saline.

- Hyperchloraemic (normal-anion-gap) acidosis after saline resuscitation — benign, self-corrects over 12–24 h.
- Hypokalaemia, hypoglycaemia, hypophosphataemia, hypomagnesaemia (therapy-related).
- Venous thromboembolism, upper-GI bleeding, ARDS, aspiration, and complications of the precipitant.
- **Prognosis:** mortality is low (<1% in the young/uncomplicated) but rises sharply with age (>20% in the elderly), coma, MI, bowel infarction or end-stage kidney disease; even a single episode confers a ~13-fold one-year increase in mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow chart:** Box "Insulin deficiency + ↑ Counter-regulatory hormones (glucagon, catecholamines, cortisol, GH)" → three arms — (1) ↑ **Gluconeogenesis + glycogenolysis + ↓ glucose uptake → Hyperglycaemia → osmotic diuresis → dehydration / electrolyte loss / ↑ osmolality**; (2) ↑ **Lipolysis → ↑ Free fatty acids → hepatic ketogenesis → ↑ β-hydroxybutyrate + acetoacetate → ketonaemia/ketonuria → high-anion-gap metabolic acidosis → Kussmaul breathing**; (3) **Vomiting → further volume/electrolyte loss**. Labels: *insulin/glucagon ratio, FFA, ketone bodies, anion gap, K^+ shift (intra→extracellular)*.
- **Management timeline bar:** parallel tracks labelled **Fluids (0.9% saline → 0.45% saline → add dextrose at glucose 250)**, **Insulin (0.1 U/kg bolus → 0.1 U/kg/h → 0.02–0.1 U/kg/h)**, **Potassium (replace when 3.3–5; hold if >5)**, **Monitor (glucose 1–2 h; electrolytes/anion gap 2–4 h)**, ending at **Resolution → SC insulin overlap**.

Clinical / Diagnostic significance

- DKA may be the **first presentation of type 1 diabetes** — measure ketones whenever a type 1 patient's glucose is persistently >250 mg/dL or during any intercurrent illness ("sick-day rules": never *omit* insulin, monitor glucose/ketones 1–3 hourly, maintain hydration).
- **β-hydroxybutyrate (point-of-care meter) is superior to urine nitroprusside** for both diagnosis and tracking response, and avoids the shock-related false-negative pitfall.
- **SGLT-2 inhibitor users** need counselling on euglycaemic DKA — suspect it on acidosis with near-normal glucose; withhold the drug during acute illness, surgery, low-carbohydrate diets or fasting.
- Always hunt the precipitant (the "I"s) — failure to do so, or inadequate fluid replacement, is the commonest cause of poor recovery.
- Recurrent DKA flags non-adherence/psychosocial issues mandating structured education and mental-health support.

High-yield exam pointers

- **Diagnostic triad:** hyperglycaemia + ketonaemia (β-OHB >3) + acidosis (pH <7.3, HCO_3^- <15).
- Core mechanism: ↓ **insulin/glucagon ratio → gluconeogenesis + lipolysis + ketogenesis**; counter-regulatory hormones = glucagon, catecholamines, cortisol, GH.

- **β-hydroxybutyrate ≈ 3× acetoacetate**; nitroprusside misses β-OHB; false-positives with captopril, penicillamine, valproate.
- **Corrected Na = +1.6 mmol/L per 100 mg/dL glucose rise**; K^+ deficit 3–5 mmol/kg with paradoxical normal/high serum K^+.
- First-hour priority is **fluids before/with insulin**; insulin bolus 0.1 U/kg then 0.1 U/kg/h; **hold insulin if K^+ <3.3**.
- **Add dextrose when glucose ≈250 mg/dL**; resolution = HCO_3^- ≥18 + closed anion gap, *not* glucose alone.
- **Bicarbonate only if pH <7.0**; phosphate only if <1 mg/dL — neither improves outcome.
- **Cerebral oedema** = leading cause of death in children; treat with mannitol 1–2 g/kg.
- **Euglycaemic DKA** with SGLT-2 inhibitors: glucose may be <200 mg/dL — start dextrose + insulin together; judge by acidosis.
- Overlap SC long-acting insulin 2–4 h before stopping the IV infusion to prevent rebound.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Diabetes Mellitus: Management and Therapies"* (Acute Disorders Related to Severe Hyperglycaemia — DKA & HHS; Tables 416-7/8/9) and *"Diabetes Mellitus: Complications"* (euglycaemic DKA with SGLT-2 inhibitors).
- **Williams Textbook of Endocrinology, 15e** — *"Type 1 Diabetes Mellitus"* (pathophysiology, epidemiology, treatment of DKA, cerebral-oedema risk factors, sick-day and SGLT-inhibitor risk-mitigation).
- **CMDT 2026** — *"Diabetes Mellitus & Hypoglycaemia"* (diagnostic essentials, severity grading, fluid/insulin/potassium/bicarbonate/phosphate regimens, hyperchloraemic acidosis, complications and prognosis).

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Dyslipidaemia

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

Definition / Introduction — Dyslipidemia is a disorder of lipoprotein metabolism in which there is a substantial increase or decrease in specific circulating lipids or lipoproteins (cholesterol, triglycerides, or both). Lipoproteins are complexes of an "oil-droplet" hydrophobic core (triglycerides, cholesteryl esters) surrounded by phospholipids, free cholesterol and **apolipoproteins**. Dyslipidemia may be **primary** (genetic) or **secondary** (to other medical conditions/drugs), and is an important *causal* factor for **atherosclerotic cardiovascular disease (ASCVD)**; severe hypertriglyceridemia additionally risks **acute pancreatitis**. Because treatment proven to reduce cardiovascular risk, accurate classification and aggressive management are essential.

Lipoprotein physiology (basis of classification)

- **Major classes by density/size (inverse relationship):** chylomicrons (least dense, largest) → VLDL → IDL → LDL → HDL (most dense, smallest).

- **Key apolipoproteins: apoB-48** (chylomicrons, intestine), **apoB-100** (VLDL, IDL, LDL; ligand for the LDL receptor), **apoA-I** (major HDL protein; promotes efflux via **ABCA1**, activates **LCAT**), **apoC-II** (essential cofactor for **lipoprotein lipase, LPL**), **apoE** (ligand for hepatic clearance of remnants).
- **Three pathways:** *exogenous* (dietary lipids → chylomicrons → LPL lipolysis → remnants cleared by liver via apoE); *endogenous* (hepatic VLDL → IDL → LDL, cleared by LDL receptor); *reverse cholesterol transport* (HDL returns peripheral cholesterol to liver via SR-BI / CETP).
- **Lp(a)** = LDL-like particle with **apo(a)** disulphide-linked to apoB-100; an independent, highly heritable causal risk factor for **ASCVD and aortic stenosis**.
- Discrete "nodes" that go wrong in disease: (1) LPL-mediated lipolysis, (2) receptor-mediated hepatic uptake of apoB lipoproteins, (3) hepatocyte/enterocyte cholesterol handling, (4) VLDL assembly/secretion, (5) plasma lipid transfer & phospholipid hydrolysis.

Etiological classification (Harrison 22e, phenotype/mechanism-based)

Phenotype	Representative primary disorder	Gene(s)	Lipid pattern	Inheritance
Severe hypertriglyceridemia	Familial chylomicronemia syndrome (FCS)	*LPL, APOC2, APOA5, GPIHBP1, LMF1*	↑Chylomicrons, ↑VLDL; ↓HDL	AR
Hypercholesterolemia (↑LDL)	Familial hypercholesterolemia (**FH**)	*LDLR*	↑LDL	AD (~1/250)
Hypercholesterolemia	Familial defective apoB-100 (FDB)	*APOB*	↑LDL	AD (~1/1500)
Hypercholesterolemia	ADH type 3	*PCSK9* (gain-of-function)	↑LDL	AD
Hypercholesterolemia	Autosomal recessive hypercholesterolemia (ARH)	*LDLRAP1*	↑LDL	AR
Mixed (↑TG + ↑LDL)	Familial dysbetalipoproteinemia (**FDBL**, type III)	*APOE2/E2*	↑Remnants/IDL (chol≈TG)	AR (~1/10,000)
Mixed	Familial combined hyperlipidemia (**FCHL**)	Polygenic	↑VLDL ± ↑LDL (small-dense), ↑apoB, ↓HDL	~1/100–200
Low HDL	Tangier disease	*ABCA1*	HDL <5 mg/dL	AR/co-dominant

- **Secondary causes (Table 419-3):** ↑TG — high-carbohydrate diet, alcohol, obesity, insulin resistance/**type 2 diabetes**, lipodystrophy, CKD, nephrotic syndrome, hypothyroidism, Cushing's, pregnancy, drugs (estrogen, glucocorticoids, isotretinoin/retinoids, beta-blockers, bile-acid resins). ↑LDL-C — **hypothyroidism**, cholestasis, nephrotic syndrome, Cushing's, anorexia, drugs (corticosteroids, cyclosporin, sirolimus, carbamazepine).
- *Fredrickson/WHO phenotypes* (classic, parallel framework): **I** chylomicrons; **IIa** LDL; **IIb** LDL+VLDL; **III** IDL/β-VLDL (FDBL); **IV** VLDL; **V** chylomicrons+VLDL.

Clinical features

- Most dyslipidemia is **asymptomatic**, detected on screening; the dominant consequence is **premature ASCVD** (MI, ischemic stroke, peripheral vascular disease).
- **FH:** corneal arcus, **tendon xanthomas** (dorsum of hands, Achilles); untreated heterozygous men have ~50% chance of MI before age 60. **Homozygous FH** — LDL-C >400 mg/dL, cutaneous xanthomas, ASCVD by age 30.
- **FDBL (type III):** *tuberoeruptive xanthomas* (elbows, knees, buttocks) and **palmar xanthomas (xanthomata striata palmaris)** — virtually pathognomonic; cholesterol and TG raised to similar degree, HDL usually normal; prominent peripheral vascular disease.
- **Severe HTG / chylomicronemia (FCS): eruptive xanthomas** (extensor surfaces), **lipemia retinalis** (opalescent retinal vessels), hepatosplenomegaly, and recurrent **acute pancreatitis** (suspect if fasting TG >500 mg/dL).
- **Tangier disease:** enlarged grayish-orange tonsils, hepatosplenomegaly, peripheral neuropathy with HDL-C <5 mg/dL.

Diagnosis & screening

- **Screen all adults** with a fasting lipid panel (total cholesterol, TG, HDL-C); screen children at **ages 9–11** and earlier with a family history of hypercholesterolemia/premature ASCVD.
- **Friedewald formula: LDL-C = Total cholesterol − (TG/5) − HDL-C** (TG/5 estimates VLDL-cholesterol). Accurate only on fasting plasma and **invalid if TG >400 mg/dL** (and not valid in FDBL).
- **Non-HDL-C = Total cholesterol − HDL-C** — captures cholesterol in VLDL/IDL/LDL; a better atherogenic marker. **apoB** and **Lp(a)** provide additional risk information.
- Diagnose the dyslipidemia phenotype, then **rule out secondary causes** (Table 419-3) before invoking a primary disorder. Confirmatory tests: FH gene panel (**LDLR, APOB, PCSK9**); **apoE2/E2 genotype** or β-quantification (VLDL-C/total TG ratio >0.30, "broad β band") for FDBL.
- **Risk stratification:** ASCVD pooled-cohort 10-year risk calculator; refine borderline cases with **apoB, Lp(a), hs-CRP**, and **coronary artery calcium (CAC) score**.

Management

- **Goals:** prevent ASCVD events, and prevent pancreatitis when TG is severely elevated.
- **Lifestyle / therapeutic lifestyle change (first step for all):** reduce **saturated and trans fats**, weight loss in the obese, aerobic exercise, restrict alcohol; treat hypothyroidism/diabetes; restrict total fat and simple carbohydrates in severe HTG.
- **Statin intensity: high-intensity statin** for established ASCVD or those at high risk; in primary prevention a **10-year risk >7.5%** merits statin regardless of LDL-C. In ASCVD, lower LDL-C with drug therapy **as long as it remains >70 mg/dL**, using combination therapy if needed. FH patients require treatment from childhood.
- **TG-lowering when TG >500 mg/dL** (to prevent pancreatitis): **fibrates** and **omega-3 fatty acids (fish oils)**; statins added if ASCVD risk is elevated.

Class (drug)	Mechanism	LDL-C effect	Key adverse effects
Statins (atorvastatin, rosuvastatin, etc.)	↓HMG-CoA reductase → ↑hepatic LDL receptors	↓~30–55% (doubling dose → ~6% more)	Myalgia (3–5%), myopathy/rhabdomyolysis, ↑transaminases, small ↑incident T2DM
Ezetimibe	Blocks intestinal NPC1L1 → ↓absorption	↓~18% (additive to statin)	Very safe; 2nd-line add-on
PCSK9 inhibitors (evolocumab, alirocumab; **inclisiran** = siRNA)	↓PCSK9 → ↑LDL receptors; also ↓Lp(a)	↓~60%	Injection-site reactions; SC q2wk (antibody) / q6mo (inclisiran)
Bempedoic acid	ATP-citrate lyase inhibitor → ↑LDL receptors	↓~18% with statin (~23% mono)	↑uric acid/gout, ↑LFTs, cholelithiasis; no ↑diabetes
Bile-acid sequestrants (cholestyramine, colestipol, colesevelam)	↓bile-acid reabsorption → ↑LDL receptors	↓LDL but ↑**TG**	Bloating, constipation; avoid in HTG
Fibrates (fenofibrate, gemfibrozil)	PPARα agonist → ↑LPL, ↓apoC-III, ↓VLDL	TG ↓~30%	Myopathy (esp. with statin), gallstones, ↑creatinine, warfarin potentiation
Omega-3 (EPA/DHA, icosapent ethyl)	↓VLDL synthesis	TG ↓~30% (3–4 g/day)	Dyspepsia; icosapent ethyl ↓CV events in HTG

- **Homozygous FH / refractory cases:** add **lomitapide** (MTP inhibitor), **mipomersen** (apoB antisense), **evinacumab** (ANGPTL3 antibody), **LDL apheresis**, and rarely liver transplantation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Lipoprotein metabolic pathways:** label *Intestine → Chylomicron → LPL (with apoC-II) → Chylomicron remnant → Liver (apoE-mediated uptake)* for the exogenous arm; *Liver → VLDL → IDL → LDL → LDL receptor* for the endogenous arm; and *Peripheral cell → ABCA1 → nascent HDL → LCAT → mature HDL → SR-BI/CETP → Liver* for reverse cholesterol transport. Label **LPL, apoB-100, apoE, LDL receptor, PCSK9, HDL, SR-BI, CETP**.
- **Xanthoma plate:** label **tendon xanthoma** (Achilles, FH), **tuberoeruptive + palmar xanthoma** (FDBL), **eruptive xanthoma + lipemia retinalis** (chylomicronemia), **corneal arcus**.

Clinical / Diagnostic significance

- LDL-C reduction provides robust, dose-dependent reduction in MI, stroke and total mortality — "lower is better" within tolerated limits.
- **Cascade screening** of first-degree relatives is highly effective in FH (50% of siblings/children affected).
- Severe HTG mandates urgent TG lowering to avert pancreatitis; **low HDL-C** (<40 mg/dL men, <50 mg/dL women) is an independent risk marker but is **no longer a therapeutic target** for pharmacologic raising.

- A discordantly elevated **apoB** (relative to LDL-C) flags small-dense LDL of FCHL/metabolic syndrome and warrants aggressive therapy.

High-yield exam pointers

- **Friedewald formula** and its limitation (invalid if **TG >400 mg/dL** or in FDBL); learn **non-HDL-C = TC – HDL-C**.
- **FH** = autosomal dominant, *LDLR/APOB/PCSK9*, LDL-C usually **>190 mg/dL**, tendon xanthomas, prevalence ~**1/250**.
- **FDBL (type III)** = **apoE2/E2**, **palmar + tuberoeruptive xanthomas** (pathognomonic), chol ≈ TG, broad-β band, VLDL-C/TG ratio **>0.30**.
- **FCS** = LPL/apoC-II axis defect, TG >500 mg/dL, eruptive xanthomas, lipemia retinalis, **pancreatitis** risk.
- **Statins** first-line; **high-intensity** for ASCVD/high risk; LDL target driven by risk, treat ASCVD while LDL **>70 mg/dL**.
- Add-on order: statin → **ezetimibe** → **PCSK9 inhibitor**; **bempedoic acid** for statin-intolerant.
- **Fibrates + fish oil** for TG >500 mg/dL to prevent pancreatitis; **bile-acid resins raise TG** (avoid in HTG).
- Statin caution: myopathy risk ↑ with **gemfibrozil**, macrolides, azole antifungals, ciclosporin; slight ↑ incident diabetes outweighed by CV benefit.
- Always **exclude secondary causes** (hypothyroidism, nephrotic syndrome, DM, cholestasis, drugs) before labelling a primary genetic disorder.

SOURCE & COVERAGE

Harrison 22e — Ch 419 "Disorders of Lipoprotein Metabolism" (D.J. Rader). *Coverage note:* All classifications, drugs, doses, eponyms and numbers above are grounded in Ch 419. Harrison 22e organises dyslipidemia by **mechanism/phenotype** (severe HTG, hypercholesterolemia, mixed hyperlipidemia, low HDL) rather than the classic **Fredrickson/WHO Types I–V**; the Fredrickson scheme is included as a universally accepted parallel framework for exam completeness (Harrison explicitly names only "type III hyperlipoproteinemia" = FDBL).

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Myxoedema coma

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

Definition / Introduction — Myxedema coma is the extreme, decompensated, life-threatening end-stage of severe, long-standing **hypothyroidism**, listed in Harrison's among the rare neurologic complications of thyroid hormone deficiency (alongside reversible cerebellar ataxia, dementia, and psychosis). It is a misnomer because frank coma is often absent; the syndrome is better understood as **decompensated hypothyroidism** characterised by a depressed sensorium, **hypothermia**, and progressive multiorgan slowing, usually unmasked by a precipitating stress in an elderly, undiagnosed or non-adherent hypothyroid patient. It is an **endocrine emergency** with a high mortality, demanding empirical thyroid hormone plus glucocorticoid and intensive supportive care before biochemical confirmation returns.

Predisposing background and precipitating factors

- **Underlying substrate:** chronic untreated or under-treated hypothyroidism — most commonly **autoimmune (Hashimoto's) hypothyroidism** (TPO and Tg antibodies positive in >95%), atrophic thyroiditis, post-radioiodine or post-thyroidectomy states, and drug-induced disease (amiodarone, lithium). Onset of hypothyroidism is insidious, so many patients present already decompensated.
- **Typical patient:** elderly woman in the **winter months**; the mean age at diagnosis of autoimmune hypothyroidism is ~60 years, and prevalence rises with age.
- **Common precipitants** (these tip compensated hypothyroidism into coma):
  - **Infection / sepsis** — pneumonia, urinary sepsis (most frequent trigger).
  - **Cold exposure** — exploits the already-impaired thermogenesis.
  - **Cardiovascular events** — myocardial infarction, congestive cardiac failure.
  - **Cerebrovascular accident, trauma, surgery, GI bleeding.**
  - **CNS-depressant drugs** — sedatives, opioids, anaesthetics, antipsychotics.
  - **Abrupt cessation of levothyroxine** (patients feel no immediate difference after missing doses, predisposing to self-discontinuation, per Harrison).
- **Coexisting adrenal insufficiency** must always be anticipated — autoimmune hypothyroidism associates with **Addison's disease (Schmidt's syndrome)** and **autoimmune polyendocrine syndrome type 2** (Addison's in 40–50%).

Pathophysiology and clinical features

The picture is one of "hypo-everything" — generalised slowing of metabolism with reduced thermogenesis, blunted respiratory drive, and reduced cardiac output, plus tissue **myxedema** (glycosaminoglycan deposition that traps water → non-pitting swelling).

- **Decreased mental status:** lethargy, obtundation, stupor, frank coma; **seizures** may occur. Memory and concentration are impaired; psychosis ("myxedema madness") may precede coma.
- **Hypothermia:** core temperature may fall below 34°C; its degree correlates with prognosis, and a "normal" temperature in a hypothyroid septic patient is a red flag.

- **Hypoventilation / respiratory failure:** from **diminished ventilatory drive**, impaired respiratory muscle function, pleural effusion, and obstructive sleep apnoea (all named in the chapter) → **CO_2 retention (hypercapnia), hypoxia, and CO_2 narcosis** that deepen the coma.
- **Cardiovascular: bradycardia**, reduced myocardial contractility, reduced stroke volume and cardiac output, increased peripheral resistance with **diastolic hypertension**, and blood diverted from skin → **cool extremities**. **Pericardial effusions occur in up to 30%** (rarely tamponade); cardiomyopathy is rare. Late hypotension and shock supervene.
- **Renal / metabolic: hyponatremia** (impaired free-water excretion / SIADH-like), **hypoglycemia** (especially if concurrent adrenal failure), and free-water retention.
- **General myxedematous facies:** puffy face with **edematous eyelids**, macroglossia, non-pitting **pretibial edema**, dry coarse skin with carotene-yellow tinge, diffuse alopecia with loss of the outer third of eyebrows, hoarse voice, and **delayed relaxation of tendon reflexes** (hung-up reflexes).
- **GI:** constipation progressing to ileus / megacolon; ascites from serous cavity effusions.

Laboratory and diagnostic evaluation

- **Thyroid function:** in primary hypothyroidism, **TSH is markedly elevated** with a **low free T4**; a normal TSH essentially excludes primary disease. In **secondary (central) hypothyroidism**, TSH may be low, normal, or only slightly raised, so a **low free T4** is the confirmatory finding — do not be falsely reassured by a non-elevated TSH.
- **Supportive abnormalities** (per chapter): elevated **creatine phosphokinase (CPK)**, raised **cholesterol and triglycerides**, and **normocytic or macrocytic anemia**.
- **Other:** hyponatremia, hypoglycemia, arterial blood gas showing hypoxia + hypercapnia + respiratory acidosis; ECG — sinus bradycardia, low-voltage complexes, prolonged QT, flattened/inverted T waves.
- **Always send a paired cortisol** (and ACTH) before steroids to detect concurrent adrenal insufficiency, and a septic screen (cultures, CXR) for the precipitant.
- Diagnosis is **clinical** — treatment must not await laboratory confirmation.

Management

Myxedema coma is treated in the **ICU**; therapy is empirical and combines thyroid hormone replacement, stress-dose glucocorticoid, and aggressive supportive care directed at the precipitant.

Component	Action / regimen	Rationale & cautions
Thyroid hormone (T4)	**Levothyroxine IV loading 200–400 µg**, then **maintenance ~1.6 µg/kg/day** reduced to ~75% when given IV	Rapidly restores a hormone pool; lower loading dose in the elderly / cardiac disease to avoid precipitating ischaemia or arrhythmia
+/- Liothyronine (T3)	May add **IV T3 5–20 µg bolus then 2.5–10 µg every 8 h** until stable	Peripheral T4→T3 conversion is impaired in critical illness; T3 acts faster but risks ischaemia — use lower doses in cardiac patients

Component	Action / regimen	Rationale & cautions
Glucocorticoid	**IV hydrocortisone 50–100 mg every 8 h**	Covers coexisting adrenal insufficiency (Schmidt's syndrome / APS-2); give *before or with* thyroid hormone, as T4 can precipitate adrenal crisis
Ventilation	Airway protection, mechanical ventilation for hypercapnic/hypoxic respiratory failure	Hypoventilation + CO_2 narcosis are leading causes of death
Rewarming	**Passive external rewarming** (blankets); avoid vigorous active rewarming	Active surface rewarming causes peripheral vasodilatation → hypotension and circulatory collapse
Hyponatremia	Fluid restriction; hypertonic saline only if severe/symptomatic	Correct slowly to avoid osmotic demyelination
Hypoglycemia	IV dextrose	Common, especially with adrenal failure
Hypotension	Cautious IV fluids; vasopressors often poorly effective until thyroid hormone given	Pressors of limited benefit in hypothyroid myocardium
Precipitant	**Empirical broad-spectrum antibiotics**, treat MI/CHF, withdraw sedatives	Infection is the commonest trigger and is often occult (no fever)

- **General measures:** continuous cardiac monitoring, avoid all CNS depressants, slow careful warming, monitor electrolytes and glucose, and treat the precipitating illness aggressively.
- **Monitoring response:** clinical (mental status, temperature, respiration, heart rate) and serial TSH/free T4.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology spider diagram of myxedema coma** — central box "Severe long-standing hypothyroidism + Precipitant (infection / cold / sedatives / MI / stopping LT4)" with radiating labelled arms: **Hypothermia**, **Hypoventilation → hypercapnia / hypoxia (CO_2 narcosis)**, **Bradycardia / low cardiac output / pericardial effusion**, **Hyponatremia**, **Hypoglycemia**, **Altered sensorium → coma / seizures**, **Non-pitting myxedema / puffy facies**.
- **Management flow box** — vertical labels: *ICU + airway/ventilation → send cortisol → IV hydrocortisone 50–100 mg q8h → IV levothyroxine load 200–400 µg then 1.6 µg/kg/d → passive rewarming → correct Na^+ / glucose → empirical antibiotics → treat precipitant.*

Clinical / Diagnostic significance

- Suspect myxedema coma in any **elderly patient with unexplained hypothermia, hyponatremia and depressed consciousness**, especially with a thyroidectomy scar, myxedematous facies, or hung-up reflexes.
- It is a **clinical diagnosis and a medical emergency** — empirical thyroid hormone + glucocorticoid must begin before TSH/T4 return; delay increases mortality.

- **Never give thyroid hormone alone** when adrenal reserve is uncertain — it can accelerate cortisol clearance and trigger an Addisonian crisis; hence hydrocortisone first.
- **Mortality remains high (~20–40%)**; outcome correlates with depth of hypothermia, hypotension, and the severity of the precipitating illness — early recognition is the main determinant of survival.
- Distinguish from non-thyroidal illness ("sick euthyroid"), sedative overdose, hypothermia of other cause, and CO_2 narcosis from primary lung disease.

High-yield exam pointers

- Triad to write first: **hypothermia + altered sensorium + precipitating stress** in a known/occult hypothyroid patient.
- Commonest **precipitant = infection** (pneumonia/UTI); commonest **season = winter**; commonest **patient = elderly woman**.
- **TSH high + free T4 low** = primary; **free T4 low with non-elevated TSH** = central — do not miss it.
- Classic biochemistry: **hyponatremia, hypoglycemia, raised CPK, hypercapnia/hypoxia on ABG**; ECG bradycardia + low voltage + prolonged QT.
- Pericardial effusion in **up to 30%** of hypothyroid patients (chapter figure).
- **Hydrocortisone before/with levothyroxine** — anticipate Schmidt's syndrome (hypothyroidism + Addison's).
- **Passive (not active) rewarming** — active rewarming → vasodilatation and shock.
- **High mortality** — treat empirically in the ICU; do not wait for thyroid assays.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 395 "Hypothyroidism"** (clinical manifestations Table 395-3; cardiovascular and respiratory features; laboratory evaluation; LT4 dosing; autoimmune/Schmidt's and APS-2 associations; myxedema coma listed among rare neurologic complications).

Coverage note: The provided ch395 text grounds the definition, predisposing causes, clinical features, cardiovascular/respiratory/renal derangements, and laboratory profile, but the file is **truncated and does not contain Harrison's dedicated myxedema-coma management paragraph** (it explicitly names myxedema coma only as a rare neurologic complication, line 259). The specific emergency **management details** — IV levothyroxine loading dose 200–400 µg then ~1.6 µg/kg/d, optional liothyronine 5–20 µg, hydrocortisone 50–100 mg q8h, passive rewarming, ventilatory support, and the ~20–40% mortality figure — are therefore drawn from **universally accepted standard internal medicine** (Harrison's myxedema-coma section / CMDT, flagged here per spec `cmdt: true`) rather than verbatim from the supplied chapter text. All such figures are standard and accurate; the candidate should treat the management table as textbook-standard rather than quoted from the provided excerpt.

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SIADH

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

Definition / Introduction — The **syndrome of inappropriate antidiuresis (SIAD/SIADH)** is a disorder of water homeostasis in which arginine vasopressin (AVP/ADH) is secreted — or its renal action is sustained — at plasma osmolalities that should normally suppress it, in the *absence* of an osmotic or appropriate haemodynamic (hypovolaemic/hypervolaemic) stimulus. The cardinal biochemical hallmark is **hypotonic, euvolaemic hyponatraemia** with inappropriately concentrated urine. It is the single most common cause of hypoosmolality in clinical practice (20–40% of all hypoosmolar patients) and is fundamentally a **diagnosis of exclusion**, defined since 1967 by the **Schwartz–Bartter criteria**.

Etiology

SIAD results either from pituitary (eutopic) hypersecretion of AVP driven by CNS/pulmonary disease and drugs, or from ectopic (paraneoplastic) AVP production. A small subset have a gain-of-function *V2-receptor* mutation (**nephrogenic SIAD**) with undetectable AVP. Causes fall into five groups:

Category	Representative causes
Malignancy (ectopic AVP)	**Small-cell lung carcinoma** (≈75% of malignancy-associated SIAD; ~10% present with Na <130), mesothelioma, head & neck/oropharyngeal, GI (stomach, duodenum, pancreas), GU (ureter, bladder, prostate), thymoma, lymphoma, Ewing sarcoma
Pulmonary disease	Bacterial/viral pneumonia, **tuberculosis**, lung abscess, aspergillosis, empyema, advanced COPD, positive-pressure ventilation, respiratory failure
CNS disorders	Subarachnoid haemorrhage, head trauma, meningitis, encephalitis, brain abscess/tumour, subdural haematoma, stroke, hydrocephalus, Guillain-Barré, SLE, acute intermittent porphyria, MS
Drugs	**SSRIs**, tricyclics, carbamazepine/oxcarbazepine, chlorpropamide, vincristine, cyclophosphamide/ifosfamide, NSAIDs, antipsychotics, nicotine, clofibrate, **MDMA ("Ecstasy/Molly")**, AVP analogues (desmopressin, oxytocin)
Other	Hereditary nephrogenic SIAD (V2R gain-of-function), HIV/AIDS, prolonged endurance exercise, pain, nausea, stress, general anaesthesia, post-operative state, idiopathic (common in the **elderly**)

Pathophysiology

- Persistent AVP action on renal **V2 receptors → aquaporin-2** insertion in collecting-duct principal cells → water retention, free-water excretion fails, and intake of free water (at thirst thresholds shifted downward) generates hyponatraemia.
- **Not truly euvolaemic** but *subclinically volume-expanded*; this triggers two adaptive escapes that limit oedema: (1) **secondary natriuresis** (volume expansion, not AVP, drives urinary Na^+ loss → patients reach a new steady state in neutral Na^+ balance — the basis of so-called "renal salt wasting"), and (2) **AVP/renal escape** — hypotonicity downregulates V2-receptor and aquaporin-2 expression.
- Proximal-tubular urate and urea handling is suppressed by the volume-expanded state → characteristic **hypouricaemia (<4 mg/dL)** and low BUN (<10 mg/dL).

- **Four patterns of AVP secretion** (independent of cause): (1) random/erratic hypersecretion (~⅓); (2) non-suppressible basal AVP with normal osmotic response; (3) **reset osmostat** (left-shifted threshold; AVP suppresses and urine dilutes if Na^+ falls low enough); (4) low/undetectable AVP (**nephrogenic SIAD**, constitutive V2R activation). A fifth copeptin-defined "barostat reset" pattern is described.

Clinical features

- Reflect **cerebral oedema** from osmotic water shift into brain cells, and depend on severity and *rate* of fall in Na^+.
- **Acute** (<48 h): headache, nausea/vomiting, lethargy → seizures, obtundation, brainstem herniation, neurogenic (non-cardiogenic) pulmonary oedema, coma, death. Premenopausal women are especially vulnerable.
- **Chronic** (>48 h): often labelled "asymptomatic" owing to brain organic-osmolyte efflux/volume regulation, but causes subtle gait/cognitive impairment, **falls, fractures** (with reduced bone density) and increased mortality.

Evaluation / Diagnosis

Schwartz–Bartter diagnostic criteria (essential):

- **Decreased effective plasma osmolality** (<275 mOsm/kg; exclude pseudo- and translocational hyponatraemia).
- **Inappropriate urinary concentration** — urine osmolality >100 mOsm/kg (not maximally dilute) at some level of hypoosmolality.
- **Clinical euvolaemia** (no orthostasis/tachycardia/dry membranes; no oedema/ascites).
- **Elevated urinary sodium** (>30–40 mmol/L) on normal salt and water intake.
- **Exclusion** of hypothyroidism, glucocorticoid deficiency (secondary/primary adrenal insufficiency), renal failure and diuretic use.

Supportive (non-essential): hypouricaemia (<4 mg/dL), low BUN, failure to excrete a standard water load, and AVP/copeptin inappropriately elevated for osmolality. **Measurement of AVP/copeptin is generally NOT clinically useful** (10–20% have undetectable AVP; levels overlap with hypovolaemic states).

Key investigations: serum osmolality (exclude pseudohyponatraemia from hyperlipidaemia/hyperproteinaemia and translocational from hyperglycaemia/mannitol), paired urine osmolality and **urine Na^+**, serum uric acid, BUN/creatinine, glucose, **TFT and 0900 cortisol/short Synacthen test**, and imaging (chest CT for occult small-cell lung cancer in smokers; MRI brain) to find the cause.

Critical differentials by urine Na^+ and volume status:

- **Cerebral salt wasting (CSW)** — hypovolaemic hyponatraemia with high urine Na^+ in intracranial disease (esp. SAH); distinguished by *clinical hypovolaemia* and *responds to saline repletion* (the opposite of SIAD). Modern series suggest true CSW is exceedingly rare; most SAH hyponatraemia is SIAD.
- **Hypovolaemic** hyponatraemia (urine Na^+ <20–30; hyperuricaemic) corrects with normal saline.

- **Hypervolaemic** hyponatraemia (heart failure, cirrhosis; urine Na^+ <10).
- **Glucocorticoid deficiency** and **hypothyroidism** mimic SIAD and must be excluded first.

Management

1. Acute / severely symptomatic (seizures, coma) — medical emergency:

- **Hypertonic 3% NaCl (513 mmol/L)**: a **100-mL bolus over ~10–15 min**, repeated up to 2–3 times until symptoms abate; each bolus raises Na^+ by ~1–2 mmol/L. Aim for a prompt rise of only **4–6 mmol/L** — sufficient to relieve cerebral oedema. Less severe symptoms: 3% saline 0.5–2 mL/kg/h.
- Monitor serum Na^+ **every 1–2 h**; supplemental O_2/ventilatory support for neurogenic pulmonary oedema.

2. Chronic hyponatraemia — treat the cause + raise Na^+ safely:

- Withdraw causative drugs; treat tumour/pneumonia; replace glucocorticoid/thyroid if deficient.
- **Fluid restriction (500–1000 mL/day, all fluids)** is first-line but often fails. The **Furst ratio (UNa + UK)/PNa >1** (i.e. urine osmolality >500 mOsm/L) predicts failure → escalate.
- **Increase solute load:** oral salt tablets ± **furosemide 20 mg BD** (blunts the medullary gradient); **oral urea 30–60 g/day** (osmotic aquaresis; palatable bicarbonate/citrate formulations).
- **AVP-receptor antagonists (vaptans): tolvaptan** (oral V2 antagonist; low-dose **7.5 mg** preferred to limit overcorrection) and **conivaptan** (IV V1A/V2). Start in hospital, *liberalise fluids >2 L/day*, monitor closely; limit duration to **<1–2 months** (hepatotoxicity); avoid in cirrhosis.
- **SGLT2 inhibitors** (glycosuric osmotic diuresis) raise Na^+ in SIAD and **demeclocycline** (induces nephrogenic DI; nephrotoxic, photosensitivity — avoided in cirrhosis) are alternatives.

3. Avoid osmotic demyelination syndrome (ODS):

- Do **not** correct Na^+ by **>8 mmol/L in 24 h** (and <18 mmol/L over 48 h); high-risk patients (Na^+ <120, alcoholism, malnutrition, **hypokalaemia**, liver disease) target only **4–6 mmol/L/day**.
- Correct hypokalaemia cautiously (raises Na^+ independently). If overcorrection occurs/anticipated, **re-lower** with IV 5% dextrose and/or a **DDAVP "clamp"** (desmopressin) to prevent aquaresis.
- ODS (central pontine + extrapontine myelinolysis) presents 2–6 days later with dysarthria, dysphagia, para-/quadriparesis, "locked-in" syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic algorithm for hyponatraemia** (flowchart): Box "Hyponatraemia (Na^+ <135) → measure serum osmolality" → branches: *Pseudo/translocational* (normal/high osm) vs *True hypotonic* (<275). Hypotonic branch → assess **volume status**: **Hypovolaemic** (Urine Na^+ <20 = extrarenal loss; >20 = renal loss/diuretics/Addison/CSW) | **Euvolaemic** (Urine Na^+ >20 → exclude hypothyroidism, glucocorticoid deficiency → **SIAD**) | **Hypervolaemic** (CHF, cirrhosis, nephrotic, renal failure). Label each box with the urine Na^+ cut-off.
- **SIAD pathophysiology loop:** *AVP → V2 receptor → aquaporin-2 ↑ → water retention → ↓plasma Na^+/osmolality + subclinical volume expansion → secondary natriuresis (high urine Na^+) + AVP/renal escape (AQP2 down-regulation)*. Label: AVP, V2 receptor, AQP2, collecting duct, hypouricaemia.

Clinical / Diagnostic significance

- **Hypouricaemia (<4 mg/dL)** and **low BUN** are quick bedside discriminators of SIAD from hypovolaemic hyponatraemia (which is hyperuricaemic).
- New-onset unexplained SIAD in a smoker mandates **CT thorax** to exclude **small-cell lung cancer**.
- Always **exclude adrenal insufficiency and hypothyroidism** before labelling SIAD — glucocorticoid replacement alone may correct euvolaemic hyponatraemia from secondary adrenal failure.
- **Thiazide-induced** hyponatraemia mimics SIAD; defer the SIAD diagnosis until 1–2 weeks after stopping the thiazide.
- The *rate* of correction, not just the target, governs outcome — ODS is iatrogenic and preventable.

High-yield exam pointers

- SIAD = **euvolaemic hypotonic hyponatraemia + inappropriately concentrated urine + high urine Na^+ + hypouricaemia**; a **diagnosis of exclusion**.
- **Schwartz–Bartter (1967):** ↓plasma osm <275, urine osm >100, euvolaemia, urine Na^+ >40, exclude thyroid/adrenal/renal/diuretic causes.
- **SCLC** = commonest malignant cause (75%); **SSRIs/carbamazepine** = commonest drug causes; **SAH** classic CNS cause.
- **Four AVP patterns**, including **reset osmostat** and AVP-negative **nephrogenic SIAD** (V2R gain-of-function).
- Acute symptomatic: **3% saline 100 mL bolus**, target rise **4–6 mmol/L**; chronic: **fluid restriction → urea/tolvaptan 7.5 mg/SGLT2i**.
- **Never correct >8 mmol/L/24 h** (4–6 in high-risk) → prevents **osmotic demyelination (central pontine myelinolysis)**.
- **Distinguish CSW** (hypovolaemic, saline-responsive) from SIAD; **AVP/copeptin assay is not diagnostically useful**.
- Overcorrection → re-lower with **D5W ± DDAVP clamp**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Fluid and Electrolyte Disturbances" (hyponatraemia classification, SIAD pathophysiology, causes table, diagnostic approach and treatment including hypertonic saline, vaptans, urea, furosemide, ODS/correction limits) and "Disorders of the Neurohypophysis" (SIAD clinical features, differential diagnosis, treatment — 100-mL 3% saline bolus, urea, tolvaptan 7.5 mg, demeclocycline, SGLT2 inhibitors).
- **Williams Textbook of Endocrinology, 15e** — "Posterior Pituitary" (Schwartz–Bartter criteria, four/five patterns of AVP secretion, nephrogenic SIAD, secondary natriuresis, renal escape/aquaporin-2, cerebral salt wasting, therapy principles, ODS correction goals).
- **CMDT 2026** — "Electrolyte & Acid-Base Disorders" (SIADH diagnostic criteria, Furst ratio, symptomatic vs chronic management, vaptans/urea/SGLT2i, ODS risk factors and correction limits, DDAVP clamp).

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Obesity

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

Definition / Introduction — Obesity is a chronic, relapsing, multifactorial disease defined as *a state of excess adipose-tissue mass that adversely affects health*. Because direct fat measurement is impractical, the **body-mass index (BMI = weight in kg / height in m^2)** is used as a proxy: the WHO classifies BMI ≥30 kg/m^2 as obesity and 25–29.9 kg/m^2 as overweight. It arises from a sustained imbalance of energy intake over expenditure on a strong genetic and obesogenic-environmental background, and it predisposes to type 2 diabetes, cardiovascular disease, several cancers and reduced life expectancy.

Etiology and Pathogenesis

- **Fundamental basis — energy imbalance:** Obesity develops when energy intake chronically exceeds expenditure; because it is *cumulative*, a surplus as small as ~**7 kcal/day** can produce obesity over years. Excess energy is stored as triglyceride in the unilocular lipid droplet of adipocytes (and ~10% of fat cells turn over yearly).
- **Genetic predisposition:** Twin/adoption studies show adiposity is strongly heritable (CMDT: genetics explain 40–90% of weight variation). Up to **20% of children with severe obesity** carry a chromosomal abnormality or highly penetrant mutation. Most common obesity is **polygenic**.
- **Leptin–melanocortin (central) pathway** — the hypothalamus integrates signals of energy stores:
  - **Leptin** (from adipose tissue) rises with fat mass; a *fall* below habitual level is a powerful drive to eat. It stimulates **POMC** neurons in the arcuate nucleus and inhibits **AGRP/NPY/GABA** neurons.
  - POMC-derived **α-/β-MSH act on the MC4 receptor** in the paraventricular nucleus → ↓intake and ↑expenditure; *AGRP* antagonises MC4R. *BDNF/TrkB* and *SIM1* act downstream.
  - **"Leptin resistance"** at high levels (blunted response to leptin excess) explains why leptin does not prevent obesity.

- **Gut/pancreatic (peripheral) signals: Ghrelin** (stomach) increases hunger pre-meal; **GLP-1, GIP, PYY, oxyntomodulin, CCK** and **insulin/amylin** promote satiety after a meal — the rationale for incretin-based drugs.
- **Monogenic obesity** (severe, early-onset, hyperphagic): mutations in **leptin** (treatable with recombinant leptin), **leptin receptor, POMC** (with red hair, ACTH deficiency), **PCSK1, carboxypeptidase E, MC4R** (the *commonest* — heterozygous variants in 5–6% of severe early-onset obesity, ~1 in 300 of the population), **SIM1, BDNF, TrkB, SH2B1**.
- **Syndromic obesity: Prader-Willi** (commonest syndrome, ~1 in 25,000; paternal chromosome-15 deletion; hypotonia, hyperphagia, hypogonadism), **Bardet-Biedl** (AR ciliopathy; polydactyly, retinal dystrophy, renal disease), **Albright hereditary osteodystrophy / pseudohypoparathyroidism** (*GNAS1*), Cohen, Carpenter, Alström, Tubby.
- **Secondary / acquired causes** — always exclude:
  - Endocrine: **hypothyroidism, Cushing's syndrome, PCOS, insulinoma, hypothalamic damage** (craniopharyngioma, trauma, inflammation).
  - **Drug-induced:** insulin, sulfonylureas, thiazolidinediones; glucocorticoids; antipsychotics (clozapine, olanzapine, risperidone); lithium; antidepressants (tricyclics, MAOIs, paroxetine, mirtazapine); antiepileptics (valproate, gabapentin, carbamazepine).
- **Obesogenic environment:** cheap, energy-dense, aggressively-marketed food in large portions, plus mechanisation, sedentary work and reduced thermoregulatory expenditure — drives the population-level rise.

Clinical Features

- **Anthropometric:** raised BMI; **central (android) adiposity** — increased waist circumference and **waist-to-hip ratio >0.9 in women, >1.0 in men** (independent marker of metabolic risk).
- **Symptoms of excess mass:** exertional dyspnoea, fatigue, mechanical low-back pain and knee pain, immobility, daytime somnolence/snoring (sleep apnoea).
- **Skin: acanthosis nigricans** (velvety hyperpigmentation of axilla/groin/nape — marker of hyperinsulinaemia), skin tags (acrochordons), striae distensae, intertrigo/fungal infection, **hidradenitis suppurativa**, stasis pigmentation, lymphoedema.
- **Reproductive:** in women — irregular menses, anovulatory infertility, hirsutism (PCOS); in men — **central hypogonadism** with low testosterone and inappropriately low/normal LH-FSH.
- **Distribution matters:** visceral/central obesity carries far higher cardiometabolic risk than gluteofemoral (lower-body) fat — the latter being relatively protective.

Diagnosis and Evaluation

The four steps are: (1) obesity-focused **history**, (2) **physical examination** for degree and type of obesity, (3) assessment of **complications/comorbidities**, and (4) assessment of **readiness to change** (motivational interviewing, 0–10 confidence/importance scale). Use neutral language ("weight," "BMI," "unhealthy weight").

Classification	BMI (kg/m²)	Obesity class	Disease risk
Underweight	<18.5	—	—

Classification	BMI (kg/m²)	Obesity class	Disease risk
Healthy weight	18.5–24.9	—	—
Overweight	25.0–29.9	—	Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

- **BMI limitations:** measures size, not body composition/fat distribution; over-estimates fat in the very muscular; **lower thresholds apply to Asia-Pacific populations** (risk at lower BMI).
- **Waist circumference** (surrogate for visceral fat; measure horizontally above iliac crest, most useful when BMI ≤35) — **ethnic-specific cut-offs:** Europeans — men >94 cm, women >80 cm; **South Asians & Chinese — men >90 cm, women >80 cm**; Japanese — men >85 cm, women >90 cm.
- **Routine investigations for all:** fasting lipid profile (total, LDL, HDL, triglycerides), chemistry panel, **HbA1c**, blood pressure; thyroid function (TSH) and, where suspected, screening for Cushing's (24-h urine free cortisol / dexamethasone suppression), PCOS work-up and obstructive-sleep-apnoea screening.
- **Severity staging (beyond BMI):**
  - **AACE/ACE staging:** Stage 0 = obesity by BMI, no complications; Stage 1 = ≥1 mild–moderate complication; Stage 2 = ≥1 severe complication — guides aggressiveness of therapy.
  - **Edmonton Obesity Staging System (EOSS):** five grades (0–4) across **medical, functional and psychological** domains, *independent of BMI*.

Complications

- **Metabolic/endocrine:** insulin resistance/hyperinsulinaemia, **metabolic syndrome, type 2 diabetes**, atherogenic **dyslipidaemia** (high triglycerides, low HDL), hyperuricaemia/**gout**, PCOS, male hypogonadism.
- **Cardiovascular:** hypertension, coronary artery disease, stroke, **heart failure (diastolic dysfunction/HFpEF)**, atrial fibrillation, varicose veins, venous thromboembolism.
- **Respiratory: obstructive sleep apnoea**, obesity-hypoventilation (**Pickwickian**) syndrome, asthma, cor pulmonale, exertional dyspnoea.
- **Hepato-gastrointestinal: MAFLD/NAFLD → NASH → fibrosis/cirrhosis/HCC**, GERD/reflux oesophagitis, cholelithiasis (and cholecystitis, pancreatitis, gallbladder cancer), hernias.
- **Musculoskeletal: osteoarthritis** of knees/hips, low back pain, carpal tunnel syndrome, immobility.
- **Malignancy:** colorectal, kidney, pancreatic, oesophageal adenocarcinoma, and (in women) endometrial and breast cancer — each 5 kg/m² BMI rise raises cancer mortality ~10%.

- **Neuro-psychological: idiopathic intracranial hypertension**, meralgia paraesthetica, increased dementia and stroke risk; depression, low self-esteem, body-image disturbance, social stigmatisation.
- **Renal/GU:** obesity-related glomerulopathy, stress incontinence, pregnancy complications.
- **Other:** worse outcomes from infection (e.g., SARS-CoV-2), surgical-wound infection; rare association with thrombotic thrombocytopenic purpura.

Management

Therapy is escalated by BMI category and comorbidity (Table 414-4): lifestyle for all, drugs from BMI ≥27 with comorbidity / ≥30, surgery from BMI ≥35 with comorbidity / ≥40. A realistic initial goal is 8–10% loss over 6 months; even 5–10% loss yields dose-related improvement in glycaemia, BP and lipids.

- **1. Lifestyle management** (modest ~3–5 kg loss; the foundation):
  - **Diet:** create a deficit of **500–750 kcal/day** (≈1200–1500 kcal/day for women, 1500–1800 for men) targeting ~1–2 lb/week loss; macronutrient ratio matters less than total calorie reduction and adherence; use low-energy-density foods, meal replacements; **very-low-calorie diets (≤800 kcal/day)** for selected motivated patients (e.g., DiRECT trial achieved diabetes remission).
  - **Physical activity: 150 min/week moderate (or 75 min vigorous)**; **>300 min/week** often needed to lose and maintain; key role in *maintenance*; reduce sedentary time.
  - **Behavioural therapy / CBT:** self-monitoring, stimulus control, stress management, problem-solving, cognitive restructuring.
- **2. Pharmacotherapy** (BMI ≥30, or ≥27 with comorbidity; adjunct to lifestyle):

Drug	Mechanism	Note (placebo-subtracted weight loss)
Phentermine	Sympathomimetic (↑CNS noradrenaline)	Short-term use only; ~4.4%
Orlistat 120 mg tid	GI lipase inhibitor (blocks ~30% dietary fat)	Steatorrhoea; supplement fat-soluble vitamins; ~4.1%
Phentermine/ topiramate	Sympathomimetic + GABA/carbonic-anhydrase	~8.0%; **teratogenic (oral cleft)**
Naltrexone SR/bupropion SR	Opioid antagonist + DA/NA reuptake inhibitor (POMC activation)	~5.1%
Liraglutide 3.0 mg SC daily	GLP-1 receptor agonist	~5.4%
Semaglutide 2.4 mg SC weekly	GLP-1 receptor agonist	~12.5%; **SELECT trial: 20% ↓ MACE**
Tirzepatide SC weekly	Dual **GLP-1/GIP** agonist	~17.8% (SURMOUNT) — most effective
Setmelanotide SC	MC4R agonist	For monogenic/syndromic obesity (POMC, PCSK1, LEPR, Bardet-Biedl)

GLP-1/GIP agonists are contraindicated with personal/family history of medullary thyroid carcinoma or MEN-2; pancreatitis is a caution. Common adverse effects are gastrointestinal (nausea, vomiting, diarrhoea, constipation).

- **3. Bariatric/metabolic surgery** (BMI ≥40, or ≥35 with comorbidity):
  - **Restrictive:** laparoscopic adjustable gastric banding (largely abandoned); **sleeve gastrectomy** (~80% greater curvature removed).
  - **Restrictive-malabsorptive: Roux-en-Y gastric bypass**, biliopancreatic diversion ± duodenal switch — typically **28–33% total-body-weight loss**.
  - Benefits act partly via altered gut hormones (ghrelin, GLP-1, PYY); **Swedish Obese Subjects study: 78% reduction in incident type 2 diabetes**; reduced all-cause and cardiovascular mortality. Mortality usually <1%.
  - Risks: stomal stenosis/marginal ulcer (RYGB), and **lifelong micronutrient deficiency (vitamin B12, iron, folate, calcium, vitamin D)** after malabsorptive procedures.
- **4. Endoscopic options** (treatment gap / poor surgical candidates): intragastric balloon (6–12% loss, removed at 6 months); **endoscopic sleeve gastroplasty** (~18% at 2 years).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hypothalamic energy-balance circuit:** Adipose tissue → **Leptin** → **Arcuate nucleus** (stimulates **POMC**, inhibits **AGRP/NPY**) → **α/β-MSH** → **MC4R** in **Paraventricular nucleus** → "↓Food intake, ↑Energy expenditure"; gut hormones into **brainstem** — label **Ghrelin (stomach, hunger), GLP-1, GIP, PYY, CCK, oxyntomodulin, Insulin, Amylin, Vagus nerve**.
- **Obesity-complication body map:** central figure labelled with **Dementia/Stroke, Sleep apnoea, Hypertension, Ischaemic heart disease, Heart failure, NAFLD/NASH, Type 2 diabetes, Dyslipidaemia, Gallstones, Reflux oesophagitis, PCOS, Osteoarthritis, Gout, Cancers (oesophagus/colon/endometrium/pancreas/kidney)**.

Clinical / Diagnostic significance

- Use **BMI + waist circumference + complication staging** together — BMI alone under-estimates risk in South Asians, hence the lower waist cut-offs (men >90 cm, women >80 cm) relevant to Indian practice.
- **Acanthosis nigricans** at the bedside flags insulin resistance and warrants HbA1c/lipids.
- Always **screen for and treat secondary/iatrogenic causes** (thyroid, Cushing's, obesogenic drugs) before labelling "simple" obesity.
- Weight loss is **disease-modifying**: 5–10% improves glycaemia/BP/lipids; semaglutide (SELECT) and bariatric surgery (SOS) provide *hard cardiovascular and diabetes outcome* benefit.

High-yield exam pointers

- BMI ≥30 = obesity; ≥40 = extreme (class III); Asia-Pacific thresholds are lower.
- Waist-hip ratio **>0.9 (women), >1.0 (men)** = adverse risk; visceral > subcutaneous fat for metabolic harm.

- **MC4R** = commonest monogenic obesity gene; **Prader-Willi** = commonest syndromic cause.
- **Leptin deficiency is the only fully treatable monogenic obesity** (recombinant leptin); leptin-receptor deficiency is not.
- **Setmelanotide** (MC4R agonist) for POMC/PCSK1/LEPR/Bardet-Biedl obesity.
- Drug ladder potency: **tirzepatide > semaglutide > phentermine-topiramate > liraglutide ≈ naltrexone-bupropion > orlistat/phentermine.**
- GLP-1/GIP agonists contraindicated in **MEN-2 / medullary thyroid cancer**.
- Surgery thresholds: **BMI ≥40, or ≥35 with comorbidity**; RYGB/sleeve give 28–33% weight loss; supplement **B12, iron, folate, Ca, vitamin D** lifelong.
- Treatment target: **8–10% loss over 6 months**; even **5% improves comorbidities.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Pathobiology of Obesity"* (O'Rahilly & Farooqi; etiology, leptin-melanocortin pathway, monogenic/syndromic causes, complications) and *"Evaluation and Management of Obesity"* (Kushner; classification tables, AACE/ACE & Edmonton staging, antiobesity drugs, bariatric surgery).
- **CMDT 2026** — *"Nutrition, Nutritional Disorders, & Obesity"* (diagnostic approach, weight-loss thresholds, pharmacotherapy and surgical/endoscopic referral criteria).
- Coverage note: All specifics (BMI/waist cut-offs, drug doses and placebo-subtracted weight-loss figures, trial names — DiRECT, SELECT, SURMOUNT, STEP, SOS) are verbatim from the Harrison and CMDT obesity chapters. The dedicated subspecialty text (Williams Textbook of Endocrinology, "Obesity and Neuroendocrine Control of Energy Stores") was consulted but added no specifics beyond those already grounded above; corpus coverage of this topic is thorough.

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Diabetic peripheral neuropathy

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

Definition / Introduction — Diabetic neuropathy is a group of clinically distinct syndromes resulting from damage to peripheral somatic and autonomic nerves by chronic hyperglycaemia and associated metabolic-syndrome factors. It occurs in roughly **50% of individuals with long-standing type 1 or type 2 DM** and is the most common cause of peripheral neuropathy in the developed world. **Distal symmetric polyneuropathy (DSPN)** is by far the commonest form. Diagnosis is essentially clinical and is one of *exclusion* — other causes (B12 deficiency, paraproteinaemia, hypothyroidism, alcohol) must be ruled out before attributing neuropathy to diabetes.

Classification (ADA / Toronto Consensus)

- **A. Diffuse neuropathy** (commonest group)
  - **Distal symmetric polyneuropathy (DSPN)** — small-fibre predominant, large-fibre predominant, or *mixed* (most common).

- **Autonomic neuropathy** — cardiovascular (CAN), gastrointestinal, urogenital, sudomotor, hypoglycaemia unawareness, abnormal pupillary function.

- **B. Mononeuropathy / mononeuritis multiplex** — isolated cranial (III, IV, VI, VII) or peripheral nerve (median, ulnar, peroneal, femoral); entrapment syndromes.
- **C. Radiculopathy / polyradiculopathy** — lumbosacral radiculoplexus neuropathy (*diabetic amyotrophy / Bruns–Garland syndrome*), thoracic (truncal) radiculopathy.
- Special form: **treatment-induced neuropathy of diabetes (TIND / "insulin neuritis")** — acute painful small-fibre neuropathy after rapid glycaemic correction.

Risk factors and pathogenesis

- **Risk factors:** duration of diabetes and poor glycaemic control (HbA1c); high BMI/central obesity; smoking; coexistent retinopathy and nephropathy; hypertension, hypertriglyceridaemia and ASCVD. In T2D the wider **metabolic syndrome** drives neuropathy as much as glucose itself.
- **Pathogenesis** — hyperglycaemia-driven microvascular and metabolic injury to both myelinated and unmyelinated fibres, with a unifying theme of mitochondrial **oxidative stress / bioenergetic failure**:
  - **Polyol pathway** — aldose reductase (AKR1B1) reduces glucose to **sorbitol** (then fructose via sorbitol dehydrogenase), consuming NADPH and depleting glutathione.
  - **Advanced glycation end-products (AGEs)** — the dicarbonyl **methylglyoxal** modifies proteins and, via **Nav1.8** sodium channels on C-fibres, contributes to neuropathic pain; AGE –RAGE signalling activates inflammation.
  - **Protein kinase C (PKC)** activation and flux through the **hexosamine pathway**.
  - Defective resolution of inflammation and nerve ischaemia (vasa nervorum) — relevant to acute mononeuropathies.

Clinical features

- **DSPN:** insidious **stocking-and-glove** sensory loss beginning in the toes, ascending up the legs and later into the fingers ("length-dependent"). Small-fibre symptoms — burning, tingling, lancinating/stabbing pain, hyperaesthesia, dysaesthesia — typically *worse at rest and at night*. Up to **50% are asymptomatic**, making screening essential. As it progresses pain may subside, leaving sensory deficit, **loss of protective sensation (LOPS)**, and later motor signs (foot-drop, small-muscle wasting, clawing of toes).
- Signs: reduced 10-g monofilament/vibration perception, **absent ankle reflexes**, impaired proprioception, distal weakness, foot deformity.
- **Autonomic:** resting tachycardia, reduced heart-rate variability, **orthostatic hypotension**, gastroparesis, diabetic diarrhoea/constipation, neurogenic bladder (cystopathy), erectile dysfunction/retrograde ejaculation, anhidrosis of feet with hyperhidrosis of trunk, **hypoglycaemia unawareness**, prolonged QTc and risk of sudden death.
- **Mononeuropathy:** acute painful **third-nerve palsy** that is *pupil-sparing* (ptosis + ophthalmoplegia, pupil intact), or VI/IV/VII (Bell's) palsy; self-limiting over 6–12 weeks.

- **Diabetic amyotrophy (Bruns–Garland):** severe unilateral low-back/hip/thigh pain with proximal quadriceps wasting and weakness, often heralded by marked weight loss; raised CSF protein and ESR; gradual self-limited recovery over 6–18 months.
- **Diabetic neuropathic cachexia:** symmetric painful neuropathy with profound weight loss; good prognosis, recovers within ~1 year.

Evaluation and diagnosis

- **When to screen:** annual examination beginning **5 years after diagnosis of T1DM** and **at diagnosis of T2DM**, aimed at detecting LOPS (the major risk factor for ulceration, falls and amputation).
- **Bedside small-fibre tests** — pinprick (sharp/dull discrimination on dorsum of toe), temperature (cool tuning-fork on cheek vs toe), cotton-wisp light touch.
- **Bedside large-fibre tests** — **128-Hz tuning-fork** vibration at the great toe, ankle (Achilles) reflexes, proprioception at the first MTP joint.
- **10-g Semmes–Weinstein monofilament (5.07 filament)** — assesses LOPS / ulcer risk; recommended as a **three-site test** (plantar great toe, 3rd and 5th metatarsal heads).
- **Validated screening scores:** Michigan Neuropathy Screening Instrument (MNSI), Modified Toronto Clinical Neuropathy Score, Neuropathy Impairment Score, Utah Early Neuropathy Score; questionnaires (DN4, LANSS) help identify *neuropathic pain*.
- **Confirmatory / atypical-case tests:**
  - **Nerve conduction studies (NCS)** — gold standard for **large-fibre** neuropathy; reduced amplitudes with mild–moderate slowing (sural, peroneal, tibial). Sural abnormality plus one other nerve = large-fibre neuropathy.
  - **Intra-epidermal nerve-fibre density (IENFD)** on 3-mm skin punch biopsy (PGP 9.5 staining) — gold standard for **small-fibre** neuropathy.
  - Quantitative sensory testing, autonomic testing (heart-rate variability, QSART/sudomotor, sympathetic skin response), corneal confocal microscopy (research).
- **Toronto Consensus severity grading:** *possible* → *probable* (≥2 of: neuropathic symptoms, decreased distal sensation, reduced/absent ankle reflexes) → *confirmed* (symptom/sign **plus** abnormal NCS or validated small-fibre measure) → *subclinical* (abnormal tests, no symptoms/signs).
- **Exclude mimics (AAN):** serum protein electrophoresis with immunofixation, **vitamin B12** (metformin lowers B12), TFTs; consider HIV, alcohol, paraneoplastic. Up to **10% of neuropathy in diabetics is non-diabetic** (Rochester study). *Red flags for an alternative diagnosis:* asymmetry, motor > sensory involvement, or rapid/aggressive course.

Treatment

- **A. Disease-modifying / preventive (the foundation):**
  - **Glycaemic control** — tight, near-normal glycaemia *prevents and slows* DSPN dramatically in **T1DM** (DCCT). In **T2DM** intensive glucose control alone is only **modestly effective**; multifactorial risk-factor control is required.

- **Treat the metabolic syndrome** — dyslipidaemia, hypertension, hypertriglyceridaemia, obesity; smoking and alcohol cessation; exercise and weight loss; correct B12/folate deficiency.
- **Caution:** lower HbA1c gradually — a fall **>1% per month** risks treatment-induced neuropathy (TIND) and accelerated retinopathy.
- **Foot protection** — daily foot inspection, appropriate footwear/accommodative insoles, callus/ulcer prevention, podiatry referral; mechanical off-loading and debridement for neuropathic ulcers.

▸ **B. Symptomatic treatment of painful DSPN** — start one agent, titrate to effect or side-effects, then add a second from a different class; ~two-thirds obtain relief:

- **Voltage-gated α2δ ligands — pregabalin** (50–100 mg tid; FDA-approved) and **gabapentin** (300–1200 mg tid).
- **SNRIs — duloxetine** (30–60 mg/day; FDA-approved), venlafaxine (37.5–150 mg/day).
- **Tricyclic antidepressants** — secondary amines preferred: amitriptyline / **nortriptyline / desipramine** (10–100 mg qhs); limited by anticholinergic effects.
- **Topical** — 5% **lidocaine** patch, **capsaicin** 0.075% cream; **alpha-lipoic acid** 600 mg/day (antioxidant, used in Europe); TENS as adjuvant.
- **Sodium-channel blockers** (carbamazepine, mexiletine) as later-line; treat coexistent sleep and mood disorders.
- **Tapentadol** is FDA-approved but, like other **opioids, is discouraged** (modest efficacy, addiction risk) — refer to a pain clinic if uncontrolled.

Class	Examples	Typical dose
α2δ ligand	Pregabalin / Gabapentin	50–100 mg tid / 300–1200 mg tid
SNRI	Duloxetine / Venlafaxine	30–60 mg/day / 37.5–150 mg/day
TCA	Amitriptyline / Nortriptyline	10–100 mg qhs
Topical	Lidocaine 5% patch / Capsaicin 0.075%	Apply to painful area

▸ **C. Autonomic neuropathy (organ-directed):**

- **Orthostatic hypotension** — adequate salt/fluids, compression stockings, head-up tilt, slow standing; **fludrocortisone** 0.1–0.2 mg/day, **midodrine** 10 mg tid, droxidopa.
- **Gastroparesis** — small, frequent low-fat/low-fibre meals; **metoclopramide** (short-term), **erythromycin** 250 mg tid (motilin agonist); avoid opioids/GLP-1 agonists; gastric electrical stimulation in refractory cases.
- **Diabetic diarrhoea** — rifaximin/metronidazole if bacterial overgrowth, loperamide; constipation — stimulant laxatives.
- **Cystopathy** — scheduled voiding, bethanechol, self-catheterisation.
- **Erectile dysfunction — PDE5 inhibitors** (sildenafil, tadalafil, vardenafil); contraindicated with nitrates.

- **D. Focal forms:** mononeuropathies and amyotrophy are largely self-limiting (analgesia + glycaemic control); entrapment (carpal tunnel) — wrist splint, NSAIDs, surgical decompression; glucocorticoids are sometimes used for severe radiculoplexus pain (unproven).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Stocking-and-glove sensory loss diagram** — outline of a body with shaded distal lower limbs (feet/calves) and hands/fingers; labels: *Distal symmetric "stocking-and-glove" pattern*, *length-dependent (longest nerves first)*, *small fibres (pain/temperature) before large fibres (vibration/proprioception)*.
- **Foot examination / screening sites** — sole of foot showing the **three monofilament test sites** (plantar great toe, 3rd metatarsal head, 5th metatarsal head); add labels: *10-g Semmes–Weinstein monofilament (LOPS)*, *128-Hz tuning fork at great toe (vibration)*, *Achilles reflex*, *pinprick/temperature (small fibre)*.

Clinical / Diagnostic significance

- DSPN with LOPS is the leading cause of **foot ulceration, Charcot neuroarthropathy ("rocker-bottom" foot) and non-traumatic lower-limb amputation** — annual foot screening is mandatory.
- **Cardiovascular autonomic neuropathy (CAN)** predicts silent ischaemia, perioperative instability, prolonged QTc and **sudden death** — assess heart-rate variability and orthostatic BP.
- Always exclude mimics (B12, paraproteinaemia, hypothyroidism) — ~10% of "diabetic" neuropathy is non-diabetic; atypical features mandate neurology referral and NCS.
- Pre-operative cardiac evaluation is prudent because **silent ischaemia** is common in autonomic neuropathy.

High-yield exam pointers

- Occurs in **~50%** of long-standing DM; **DSPN** is the commonest form; up to **50% asymptomatic**.
- Screen **annually**: from **5 years** after T1DM diagnosis and **at diagnosis** of T2DM.
- **10-g Semmes–Weinstein monofilament (5.07)** detects LOPS; **128-Hz tuning fork** tests large fibre; **IENFD on skin biopsy** = gold standard for small-fibre; **NCS** = gold standard for large-fibre.
- **Toronto Consensus:** possible → probable → confirmed → subclinical.
- Diabetic **3rd-nerve palsy is pupil-sparing**; **diabetic amyotrophy = Bruns–Garland syndrome**.
- Tight glycaemic control prevents DSPN strongly in **T1DM**, only modestly in **T2DM**.
- Painful DSPN first-line classes: **α2δ ligands (pregabalin/gabapentin), SNRIs (duloxetine), TCAs**; FDA-approved = pregabalin, duloxetine, tapentadol; **avoid opioids**.
- Avoid lowering HbA1c **>1%/month** — risk of **treatment-induced neuropathy (TIND / "insulin neuritis")**.
- Orthostatic hypotension: **midodrine / fludrocortisone**; gastroparesis: **metoclopramide / erythromycin**; ED: **PDE5 inhibitors**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Complications" and "Peripheral Neuropathy" (including Table: *Treatment of Painful Sensory Neuropathies*).
- **Williams Textbook of Endocrinology, 15e** — "Complications of Diabetes Mellitus" (diabetic neuropathies — classification per ADA/Pop-Busui position statement, Toronto Consensus criteria, Box 38.3 diagnosis, disease-modifying and painful-DSPN treatment, pathogenesis: polyol pathway/AGEs/PKC/hexosamine).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycemia" (current management of peripheral and autonomic neuropathy, Charcot foot, drug doses).

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Gestational diabetes mellitus

Asked in: Paper IV Dec 2023 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Gestational diabetes mellitus (GDM) is glucose intolerance with onset or first recognition during the **second or third trimester** of pregnancy that is not clearly overt (pre-existing) diabetes. It complicates roughly **8% of pregnancies** (the International Diabetes Federation estimated in 2021 that **~16% of pregnancies worldwide** are affected by GDM or pre-existing diabetes), and it arises when maternal pancreatic β-cell insulin secretion fails to compensate for the physiological insulin resistance of pregnancy. By current **ADA** convention, hyperglycaemia *diagnosed in the first trimester* is reclassified as **pre-existing (pregestational) diabetes**, not GDM. GDM matters because it is both an immediate threat to mother and fetus and a powerful marker of future maternal type 2 diabetes (T2DM) and cardiovascular disease.

Classification and definitional boundaries

- **ADA aetiologic classification of diabetes** places GDM as a distinct category (Type IV) alongside: I — Type 1 DM; II — Type 2 DM; III — Specific/"other" types (MODY/monogenic, exocrine pancreatic disease, endocrinopathies, drug-/chemical-induced, etc.); **IV — Gestational diabetes mellitus**.
- **Pregestational (pgDM)** = type 1 or type 2 diabetes antedating pregnancy (complicates ~1% of pregnancies; prevalence is higher in obese vs normal-weight women, ~2.2% vs 0.5%). The crucial clinical separation: **pgDM is teratogenic** because hyperglycaemia is present during organogenesis (first 5–8 weeks), whereas **GDM appears after organogenesis** and so chiefly causes *fetal overgrowth* rather than malformation.
- Glucose tolerance in GDM is typically **bidirectional** — most women revert to normal (or impaired) glucose tolerance postpartum.

Pathophysiology and risk factors

- **Physiology of normal pregnancy:** the fetoplacental unit drives major metabolic change — glucose and amino acids are shunted to the fetus while the mother shifts to ketones/triglycerides, producing **"accelerated starvation" / accelerated ketosis** on fasting (lower glucose, higher β-hydroxybutyrate and acetoacetate). Progressive **insulin resistance** develops, mediated by

placental production of **steroids, a placental growth-hormone variant, and human placental lactogen** (other candidates: placenta-derived pro-inflammatory exosomes and miRNAs).

- **β-cell compensation:** to maintain euglycaemia, maternal insulin secretion rises by up to ~**250%**. **GDM develops when this β-cell compensation is inadequate** for the rising insulin resistance.
- That the driver is *placental* (not merely weight gain) is shown by the fact that **euglycaemia returns within days of delivery** once the placenta is removed.
- **Risk factors:** prepregnancy **obesity** (a major risk factor), excessive gestational weight gain, advancing age, ethnicity (South Asian, etc.), prior GDM, prior macrosomic infant, family history of T2DM, PCOS/insulin-resistant states, and offspring of women who had diabetes in pregnancy (intergenerational transmission).

Screening and diagnosis

- **Universal screening** of asymptomatic pregnant women at **24–28 weeks** is routine prenatal care (USPSTF grade **B** recommendation). Women with high-risk features may be screened earlier; if hyperglycaemia meets standard non-pregnant diabetes criteria in the **first trimester**, label as pre-existing diabetes.
- Two validated approaches exist. The **two-step (ACOG-preferred)** strategy is detailed in the corpus; the **one-step (IADPSG/ADA)** 75-g test is the widely-used alternative.

Strategy	Test	Diagnostic thresholds	Rule for diagnosis
Two-step — Step 1 (screen)	**50-g** oral glucose challenge, non-fasting; 1-h plasma glucose	≥130–140 mg/dL (7.2–7.8 mmol/L)*	If abnormal → proceed to Step 2
Two-step — Step 2 (diagnostic)	**100-g** 3-h OGTT (fasting) — *Carpenter–Coustan*	Fasting ≥95; 1-h ≥180; 2-h ≥155; 3-h ≥140 mg/dL	GDM if **≥2 values** met/exceeded
One-step (IADPSG/ADA)	**75-g** 2-h OGTT (fasting)	Fasting ≥92; 1-h ≥180; 2-h ≥153 mg/dL	GDM if **≥1 value** met/exceeded

- *The 50-g screen cut-off is given as >130 mg/dL (Harrison) or ≥140 mg/dL** (CMDT/ACOG); 135 mg/dL is also used — higher cut-offs trade sensitivity for specificity.
- The 100-g OGTT is performed after an **overnight fast (8–14 h)**, following ≥3 days of unrestricted diet (>150 g carbohydrate/day); the patient stays seated and does not smoke.
- **HbA1c is unreliable for monitoring** in pregnancy (high red-cell turnover gives falsely low values), so it is not used for serial glycaemic monitoring.

Maternal, fetal and neonatal complications

- The mechanistic link is the **Pedersen hypothesis**: maternal hyperglycaemia crosses the placenta → **fetal hyperinsulinaemia** → fetal overgrowth and, at delivery, neonatal hypoglycaemia.

Domain	Complications
Maternal	Preeclampsia, polyhydramnios, increased **caesarean delivery**, birth trauma/lacerations; long-term T2DM and cardiovascular disease

Domain	Complications
Fetal / obstetric	**Macrosomia** (birth weight >4000 g) → **shoulder dystocia**, **brachial plexus injury (Erb palsy)** and birth trauma; large-for-gestational-age fetus, polyhydramnios
Neonatal	**Hypoglycaemia** (fetal hyperinsulinaemia), **hyperbilirubinaemia**, **polycythaemia**, **respiratory distress syndrome**

- In **pgDM** (contrast for the exam) add: spontaneous abortion, **congenital malformations** (cardiac, skeletal, neural-tube defects; *caudal regression/sacral agenesis* is the classically associated anomaly), stillbirth and worsening of maternal nephropathy/retinopathy. These reflect first-trimester hyperglycaemia and are **not** features of pure GDM.

Management

- **Goal-directed glycaemic targets (pregnancy): fasting <95 mg/dL (5.3 mmol/L), 1-h postprandial <140 mg/dL (7.8 mmol/L), 2-h postprandial <120 mg/dL (6.7 mmol/L)**; aim **HbA1c <6%**. Self-monitor capillary glucose ~**4 times/day** (fasting + post-meals).
- **Step 1 — Medical nutrition therapy (MNT)** and appropriate gestational weight gain control normalise glucose in the **majority** of women; combine with physical activity.
- **Step 2 — Pharmacotherapy if targets exceeded: insulin is the preferred/first-line agent** (does not cross the placenta, low treatment-failure rate). Use a **basal–bolus** regimen — intermediate/short-acting combinations such as **NPH + regular**, or rapid analogues **lispro/aspart** (placenta-impermeant).
- **Oral agents — metformin and glyburide** are alternatives when insulin is declined or impractical. Contemporary data show **metformin** gives **lower mean birth weight, less gestational weight gain and less preeclampsia** than glyburide or insulin; however, both are **off-label**, cross the placenta, and metformin's **uncertain long-term offspring effects (higher childhood adiposity)** keep insulin first-line.
- **Insulin requirements rise** through gestation in diabetic pregnancy: ~**0.7–0.8 U/kg/day** (1st trimester) → **0.8–1.0** (2nd) → **0.9–1.2 U/kg/day** (3rd) as placental insulin resistance increases.
- **Fetal surveillance:** serial ultrasound for growth/macrosomia and polyhydramnios (markers of suboptimal control). **Timing/mode of delivery:** induction often in the early-term window (37–39 weeks) when indicated; **caesarean** considered for estimated fetal weight **≥4500 g** to avoid shoulder dystocia. **Tight intrapartum control** minimises neonatal hypoglycaemia.
- **Benefit of treatment:** randomised data show treating GDM **reduces preeclampsia, birth weight >4000 g and shoulder dystocia**.

Postpartum and long-term follow-up

- GDM usually **resolves immediately after delivery**, but it unmasks a high lifetime risk of dysglycaemia: a **7- to 10-fold increased risk of T2DM**, with **~10% developing diabetes within 5 years**; **~35–60% develop diabetes over 10–20 years** (and 50–70% over 15–25 years in some series — a 10- to 18-fold increase).
- **Postpartum re-test:** a **75-g 2-h OGTT at 4–12 weeks** after delivery to detect persisting diabetes or impaired glucose tolerance, then **lifelong screening at least every 3 years**.

- **Risk reduction:** breastfeeding, weight loss, exercise and **metformin** reduce progression to T2DM; counsel on cardiovascular risk and the need for primary-care follow-up.
- **Offspring** of GDM pregnancies carry increased risk of childhood obesity, metabolic syndrome and later T2DM — an intergenerational, partly *in-utero–programmed* effect attenuated by good maternal control.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Two-step GDM screening/diagnosis flowchart:** Box 1 "All pregnant women, 24–28 wk" → "**50-g GCT (non-fasting), 1-h glucose**" → decision node "**≥130–140 mg/dL?**" → if No "Normal — no GDM"; if Yes → "**100-g 3-h OGTT (fasting)**" → list thresholds "Fasting 95 / 1-h 180 / 2-h 155 / 3-h 140 mg/dL" → decision "**≥2 values exceeded?**" → "**GDM**" vs "Not GDM". Add a side branch "**One-step 75-g OGTT: 92 / 180 / 153 → ≥1 value = GDM**".
- **Pathophysiology schematic:** "**Placenta** → human placental lactogen + placental GH-variant + steroids" → arrow "**maternal insulin resistance** ↑" → "β-cell secretion ↑ up to 250% (compensation)"; a second arrow showing "**inadequate compensation → GDM → maternal hyperglycaemia → (placental transfer) → fetal hyperinsulinaemia → macrosomia**, and at birth → **neonatal hypoglycaemia** (*Pedersen hypothesis*)".

Clinical / Diagnostic significance

- Distinguishing **GDM from pgDM** changes the whole risk profile: pgDM mandates **preconception** optimisation (target HbA1c <6%, insulin before conception) to cut malformation risk; GDM care centres on third-trimester glycaemia and macrosomia prevention.
- A positive GDM diagnosis is an **opportunity for cardiometabolic prevention** — the postpartum OGTT and triennial screening identify future diabetes early.
- HbA1c's unreliability in pregnancy means **SMBG/continuous glucose monitoring**, not HbA1c, guides titration.
- Ultrasound estimated fetal weight and polyhydramnios are **surrogate alarms** for inadequate control and drive delivery planning.

High-yield exam pointers

- GDM = glucose intolerance **first recognised in 2nd/3rd trimester**; first-trimester hyperglycaemia = **pre-existing diabetes**, not GDM.
- Screen **all** women at **24–28 weeks** (USPSTF grade B).
- **Two-step:** 50-g GCT (≥130–140 mg/dL) → 100-g 3-h OGTT, **≥2 of** 95/180/155/140 mg/dL = GDM. **One-step:** 75-g 2-h OGTT, **≥1 of** 92/180/153 mg/dL = GDM.
- Targets: **fasting <95, 1-h <140, 2-h <120 mg/dL**, HbA1c <6%.
- **Insulin is first-line** drug therapy; metformin/glyburide are off-label alternatives; lispro, aspart, regular and NPH **do not cross the placenta**.
- Key sequelae via **fetal hyperinsulinaemia**: macrosomia → shoulder dystocia/Erb palsy; neonatal hypoglycaemia, hyperbilirubinaemia, polycythaemia, RDS.
- **Caesarean** considered at **EFW ≥4500 g**; treating GDM lowers preeclampsia, macrosomia and shoulder dystocia.

- Postpartum **75-g OGTT at 4–12 weeks**; lifelong screening **every 3 years**; **7–10× risk of T2DM** (~10% within 5 years).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Medical Disorders During Pregnancy" (Endocrine/Metabolic Disorders — Gestational Diabetes); "Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology" (Gestational DM, ADA classification, screening recommendations).
- **Williams Textbook of Endocrinology, 15e** — "Pathophysiology of Type 2 Diabetes Mellitus" (gestational diabetes / pregnancy insulin resistance, β-cell compensation ~250%, placental drivers) and "Therapeutics of Type 2 Diabetes Mellitus" (pregnancy management, postpartum risk).
- **CMDT 2026** — "Obstetrics & Obstetric Disorders" (GDM screening/diagnostic criteria table, glycaemic targets, insulin and oral-agent therapy, postpartum 75-g OGTT) and "Diabetes Mellitus & Hypoglycemia" (pregnancy targets).
- **Coverage note:** The corpus fully supports the two-step (50-g/100-g Carpenter–Coustan) pathway, targets, complications and management. The **one-step IADPSG/ADA 75-g criteria (92/180/153 mg/dL)**, the eponyms **Pedersen hypothesis** and **caudal regression/sacral agenesis**, and **Erb palsy** as the brachial-plexus lesion are universally accepted standard internal medicine added for completeness but are not stated verbatim in these chapters. The historical **White classification** of diabetes in pregnancy is not covered in this corpus and is omitted.

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GLP-1 analogues

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

Definition / Introduction — Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), also called *incretin mimetics* or *GLP-1 analogues*, are injectable (and now oral) peptide drugs that are homologs or analogues of the gut incretin hormone GLP-1, engineered to resist degradation by *dipeptidyl peptidase-4 (DPP-4)*. They lower glucose in a **glucose-dependent** manner, produce **weight loss** without intrinsic hypoglycaemia, and several confer proven **cardiovascular and renal protection**. They have transformed the management of type 2 diabetes mellitus (T2DM) and obesity, and now occupy a preferred place in glucose-lowering and weight-management algorithms.

Incretin physiology and rationale (mechanism of action)

- The "**incretin effect**": an oral glucose load evokes a far greater insulin response than an equivalent intravenous load, because of gut-derived hormones released with nutrient ingestion — **GLP-1** (from intestinal **L-cells**) and **glucose-dependent insulinotropic polypeptide (GIP)**, a 42-amino-acid peptide from duodenal/jejunal **K-cells**. This incretin effect is *blunted* in T2DM.

- Native GLP-1 is rapidly inactivated by the enzyme **DPP-4** (half-life ~1–2 min) and cleared by the kidney, so it cannot be used as a drug; analogues are made DPP-4-resistant or are given as DPP-4 inhibitors (incretin *enhancers*) instead.
- **Pleiotropic actions of GLP-1RAs:**
  - **Pancreas** — potentiate *glucose-dependent* insulin secretion from beta cells and suppress postprandial **glucagon** (alpha-cell) secretion; insulinotropy ceases as glucose falls toward normal, hence minimal hypoglycaemia.
  - **Stomach** — **delay gastric emptying**, flattening postprandial glucose excursions.
  - **CNS** — stimulate GLP-1 receptors in the hypothalamic **arcuate nucleus**, the brainstem **nucleus tractus solitarius** and connected appetite-relay nuclei to promote **satiety** and reduce energy intake → weight loss.
  - Additional benefits: improved lipid profile, lower blood pressure, anti-inflammatory/anti-atherogenic endothelial effects, and reduction of hepatic steatosis.

Classification

Group	Agents	Salient feature
Short-acting GLP-1RA	Exenatide (synthetic *exendin-4*), Lixisenatide	Dominant effect on *postprandial* glucose via gastric slowing; more nausea per unit HbA1c fall
Long-acting GLP-1RA	Liraglutide (daily); Dulaglutide, exenatide-ER, Semaglutide (weekly)	Greater *fasting* glucose & HbA1c reduction; CV outcome benefit; better tolerated
Oral GLP-1RA	Oral semaglutide (with absorption enhancer **SNAC**)	First peptide GLP-1RA absorbed enterally
Dual incretin (GIP/GLP-1) agonist	**Tirzepatide**	"Twincretin"; superior HbA1c & weight loss

- **Origin pearl:** *exendin-4* is a naturally occurring peptide in the saliva of the *Gila monster (Heloderma suspectum)*, shares ~53% sequence identity with human GLP-1, and is intrinsically DPP-4-resistant; **exenatide** is its synthetic form and was the first GLP-1RA approved (2004). **Liraglutide** has 97% homology with human GLP-1.

Individual agents — dosing and pharmacology

Agent	Route / frequency	Typical dose	Half-life	HbA1c fall
Exenatide	SC twice daily (before breakfast & dinner)	5–10 mcg BD	~2.4 h (≤6 h action)	~1.0%
Lixisenatide	SC once daily (before breakfast)	10–20 mcg OD	~3 h	~0.4–0.6%
Liraglutide	SC once daily	0.6 → 1.2 → 1.8 mg (3.0 mg for obesity)	~12–15 h	~0.6–1.5%
Dulaglutide	SC once weekly	0.75 → up to 4.5 mg	~5 days	~1.5–1.8%

Agent	Route / frequency	Typical dose	Half-life	HbA1c fall
Semaglutide (SC)	SC once weekly	0.25 → 0.5 → 1 → 2 mg (2.4 mg for obesity)	~1 week	~1.5–2.1%
Semaglutide (oral)	Oral once daily, fasting, ≥30 min before food	3 → 7 → 14 mg	~1 week	comparable to injectable
Tirzepatide (GIP/GLP-1)	SC once weekly	2.5 → up to 15 mg	~117 h	up to ~2.3%

- Doses are **titrated slowly** (over weeks) to limit gastrointestinal intolerance.
- **Fixed-ratio combinations with basal insulin:** *liraglutide/degludec (Xultophy)* and *lixisenatide/glargine (Soliqua)*.
- **Tirzepatide** is engineered from the GIP backbone with agonist activity at both receptors; its GLP-1-receptor affinity is ~5-fold weaker than native GLP-1, while GIP agonism equals native GIP — central GIP action appears to act synergistically with GLP-1 to magnify weight loss.

Clinical efficacy and cardiovascular / renal outcomes

- **Glycaemia & weight:** the most effective non-insulin injectables for HbA1c lowering; consistent weight loss (≈2–6 kg with most agents; ≥10–15% with semaglutide 2.4 mg and tirzepatide). Only **liraglutide 3.0 mg** and **semaglutide 2.4 mg** are licensed specifically for chronic weight management; **tirzepatide** is approved for obesity (and obstructive sleep apnoea in obesity).
- **Head-to-head:** tirzepatide 5/10/15 mg gave superior HbA1c reduction versus semaglutide 1 mg (SURPASS-2); the 15 mg dose lowered HbA1c ~2.3% from a baseline of 8.3% with >10% weight loss in 57%.
- **Cardiovascular outcome trials (CVOTs) — long-acting agents (MACE = CV death, non-fatal MI, non-fatal stroke):**

Trial	Agent	MACE HR (95% CI)	Key extra findings
LEADER	Liraglutide	0.87 (0.78–0.97)	↓CV death (0.78), ↓all-cause death (0.85), ↓albuminuria
SUSTAIN-6	Semaglutide (SC)	0.74 (0.58–0.94)	↓stroke (0.61); transient ↑retinopathy signal
REWIND	Dulaglutide	0.88 (0.79–0.99)	↓stroke (0.76); primary-prevention population
EXSCEL	Exenatide-ER	0.91 (0.83–1.00)	Not statistically significant for MACE
HARMONY	Albiglutide	0.78 (0.68–0.90)	↓MI

- CV benefit is a **class property of long-acting agents** in high-risk T2DM; *short-acting* agents have not shown it consistently. Notably, GLP-1RAs reduced **atherosclerotic (MI/stroke)** events but **not heart-failure hospitalisation**.
- **Beyond diabetes: SELECT** showed a 20% reduction in MACE with semaglutide 2.4 mg in patients with established CV disease and obesity/overweight **without** diabetes; **STEP-HFpEF** improved heart-failure symptoms and exercise capacity in obesity-related HFpEF.

- **Renoprotection:** GLP-1RAs reduce albuminuria; dedicated trial data (semaglutide in CKD) demonstrate slowing of kidney-disease progression, supporting renal benefit.

Adverse effects, contraindications and precautions

- **Gastrointestinal (commonest):** nausea (11–40%), vomiting (4–13%), diarrhoea (9–17%), constipation, abdominal pain — dose-related, usually mild/transient, mitigated by slow titration; ~1–5% discontinue.
- **Hypoglycaemia:** not caused by GLP-1RAs alone, but occurs when combined with a **sulfonylurea or insulin** — pre-emptively reduce the secretagogue, and reduce insulin by ~20% (unless HbA1c >8%).
- **Pancreatitis:** post-marketing reports; advise patients to stop the drug and seek care for severe, persistent abdominal pain. (Avoid in prior pancreatitis.)
- **Medullary thyroid carcinoma / MEN-2:** rodent C-cell tumours seen pre-clinically; **contraindicated** with personal/family history of medullary thyroid cancer or MEN type 2.
- **Renal:** acute kidney injury (usually pre-renal, from volume depletion due to nausea/vomiting) — stop if unable to tolerate fluids >4 h. **Exenatide** is renally cleared and contraindicated at **eGFR <30 mL/min**; liraglutide/dulaglutide/semaglutide are proteolytically metabolised and preferred in renal impairment.
- **Diabetic retinopathy:** transient worsening (SUSTAIN-6) attributed to rapid glucose lowering.
- **Others:** cholelithiasis (with rapid weight loss); caution with gastroparesis and drugs that slow GI motility; a regulatory caution regarding mood change/suicidal ideation is under review.
- **Absolute contraindications:** type 1 DM / DKA, medullary thyroid carcinoma or MEN-2; relative — pancreatitis history, confirmed gastroparesis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **GLP-1 action diagram** — label: *intestinal L-cell → GLP-1 release on nutrient ingestion*; arrows to **pancreatic beta cell (↑ glucose-dependent insulin)**, **alpha cell (↓ glucagon)**, **stomach (↓ gastric emptying)**, **brain/hypothalamus (↑ satiety, ↓ appetite)**; show **DPP-4** degrading native GLP-1 (with GLP-1RA = DPP-4-resistant).
- **Classification tree** — *GLP-1RA* → branches: **short-acting** (exenatide, lixisenatide) / **long-acting** (liraglutide; dulaglutide, semaglutide, exenatide-ER) / **oral** (semaglutide-SNAC) / **dual GIP-GLP-1** (tirzepatide).

Clinical / Diagnostic significance

- **Place in therapy (T2DM):** preferred add-on (or first-line with metformin) when **atherosclerotic CVD, high CV risk, CKD, or obesity** predominates; combine with SGLT2 inhibitors for layered cardiorenal benefit.
- **Do not co-prescribe** a GLP-1RA with a **DPP-4 inhibitor** (mechanistically redundant).
- **Weight management:** semaglutide 2.4 mg, liraglutide 3.0 mg and tirzepatide give clinically meaningful, durable weight loss with cardiometabolic improvement, including in non-diabetic obesity.

- **Monitoring/counselling:** titrate slowly; counsel on GI symptoms, dehydration-related AKI, pancreatitis warning signs; screen for MTC/MEN-2 history before starting; review at intervals for efficacy and tolerability.

High-yield exam pointers

- **Exenatide = exendin-4** from *Gila monster* saliva; DPP-4-resistant; first GLP-1RA. **Liraglutide** 97% homologous to human GLP-1.
- Mechanism quartet: ↑ **glucose-dependent insulin,** ↓ **glucagon,** ↓ **gastric emptying,** ↑ **satiety.**
- **No hypoglycaemia alone**; cause **weight loss**; effective HbA1c reduction (~1–2%).
- Weekly long-acting agents: **dulaglutide, semaglutide, exenatide-ER**; daily: **liraglutide**; **oral semaglutide** uses absorption enhancer **SNAC**.
- **CVOTs:** LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide) positive; **EXSCEL (exenatide) neutral**; benefit on **atherosclerotic events, not HF hospitalisation.**
- **Tirzepatide** = dual **GIP/GLP-1** agonist ("twincretin"), most potent for HbA1c and weight.
- Key cautions: **medullary thyroid carcinoma / MEN-2**, **pancreatitis**, **exenatide in eGFR <30**, transient **retinopathy** worsening, AKI from volume depletion.
- **SELECT** trial — CV benefit of semaglutide in obesity **without diabetes**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Management and Therapies" and "Evaluation and Management of Obesity."
- **Williams Textbook of Endocrinology, 15e** — "Therapeutics of Type 2 Diabetes Mellitus" (GLP-1 receptor agonists, GIP/GLP-1 dual agonist, CVOT tables) and "Physiology of Insulin Secretion" (incretin effect).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycemia" (current dosing, safety) and "Nutrition, Nutritional Disorders, & Obesity."

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Graves' disease

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

Definition / Introduction — *Graves' disease* is an organ-specific **autoimmune disorder** caused by **thyroid-stimulating immunoglobulins (TSIs)** — IgG antibodies directed against the **TSH receptor (TSH-R)** that mimic TSH and drive unregulated thyroid hormone synthesis. It is the commonest cause of **thyrotoxicosis**, accounting for **60–80%** of cases, and is the only cause that classically combines goitre, **ophthalmopathy (thyroid eye disease)**, **dermopathy (pretibial myxoedema)** and **acropachy**. Thyrotoxicosis (thyroid-hormone excess) must be distinguished from hyperthyroidism (excessive *gland function*) — Graves' produces both.

Epidemiology & Pathogenesis

- **Epidemiology:** affects up to **2% of women**, one-tenth as frequent in men; peak onset **20–50 years**; high dietary iodine intake increases prevalence. Concordance in **monozygotic twins is 20–30%** versus **<5%** in dizygotic twins, confirming a strong genetic component.
- **Susceptibility genes:** polymorphisms in **HLA-DR**, immunoregulatory genes **CTLA-4, CD25, CD40, PTPN22, FCRL3, CD226**, and the **TSH-R** gene itself.
- **Environmental triggers:** smoking (a moderate risk for Graves' but a **major risk for ophthalmopathy**), stress, sudden iodine load, the **postpartum period** (threefold rise), and immune reconstitution after HAART, **alemtuzumab**, or **immune checkpoint inhibitors** (nivolumab, pembrolizumab).
- **Mechanism of hyperthyroidism: TSIs / TRAb** synthesised by intrathyroidal, marrow and lymph-node lymphocytes bind and activate the TSH-R → continuous stimulation of hormone synthesis and gland growth, *unrestrained by feedback*. Coexisting **TPO and thyroglobulin (Tg) antibodies** are present in up to **80%**; because lymphocytic thyroiditis coexists, there is **no direct correlation** between TSI titre and hormone level.
- **Ophthalmopathy mechanism:** activated T-cell infiltration of extraocular muscles → release of **IFN-γ, TNF, IL-1** → fibroblast activation and **glycosaminoglycan** deposition that traps water → muscle swelling; increased orbital fat adds to retrobulbar expansion. The **TSH-R is a shared orbital autoantigen**, and aberrant signalling via the **insulin-like growth factor-1 receptor (IGF-1R)** on orbital fibroblasts underpins disease and is the target of **teprotumumab**.

Clinical Features

- **General thyrotoxic features** (descending frequency): hyperactivity, irritability, **heat intolerance and sweating**, palpitations, fatigue, **weight loss with increased appetite**, diarrhoea, oligomenorrhoea. Signs: **sinus tachycardia / atrial fibrillation** (esp. >50 y), fine **tremor**, goitre, warm moist skin, **proximal myopathy**, lid retraction/lag.
- In the elderly, presentation may be subtle — **apathetic thyrotoxicosis** (fatigue, weight loss, AF) mistaken for depression or malignancy.
- **Cardiovascular:** high-output state — bounding pulse, widened pulse pressure, aortic flow murmur; AF reverts to sinus rhythm in up to **75%** once euthyroid.
- **Neuromuscular:** hyperreflexia, proximal myopathy without fasciculation; **thyrotoxic hypokalaemic periodic paralysis** — sudden flaccid paralysis, common in **Asian/American-**

Indian men (~15%; up to 30× commoner in men), often after carbohydrate/dextrose load or exercise.

- **Graves'-specific signs (diagnostic triad clues):**
  - *Goitre* — diffuse, firm, **2–3× enlarged**, often with a **bruit/thrill** at the inferolateral poles (hypervascularity).
  - *Ophthalmopathy / thyroid eye disease (TED)* — clinically present in **~one-third**; grittiness, excess tearing, **proptosis**, periorbital oedema, chemosis, scleral injection, **diplopia**, and, most seriously, **optic-nerve compression** at the orbital apex → visual loss. Occurs **without hyperthyroidism in 10%** (euthyroid Graves' ophthalmopathy); onset within 1 year of thyrotoxicosis in 75%.
  - *Thyroid dermopathy (pretibial myxoedema)* — **<5%** (CMDT ~3%); non-inflamed indurated plaque, "**orange-peel**" appearance, over anterolateral shins; almost always with moderate-severe eye disease.
  - *Thyroid acropachy* — **<1%**; clubbing with phalangeal periostitis, virtually always with dermopathy.

Classification of Ophthalmopathy (NO SPECS & CAS)

Class	"NO SPECS" feature (Werner)
0	No signs or symptoms
1	Only signs (lid retraction/lag), no symptoms
2	Soft tissue involvement (periorbital oedema)
3	Proptosis (>22 mm)
4	Extraocular muscle involvement (diplopia)
5	Corneal involvement
6	Sight loss (optic nerve)

- *NO SPECS* is a useful mnemonic but inadequate for monitoring; activity is better graded by the **7-point Clinical Activity Score (CAS)** of EUGOGO (spontaneous retrobulbar pain, pain on gaze, lid redness, conjunctival redness, lid swelling, caruncle/plica swelling, chemosis). **CAS ≥3 = active disease**; the **EUGOGO** system grades severity (mild / moderate-to-severe / sight-threatening).

Laboratory Evaluation & Differential Diagnosis

- **First-line:** suppressed **TSH** with raised **free (and total) T4 and T3**. In 2–5% only **T3 is raised** (*T3 toxicosis*); rarely *T4 toxicosis* (iodine-induced).
- **Confirm aetiology:** measure **TRAb/TSI** (high sensitivity & specificity for Graves'; also predicts neonatal thyrotoxicosis in pregnancy and GO course). Positive **TPO antibodies** in ~80%.
- **Radionuclide (^{24}Tc/^{123}I/^{131}I) scan & uptake:** *diffuse, high uptake* in Graves' — distinguishes it from **destructive thyroiditis, factitia and iodine excess (low uptake)** and from focal uptake of toxic adenoma/toxic MNG. **Colour-flow Doppler** (increased flow) is a radiation-free alternative.

- **Ancillary abnormalities:** mild rise in bilirubin, transaminases, ferritin, alkaline phosphatase; mild **hypercalcaemia/hypercalciuria**; microcytic anaemia; thrombocytopenia.
- **Differential:** toxic MNG, toxic adenoma, subacute/silent thyroiditis, factitious thyrotoxicosis, struma ovarii, TSH-secreting pituitary adenoma (non-suppressed TSH + diffuse goitre), and non-thyroid mimics (panic, phaeochromocytoma, malignancy). A **normal TSH excludes Graves'**.

Management

- **Three definitive options** — antithyroid drug (ATD), radioiodine (^{131}I) and surgery; ATD is first-line in Europe/Japan/India and increasingly the USA.
- **Antithyroid (thionamide) drugs** — inhibit **thyroid peroxidase** (↓ organification); also lower antibody levels:
  - **Methimazole/carbimazole** preferred: start **10–20 mg q12h**, maintenance 2.5–10 mg; PTU 100–200 mg q6–8h. **PTU** uniquely blocks peripheral **T4→T3 conversion** but has short half-life (90 min vs 6 h) and **hepatotoxicity** — now restricted to **first-trimester pregnancy, thyroid storm, and methimazole intolerance**.
  - **Titration** regimen (most common) or **block-and-replace** (high ATD + LT4). Review at 4–6 weeks (titrate to free T4; TSH stays suppressed for months). **Remission 30–60% by 12–18 months**, higher if TRAb becomes undetectable.
  - **Side effects:** rash/urticaria/arthralgia (1–5%); rare major — **agranulocytosis (<1%, idiosyncratic; stop drug, urgent CBC for sore throat/fever)**, hepatitis (PTU), cholestasis, vasculitis.
- **β-blockers** for adrenergic relief: **propranolol 20–40 mg q6h** (or atenolol); also for thyrotoxic periodic paralysis.
- **Radioiodine (^{131}I):** progressive ablation; typical dose **370 MBq (10 mCi) – 555 MBq (15 mCi)**; stop methimazole 2–3 days prior. Risks: transient worsening of thyrotoxicosis, **GO flare in smokers** (cover with prednisone **0.3–0.5 mg/kg/day**), and inevitable **hypothyroidism (10–20% first year, ~5%/yr thereafter)**. **Absolutely contraindicated in pregnancy and lactation** (conceive only ≥6 months later); avoid in active moderate-to-severe eye disease.
- **Surgery (total/near-total thyroidectomy):** for large goitre, relapse, or patient preference. Render euthyroid with ATD, then **potassium iodide (SSKI 1–2 drops tid × 10 days)** to reduce vascularity. Complications: bleeding, laryngeal oedema, **hypoparathyroidism**, **recurrent laryngeal nerve** injury.
- **Pregnancy: PTU until 14–16 weeks** (avoids methimazole embryopathy — **aplasia cutis, choanal atresia, tracheo-oesophageal fistula**), then switch to methimazole; titrate to keep free T4 at/just above the upper reference range; monitor TRAb (transplacental TSI → fetal/neonatal thyrotoxicosis if >3× normal).
- **Ophthalmopathy:** stop smoking, restore euthyroidism, artificial tears, selenium for mild disease. **Active moderate-to-severe GO → IV methylprednisolone** (cumulative 4.5 g: **500 mg weekly ×6 then 250 mg weekly ×6**, ± mycophenolate). **Teprotumumab** (anti-IGF-1R) is now first-line for active disease with significant proptosis/diplopia; rituximab/tocilizumab are second-line. **Sight-**

threatening GO (optic neuropathy/corneal breakdown) → high-dose IV methylprednisolone ± **orbital decompression**.

Thyrotoxic Crisis (Thyroid Storm)

- Life-threatening decompensated thyrotoxicosis precipitated by infection, surgery, trauma, DKA, parturition or ^{131}I in untreated patients; **mortality 4–17%**. Features: hyperpyrexia, delirium/coma, seizures, vomiting, diarrhoea, jaundice, **high-output cardiac failure/arrhythmia**. Severity graded by the **Burch-Wartofsky point scale**.
- **Treatment (combine all): PTU** 500–1000 mg load then 250 mg q4h (blocks T4→T3); **iodide (SSKI 5 drops q6h) given ≥1 h after PTU** (Wolff-Chaikoff block of release); **propranolol** 60–80 mg PO q4h or 2 mg IV q4h; **hydrocortisone 300 mg IV then 100 mg q8h**; plus cooling, oxygen, IV fluids, treat the trigger; **cholestyramine** sequesters hormone.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis of Graves' disease** — draw a thyroid follicular cell with a **TSH receptor**; a plasma cell/B-lymphocyte releasing **TSI (TRAb, IgG)** binding the receptor → arrow to "**unregulated T3/T4 synthesis & goitre**". Side arrow showing the same antibody/IGF-1R acting on **orbital fibroblast → GAG deposition → proptosis**. Labels: *TSH receptor, TSI/TRAb, B-cell/plasma cell, T-cell + cytokines (IFN-γ, TNF, IL-1), IGF-1R, orbital fibroblast, glycosaminoglycans, extraocular muscle swelling*.
- **Evaluation-of-thyrotoxicosis algorithm** — Box 1: "**↓TSH, ↑free T4**" → Box 2: "**Features of Graves'? (diffuse goitre, TRAb+, TPO+, ophthalmopathy, dermopathy)**" → **Yes = Graves'**; **No → radionuclide uptake**: *diffuse high = Graves', focal/patchy = toxic nodule/MNG, low/absent = thyroiditis, iodine excess, factitia*. Labels: *TSH, free T4, free T3, TRAb, RAIU, ^{24}Tc/^{123}I scan*.

Clinical / Diagnostic significance

- **TRAb** is the confirmatory autoantibody: clinches Graves' when eye/skin signs are absent, predicts relapse after ATD, and guides pregnancy monitoring (neonatal thyrotoxicosis risk).
- Distinguishing **Graves' (high RAIU)** from **destructive thyroiditis (low RAIU)** is decisive — the latter is *not* treated with thionamides.
- Untreated thyrotoxicosis risks **AF, thromboembolism, osteoporosis, high-output failure and thyroid storm**; AF often reverts with euthyroidism, so rate control + anticoagulation (CHA_2DS_2-VASc) is interim.
- New-onset AF, unexplained weight loss, or proximal myopathy in any adult warrants **TSH testing**.

High-yield exam pointers

- Commonest cause of thyrotoxicosis (**60–80%**); **autoimmune**, driven by **TSI/TRAb** against **TSH-R**; F:M ≈ 10:1.
- Classic tetrad: **diffuse goitre + ophthalmopathy + dermopathy + acropachy**; goitre bruit signifies hypervascularity.

- **Smoking** is the key modifiable risk for **ophthalmopathy** progression and ^{131}I-induced flare.
- **NO SPECS** (0–6) and **CAS (≥3 = active)** classify eye disease; proptosis cut-off **>22 mm**.
- **Methimazole** first-line; **PTU** only in first-trimester pregnancy, thyroid storm, methimazole intolerance; watch **agranulocytosis (<1%)**.
- **^{131}I** contraindicated in pregnancy/lactation and active severe GO; causes hypothyroidism.
- **Teprotumumab** = anti-**IGF-1R** monoclonal, first-line for active moderate-severe GO.
- **Thyroid storm:** PTU → iodide (≥1 h later) → β-blocker → steroid; mortality up to ~17%.
- T3 toxicosis in 2–5%; thyrotoxic **hypokalaemic periodic paralysis** classically in Asian men.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hyperthyroidism and Other Causes of Thyrotoxicosis" (epidemiology, pathogenesis, NO SPECS, antithyroid-drug regimens, radioiodine, surgery, pregnancy, thyroid storm).
- **Williams Textbook of Endocrinology, 15e** — "Hyperthyroid Disorders" (TSH-R/IGF-1R immunopathology, Clinical Activity Score, EUGOGO severity grading, IV methylprednisolone protocol, teprotumumab/OPTIC data, first-line treatment patterns).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (current drug doses, dermopathy/acropachy frequency, thyrotoxic-crisis presentation and management, hypokalaemic periodic paralysis).

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Gynaecomastia

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

Definition / Introduction — Gynaecomastia is the benign enlargement of the male breast due to proliferation of true **glandular** (ductal–stromal) tissue, clinically palpable as a firm, rubbery, mobile, often tender disc extending concentrically from beneath the nipple–areola. It results from an **increased estrogen-to-androgen ratio** acting on breast tissue and must be distinguished from *pseudogynaecomastia* (excess adipose tissue, soft and diffuse, common in obesity) and from **male breast carcinoma**. It may be a benign physiological variant or the first clue to serious endocrine, systemic or neoplastic disease.

Hormonal basis & pathogenesis

- **Estrogens** stimulate growth and differentiation of ductal epithelium (ductal hyperplasia); **progesterone** drives acinar/glandular bud formation; **androgens inhibit** breast growth and differentiation. GH, IGF-1, insulin, thyroid hormone and cortisol play permissive roles; prolactin promotes milk production in already-developed glands.
- The unifying mechanism is a **raised estrogen : androgen ratio** at the breast, achieved by *estrogen excess*, *androgen deficiency/resistance*, or both. Even small rises in serum estradiol (within the normal male range) produce large proportional effects on breast tissue.

- *Galactorrhoea is rare* even with hyperprolactinaemia, because male progesterone levels are too low for acinar development/lactogenesis.
- In primary hypogonadism (e.g. *Klinefelter syndrome*), high **LH** stimulates aromatase in Leydig cells → relatively more estradiol than testosterone. In obesity/ageing, increased adipose **aromatase** raises peripheral androgen→estrogen conversion.

Natural history & histological phases

- **Florid / proliferative (early, <6 months):** ductal proliferation, periductal inflammation and oedema, subareolar fat accumulation → tender, painful; **responsive to medical therapy**.
- **Inactive / fibrotic (late, >6–12 months):** progressive stromal fibrosis, hyalinisation; non-tender; **only partial spontaneous regression** and generally **unresponsive to drugs** — requires surgery.
- Absence of breast tenderness usually signals the chronic fibrotic stage that will not remit.

Classification of causes

Category	Representative causes
Physiologic	Neonatal (transplacental maternal/placental estrogens; in 60–90%, resolves in weeks); pubertal (transient ↑estrogen:testosterone, ~60% of boys by age 14, regresses in 1–2 yr); ageing/obesity (↑aromatase, ↓testosterone; up to ~65% of men aged 50–80)
Estrogen excess	Exogenous estrogens (diethylstilbestrol for prostate Ca, estrogen creams/cosmetics, phytoestrogens, lavender/tea-tree oils); ER agonists (marijuana, digitoxin); **estrogen-secreting tumours** — adrenal carcinoma, Leydig/Sertoli cell tumours (Sertoli ± *Peutz-Jeghers*, *Carney complex*); **hCG-secreting tumours** — germ cell, lung, hepatic, gastric, renal; familial/sporadic **aromatase excess syndrome**
Androgen deficiency / resistance	Primary or secondary hypogonadism (incl. **Klinefelter 47,XXY**); androgen insensitivity syndromes; hyperprolactinaemia (suppresses GnRH → hypogonadism)
Drug-induced (~20% of adult cases)	**Spironolactone** (common), AR antagonists (flutamide, bicalutamide, enzalutamide), **5α-reductase inhibitors** (finasteride/dutasteride), ketoconazole, **cimetidine/H2 blockers**, GnRH agonists, digitalis, **HAART/efavirenz**, anabolic steroids, ketoconazole, CCBs, amiodarone, TCAs/SSRIs, alcohol, opioids, methadone, isoniazid, metoclopramide, antipsychotics
Systemic disease	**Hepatic cirrhosis** (↓androstenedione catabolism, ↑SHBG → ↑free E2/T), **CKD stage 4–5** (often with dialysis), **hyperthyroidism** (↑SHBG, ↑LH-driven E2), acromegaly, Cushing syndrome, **refeeding** after starvation/chronic illness ("second puberty")

Clinical evaluation

- **History:** speed of onset and growth, pain/tenderness, drugs & substances (above), alcohol, recreational drugs, cosmetics/supplements; symptoms of hypogonadism (low libido, ED); features of liver/renal/thyroid disease, weight change, recent refeeding.
- **Examination (technique):** with thumb and forefinger as pincers, palpate the subareolar disc both **seated and supine** and compare with nearby fat. **True glandular tissue** is firm, rubbery, finely lobular, mobile, concentric to the nipple; **pseudogynaecomastia** is soft, diffuse, non-discrete adipose tissue.

- Also assess **virilisation**, **testicular size and masses** (orchidometer; small/firm testes → Klinefelter; a testicular mass → tumour), penis for hypospadias.
- **Red flags for carcinoma:** unilateral/markedly asymmetric, eccentric (not directly sub-areolar), rock-hard or fixed, skin dimpling (*peau d'orange*), nipple retraction, bloody discharge, axillary lymphadenopathy.
- **Thresholds:** glandular tissue **>4 cm** (Harrison) or **≥5 cm** with recent/rapid onset, tenderness or suspicious features warrants work-up; non-tender lesions **≤2.5 cm** are a common normal variant; up to two-thirds of pubertal boys and ~half of hospitalised men have benign palpable glandular tissue.

Investigations

- **First-line hormonal panel:** total and free **testosterone**, **LH**, **FSH**, **estradiol (E2)**, **β-hCG**, **TSH/FT4**, **prolactin**.
- **Interpretation:** ↓T + ↑LH → **primary hypogonadism** (do **karyotype** for Klinefelter if testes very small); ↓T + low/normal LH → **secondary hypogonadism**; ↑T + ↑LH → partial androgen insensitivity; **↑hCG** → testicular germ-cell/Sertoli tumour or ectopic (lung, liver); **↑E2 with suppressed LH** → estrogen-secreting testicular/adrenal tumour.
- **Organ work-up:** liver and renal function; TSH for thyrotoxicosis.
- **Imaging/biopsy: testicular ultrasound** if hCG/E2 elevated; **CT adrenal** for high E2 with normal testes, **CT chest/abdomen** for hCG-source search; **mammography ± ultrasound-guided FNA/biopsy** for any features suspicious of malignancy. (Note: routine commercial E2 assays are inaccurate at male levels — prefer **mass spectrometry**; use an assay detecting total hCG/β-subunit.)
- Despite full evaluation, the cause is established in only a minority — many adult cases remain **idiopathic**.

Treatment

- **Treat the cause:** stop/replace the offending drug; correct hypogonadism, thyrotoxicosis, liver/renal disease, tumour. If addressed early, gynaecomastia usually subsides over months.
- **Reassurance/observation:** physiological neonatal and pubertal gynaecomastia regress spontaneously (pubertal in ~90% by age 18, within 1–2 yr).
- **Medical therapy (effective only in the early proliferative phase, <6 months):**
  - **SERMs** — *Tamoxifen* 10–20 mg/day (reduces volume >50% in ~60%) and *Raloxifene* 60 mg/day (>50% reduction in ~90%); tamoxifen also prevents/treats antiandrogen-induced gynaecomastia in prostate-cancer patients.
  - **Aromatase inhibitors** — *Anastrozole* (e.g. 0.5 mg thrice weekly, titrated to mid-range male E2) helps some early/pubertal cases but in a randomised trial was **no better than placebo** for *established* gynaecomastia; avoid long-term AI in adolescents (risk of osteoporosis and delayed epiphyseal fusion).
- **Prevention:** prophylactic **low-dose breast irradiation (≈10–15 Gy over 1–3 days)** or tamoxifen before androgen-deprivation therapy in prostate cancer.

- **Surgery:** definitive for long-standing (>6–12 months), fibrotic, large, painful, disfiguring or drug-refractory disease, or when malignancy is suspected — **subcutaneous mastectomy ± liposuction (reduction mammoplasty)**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hormonal pathophysiology schematic:** central box "↑ Estrogen : Androgen ratio at breast → ductal proliferation" with three feeding arrows — (1) *Estrogen excess* (tumour E2 / hCG-driven aromatisation / exogenous estrogen / ↑peripheral aromatase in fat); (2) *Androgen deficiency* (primary & secondary hypogonadism, hyperprolactinaemia); (3) *Drugs* (spironolactone, AR blockers, 5-ARIs, cimetidine). Label "Estrogen → ductal hyperplasia", "Progesterone → acini", "Androgen ⊥ inhibits".
- **Evaluation algorithm (Harrison Fig. 403-7):** Breast enlargement → *true glandular* vs *adipose (pseudogynaecomastia)* → if glandular, measure **Total/Free T, SHBG, LH, FSH, E2, TSH, hCG** → four branches: ↓T+↑E2:T ratio = T-deficiency; ↑E2 with low/normal T = search testis/adrenal tumour; ↑β-hCG = ultrasound testis + CT for hCG tumour; very high SHBG = check free T/E2.

Clinical / Diagnostic significance

- New, rapidly growing, tender gynaecomastia **in a lean adult** demands evaluation — may signal a testicular/adrenal tumour or hCG-secreting malignancy.
- **Klinefelter syndrome (47,XXY):** classic gynaecomastia with small firm testes; carries an **increased risk of male breast cancer** → periodic **mammographic surveillance** is recommended.
- Gynaecomastia is a sensitive physical sign of **chronic liver disease** and **chronic kidney disease**, and a flag for drug toxicity (spironolactone, digoxin, antiretrovirals).
- The relative risk of **male breast carcinoma** is increased in men with gynaecomastia (absolute risk small) — unilateral, hard, eccentric or bloody-discharge lesions must be imaged/biopsied.

High-yield exam pointers

- Core mechanism = ↑ **estrogen : androgen ratio**; estrogen → ducts, progesterone → acini, androgen inhibits.
- **True (glandular, ≥4 cm, tender, mobile disc)** vs **pseudogynaecomastia (fatty, soft, obese)** vs **carcinoma (hard, fixed, eccentric, peau d'orange, nipple bleed)**.
- Three physiological peaks: **neonatal, pubertal, ageing/obesity**.
- **~20% of adult cases are drug-induced**; remember **spironolactone, ketoconazole, cimetidine, 5-ARIs, AR antagonists, digoxin, marijuana, efavirenz/HAART, anabolic steroids**.
- First-line tests: **testosterone, LH, FSH, estradiol, β-hCG, TSH, prolactin**; karyotype if small testes (Klinefelter).
- **↑hCG → germ-cell/ectopic tumour; ↑E2 + suppressed LH → estrogen-secreting tumour.**
- Drugs (SERMs/AI) work only in the **early proliferative phase (<6 months)**; **tamoxifen 10–20 mg/day**, **raloxifene 60 mg/day**; fibrotic disease needs **subcutaneous mastectomy**.
- **Refeeding gynaecomastia** — first described in liberated WWII prisoners of war; "second puberty" mechanism.

- **Familial aromatase excess syndrome** — CYP19 activation (chromosome 15q21) → prepubertal gynaecomastia, advanced bone age, short stature.
- Spironolactone causes it; **eplerenone does not**.

> **SOURCE & COVERAGE**
>
> - **Harrison's Principles of Internal Medicine, 22e** — "Disorders of the Testes and Male Reproductive System" (Gynecomastia section; evaluation Fig. 403-7).
> - **Williams Textbook of Endocrinology, 15e** — "Testicular Disorders" (Gynecomastia: pathophysiology, Table 17.3 Causes of Gynecomastia, evaluation and treatment).
> - **CMDT 2026** — "Male Hypogonadism & Gynecomastia" (Essentials of diagnosis, Table 31–3, current SERM/aromatase-inhibitor regimens).

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Hirsutism

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — **Hirsutism** is the presence of excessive **terminal hair** (long, coarse, pigmented) growing in a **male (androgen-dependent) pattern** in a woman — face (upper lip, chin), chest, upper abdomen, midline, and back. It affects roughly **10%** of reproductive-age women and is most often **idiopathic** or due to **androgen excess from polycystic ovary syndrome (PCOS)**; less commonly it reflects **nonclassic congenital adrenal hyperplasia (NCCAH)** or, rarely, an androgen-secreting tumour. It must be distinguished from **hypertrichosis** (androgen-independent, generalised vellus hair) and from **virilization** (a more severe androgenic state with masculinising features).

Hair biology and androgen physiology

- Hair is **vellus** (fine, soft, non-pigmented) or **terminal** (long, coarse, pigmented). Androgens drive the conversion of vellus to terminal hair within the **pilosebaceous unit (PSU)** at androgen-sensitive sites (face, chest, upper abdomen, back).
- Hair-growth cycle has three phases: **anagen** (growth), **catagen** (involution) and **telogen** (rest). Paradoxically, scalp androgen excess shortens anagen, causing **androgenetic alopecia/thinning**.
- **Testosterone** is the principal circulating androgen in hirsutism, but it is a *precursor*: it is converted in the PSU by **5α-reductase** to **dihydrotestosterone (DHT)** — a more potent androgen (higher affinity, slower dissociation from the androgen receptor) that is the **primary local mediator**. Two isoenzymes: **type 2** (prostate, hair follicles) and **type 1** (sebaceous glands).
- Ovaries and adrenals contribute about **equally** to testosterone; ~½ from direct glandular secretion, ½ from peripheral conversion of **androstenedione and DHEA/DHEAS**. Ovarian androgen is driven by **LH**, adrenal androgen by **ACTH**.
- **Sex hormone-binding globulin (SHBG)** governs the *free* (bioavailable) fraction. **Hyperinsulinaemia and androgen excess suppress hepatic SHBG**, so **free testosterone** rises even when total testosterone is high-normal — central to PCOS and obesity-related hirsutism.

Causes / Classification

Category	Representative causes
Ovarian hyperandrogenism	**PCOS** (commonest, ~50–70% of cases), hyperthecosis, ovarian steroidogenic blocks, severe insulin-resistance syndromes, ovarian neoplasms (arrhenoblastoma/Sertoli–Leydig, hilar cell tumours)
Adrenal hyperandrogenism	**Nonclassic & classic CAH** (chiefly **21-hydroxylase deficiency**), premature adrenarche, functional adrenal hyperandrogenism, adrenal neoplasms
Other endocrine	**Cushing's syndrome**, hyperprolactinaemia, acromegaly
Peripheral overproduction	**Obesity**, **idiopathic hirsutism**
Pregnancy-related	Hyperreactio luteinalis, luteoma/thecoma of pregnancy
Drug-induced	Androgens/anabolic steroids, **androgenic progestins** (norgestrel, levonorgestrel), minoxidil, phenytoin, diazoxide, cyclosporine, valproate

- **AES prevalence (Azziz cohort, Williams):** PCOS **72%**, idiopathic hyperandrogenism **16%**, idiopathic hirsutism **7.6%**, NCCAH (21-OHD) **4.3%**, androgen-secreting tumours **0.2%**.
- **Idiopathic hirsutism** = hirsutism with **cyclic ovulatory menses and normal serum testosterone**; reflects increased end-organ 5α-reductase sensitivity (elevated androstanediol/androsterone glucuronide).

Clinical assessment

- **History:** age at onset and **rate of progression**. Onset in 2nd–3rd decade, slow and progressive favours PCOS/idiopathic; **sudden onset with rapid progression and virilization** suggests an **androgen-secreting neoplasm**. Menstrual history (**oligomenorrhoea <8 cycles/year** points to ovarian excess), galactorrhoea (prolactin/thyroid), family history of hirsutism/infertility (NCCAH), and **drug history**.
- **Examination:** height, weight, **BMI** (>25 overweight; >30 commonly associated with hirsutism via peripheral conversion), blood pressure (adrenal causes), and cutaneous markers of insulin resistance — **acanthosis nigricans, skin tags**. Look for Cushingoid features (striae, bruising, centripetal obesity).
- **Quantification — modified Ferriman–Gallwey (mFG) score: 9 androgen-sensitive sites** (upper lip, chin, chest, upper abdomen, lower abdomen/pelvis, upper arms, thighs, upper back, lower back), each graded **0 (none) to 4 (frankly virile)**; **maximum 36**. **Score >8** = abnormal in most non-Hispanic white and African-American women (~95% score <8) and warrants hormonal work-up. Asian and Native-American women manifest hirsutism less readily (acne and scalp thinning may be the only clues).
- **Hirsutism vs virilization vs hypertrichosis:**
  - **Virilization** (markedly higher androgens — think tumour/hyperthecosis): deepening voice, temporal/frontal balding, breast atrophy, ↑muscle bulk, loss of female contour, **clitoromegaly** (clitoral length >10 mm or **clitoral index >35 mm²** abnormal), ↑libido.

- **Hypertrichosis:** androgen-**independent**, diffuse **vellus** hair (non-sexual distribution) from drugs (phenytoin, minoxidil, cyclosporine) or systemic disease — not a sign of androgen excess.

Hormonal evaluation and investigations

- **First-line: total testosterone ± free testosterone** (calculated from total testosterone and SHBG, or by **LC-MS/MS**) and **DHEAS**. Free testosterone is the more sensitive index given SHBG suppression.
- **"Tumour" thresholds (red flags):**

Test	Value	Implication
Total testosterone	**>7 nmol/L (>2 ng/mL)**	Suggests tumour or hyperthecosis
Total testosterone	**>12 nmol/L (>3.5 ng/mL)**	Strongly indicates androgen-producing tumour (CMDT: >200 ng/dL → image)
Androstenedione	**>1000 ng/dL (>34.9 nmol/L)**	Ovarian/adrenal neoplasm
DHEAS	**>18.5 µmol/L (>7000 µg/L; CMDT >700 µg/dL)**	Adrenal source/tumour
17-hydroxyprogesterone (morning, follicular)	**<6 nmol/L (<2 µg/L)**	Excludes 21-OHD; **>300 ng/dL** suggests NCCAH

- **PCOS: ↑LH:FSH ratio (>2)** is characteristic but *random LH/FSH is unreliable* (pulsatile); transvaginal ultrasound shows enlarged ovaries with multiple peripheral follicles, but **25–30% of normal women have "cystic" ovaries**, so imaging has low specificity — PCOS is a **clinical/biochemical diagnosis of exclusion** (Rotterdam: 2 of 3 — hyperandrogenism, oligo-anovulation, polycystic morphology).
- **NCCAH:** screen high-risk women with **morning follicular 17-OHP**; if borderline, **ACTH (cosyntropin) 250 µg IV** stimulation test confirms 21-hydroxylase deficiency.
- **Adrenal vs ovarian source: dexamethasone androgen-suppression test (0.5 mg every 6 h × 4 days)** — suppression of free testosterone to normal = adrenal source; incomplete suppression = ovarian.
- **Cushing's:** overnight **1-mg dexamethasone suppression test** if clinical suspicion. **Imaging: CT/MRI adrenals** for adrenal mass; **transvaginal USG** for ovarian mass; selective venous sampling for occult small virilizing tumours.

Management

- **Set expectations:** suppression slows *new* hair growth only — benefit not evident for **4–6 months**, maximal at **9–12 months** (hair-cycle length); existing terminal hair needs mechanical removal. Treat any **underlying cause** (stop offending drugs; surgery for tumours/Cushing's).
- **Non-pharmacological (adjunct or sole therapy):** bleaching; shaving (does **not** increase growth rate/density); chemical depilatories; **plucking/waxing/electrolysis**; **laser and intense pulsed light (IPL)** photothermolysis for permanent reduction of pigmented terminal hair; **topical eflornithine 13.9% cream** (slows facial hair, esp. with laser).
- **Pharmacological — interrupt androgen synthesis/action:**

Drug class	Agent / dose	Mechanism / notes
Combined OCP (first-line)	Ethinyl-estradiol 30–35 µg + low-androgenic progestin	↓LH → ↓ovarian androgen; ↑SHBG; choose **non-androgenic** progestins (norgestimate) or **antiandrogenic drospirenone**/cyproterone; avoid androgenic levonorgestrel/norgestrel
Androgen-receptor antagonist	**Spironolactone 100–200 mg/day**	Most-used antiandrogen; also inhibits 5α-reductase; monitor **K^+/BP**; menstrual irregularity; **teratogenic (feminises male fetus)** — needs contraception; synergistic with OCP
Antiandrogen + progestin	**Cyproterone acetate** (50–100 mg days 1–15) + EE — reverse-sequential	Competitive AR blockade + ↑testosterone clearance; not available in USA
5α-reductase inhibitor	**Finasteride 5 mg/day**	Inhibits type 2 (PSU has type 1 too → partial efficacy); teratogenic; **dutasteride** blocks types 1 & 2
Non-steroidal antiandrogen	Flutamide	Effective but **hepatotoxic** → not preferred
Insulin sensitiser	Metformin (± lifestyle)	Modest hirsutism benefit in PCOS; aids ovulation
Glucocorticoid	Dexamethasone 0.2–0.5 mg / prednisone 5–10 mg at bedtime	Second-line in CAH (OCP preferred); suppresses nocturnal ACTH surge
Newer (CAH)	**Crinecerfont** 100 mg BD	CRF-receptor antagonist; ↓androstenedione in 21-OHD CAH

- **Preferred regimen for the common causes** (PCOS, NCCAH, idiopathic): **combined OCP + spironolactone** plus weight loss (500 kcal/day deficit + exercise) — an ovary-suppressing agent combined with a peripheral antiandrogen; continue ≥2 years before reassessing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Modified Ferriman–Gallwey scoring chart:** a female body outline with the **9 androgen-sensitive sites labelled** — *Upper lip, Chin, Chest, Upper abdomen, Lower abdomen (pelvis), Upper arms, Thighs, Upper back, Lower back* — each scored *0–4 (max 36; abnormal >8)*.
- **Androgen physiology / site of drug action flow diagram:** *Ovary (LH) + Adrenal (ACTH) → Androstenedione/DHEA → Testosterone → [5α-reductase] → DHT → Androgen receptor in pilosebaceous unit → terminal hair*; label drug targets — *OCP (↓LH, ↑SHBG); Spironolactone/Cyproterone/Flutamide (AR block); Finasteride/Dutasteride (5α-reductase); Eflornithine (follicle).*

Clinical / Diagnostic significance

- A **normal mFG with menstrual irregularity** still warrants screening; **rapid-onset hirsutism + virilization + very high testosterone/DHEAS** mandates urgent tumour search (ovarian USG, adrenal CT/MRI).
- Free testosterone (not total) best reflects bioactivity because **SHBG is suppressed** by insulin/androgens — explains hirsutism with "normal" total testosterone.

- PCOS carries **metabolic risk** (insulin resistance, dyslipidaemia, type 2 diabetes, endometrial hyperplasia from unopposed estrogen) — screen accordingly; the cosmetic complaint is a window to systemic disease.
- All antiandrogens (spironolactone, finasteride, flutamide, cyproterone) are **teratogenic to a male fetus** — reliable contraception is mandatory in reproductive-age women.

High-yield exam pointers

- **Hirsutism = androgen-dependent terminal hair, male pattern;** hypertrichosis = androgen-independent vellus hair (drugs/systemic illness).
- **Commonest cause = PCOS;** most cases overall are idiopathic or PCOS-related; tumours are <1%.
- **DHT (via 5α-reductase) is the key local mediator;** testosterone is the precursor.
- **mFG score:** 9 sites × 0–4, **max 36, abnormal >8.**
- **Tumour thresholds:** testosterone **>7 nmol/L (>2 ng/mL)** suggestive, **>12 nmol/L (>3.5 ng/mL)** likely tumour; **DHEAS >7000 µg/L** = adrenal.
- **NCCAH screen:** morning follicular **17-OHP** (<6 nmol/L excludes); confirm with **ACTH/cosyntropin 250 µg** test.
- **Dexamethasone suppression (0.5 mg q6h × 4 days)** distinguishes adrenal (suppresses) from ovarian (does not).
- **First-line drug = combined OCP;** best results = **OCP + spironolactone;** response takes **6–9 months;** combine with laser/electrolysis for existing hair.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hirsutism" (Ehrmann); algorithm for evaluation and treatment.
- **Williams Textbook of Endocrinology, 15e** — "Physiology and Pathology of the Female Reproductive Axis" (androgen physiology, virilization/clitoral index, Ferriman–Gallwey quantification, comprehensive treatment strategy and drug efficacy data).
- **CMDT 2026** — "Hirsutism & Virilization" (diagnostic thresholds, eflornithine, crinecerfont, current drug regimens).

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Hyperaldosteronism

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

Definition / Introduction — Hyperaldosteronism denotes a state of inappropriately high aldosterone secretion relative to volume/sodium status. It is **primary** when aldosterone production by the adrenal zona glomerulosa is *autonomous* of the renin–angiotensin–aldosterone (RAA) system (low/suppressed renin), and **secondary** when aldosterone rises appropriately in response to an *activated* RAA system (high renin). Primary aldosteronism (PA), first described by *Jerome W. Conn* in 1955, is now recognised as the commonest *curable/specifically-treatable* endocrine cause of hypertension, present in ~5–12% of all hypertensives and a higher proportion of resistant/hypokalaemic hypertension. Its clinical hallmark is **hypokalaemic hypertension** with metabolic alkalosis, though most patients are normokalaemic.

Physiology & pathogenesis

- **Normal control:** aldosterone synthesis (via *aldosterone synthase, CYP11B2*) is driven mainly by **angiotensin II** and **serum potassium**, with only a permissive role for ACTH; volume/salt loading suppresses renin and hence aldosterone. Aldosterone acts on the **mineralocorticoid receptor (MR)** in the distal nephron, increasing **ENaC**-mediated Na^+ reabsorption and K^+/H^+ secretion.
- **In PA**, autonomous aldosterone → Na^+/water retention, plasma-volume expansion, hypertension, renal K^+ and H^+ wasting (→ hypokalaemia, metabolic alkalosis), and feedback **suppression of renin**.
- **"Mineralocorticoid escape"** (pressure natriuresis + atrial natriuretic peptide) limits sodium retention, so overt oedema is uncharacteristic.
- Aldosterone also exerts **direct, blood-pressure-independent target-organ injury** — cardiac fibrosis/remodelling, vascular stiffening, and glomerular damage — explaining the excess cardiovascular, renal, metabolic and bone morbidity in PA versus essential hypertension of equal severity.

Classification & causes

Category	Renin	Aldosterone	Principal causes
Primary	Low / suppressed	High	Bilateral idiopathic adrenal hyperplasia (IHA); aldosterone-producing adenoma (*Conn's adenoma*); unilateral (primary) adrenal hyperplasia; familial forms; rarely adrenocortical carcinoma
Secondary	High	High	Renovascular (renal artery stenosis), renin-secreting (juxtaglomerular) tumour, malignant/accelerated hypertension, oedematous states (CHF, cirrhosis, nephrotic syndrome), diuretics, *Bartter / Gitelman* syndromes (normotensive)
Pseudo-aldosteronism (mimics, low renin **and** low aldosterone)	Low	Low	Liddle syndrome; apparent mineralocorticoid excess (AME)/liquorice; CAH (11β- & 17α-OHase deficiency); Cushing syndrome; DOC-secreting tumour

Subtypes of primary aldosteronism (approximate frequency):

- **Bilateral idiopathic hyperplasia (IHA)** — ~60% (60–70%); the commonest cause; treated medically.
- **Aldosterone-producing adenoma (Conn's syndrome)** — ~30–40%; usually a small (<2 cm), lipid-rich, golden-yellow unilateral nodule; surgically curable.
- **Unilateral (primary) adrenal hyperplasia** — ~2%.
- **Aldosterone-producing adrenocortical carcinoma** — <1% (suspect if tumour ≥4 cm, heterogeneous).
- **Familial hyperaldosteronism (FH)** — ~1–6%.

Genetics — somatic mutations drive most APAs by upregulating CYP11B2: **KCNJ5** (potassium channel *GIRK4*, ~40–70% of APAs; commoner in women, larger adenomas, overproduce hybrid steroids), **ATP1A1** (Na^+/K^+-ATPase), **ATP2B3** (Ca^{2+}-ATPase), **CACNA1D / CACNA1H** (voltage-gated Ca^{2+} channels), **CLCN2** (chloride channel) and **CTNNB1** (β-catenin).

Familial hyperaldosteronism:

- **FH type I — Glucocorticoid-remediable aldosteronism (GRA / dexamethasone-suppressible):** autosomal dominant; a *CYP11B1/CYP11B2* **chimeric gene** places aldosterone synthesis under **ACTH** control. Severe early-onset hypertension, high risk of haemorrhagic stroke from ruptured intracranial aneurysm; high urinary **18-oxocortisol & 18-hydroxycortisol**; aldosterone suppressible by glucocorticoid.
- **FH type II:** germline **CLCN2**; the commonest familial form (<6%); early-onset hypertension; *not* dexamethasone-suppressible.
- **FH type III:** germline **KCNJ5**; severe childhood hypertension with **massive bilateral adrenal hyperplasia**.
- **FH type IV:** germline **CACNA1H**; early-onset hypertension ± developmental disorders.
- **PASNA:** de novo **CACNA1D**; **P**rimary **A**ldosteronism with **S**eizures and **N**eurologic **A**bnormalities.

Clinical features

- **Hypertension** — moderate-to-severe, often drug-resistant; commonest curable secondary cause in young/middle-aged adults.
- **Hypokalaemia** — present in only ~10–40% (≈37%); ~72% are normokalaemic. May be unmasked/worsened by thiazide or loop diuretics. Manifestations: muscle weakness, cramps, fatigue, **hypokalaemic periodic paralysis** (notably in Asians), polyuria/nocturia (nephrogenic diabetes insipidus from a renal concentrating defect), arrhythmias, rhabdomyolysis.
- **Metabolic alkalosis** (raised HCO_3^-); severe alkalosis → tetany/cramps. **Hypomagnesaemia** common.
- **High-normal serum sodium** (reset osmostat) — a useful clue; oedema usually absent (escape).
- **End-organ disease** out of proportion to BP: LVH/diastolic dysfunction, atrial fibrillation, stroke, CKD/proteinuria (masked early by glomerular hyperfiltration), osteoporosis, type 2 diabetes, impaired quality of life.
- **"Connshing" syndrome** — concurrent mild autonomous cortisol secretion (MACS) in a subset.

Diagnostic approach

A three-step pathway — **case detection → confirmation → subtyping**.

- **Whom to screen:** sustained BP >150/100; resistant hypertension (≥3 drugs incl. diuretic) or controlled on ≥4 drugs; hypertension + spontaneous/diuretic-induced hypokalaemia; adrenal incidentaloma; onset <40 yr or family history of early-onset hypertension/stroke; first-degree relative with PA; obstructive sleep apnoea.
- **Case-detection — Aldosterone–Renin Ratio (ARR):** paired morning (8–10 am, seated/ambulant) **plasma aldosterone concentration (PAC)** and **plasma renin activity (PRA)/concentration**. Correct hypokalaemia first. PA is suggested by **suppressed renin (PRA <1 ng/mL/h)** with **raised PAC (≥10–15 ng/dL)**; an elevated ARR (Endocrine Society cutoff ~ARR >750 pmol/L per ng/mL/h, or aldosterone:PRA ratio >30) is positive.
- **Drug effects (correct before testing): MR antagonists** must be stopped 4–6 weeks beforehand (cause false-negatives). β-blockers/clonidine/NSAIDs → false-positives (low renin); ACE-inhibitors/ARBs/diuretics → false-negatives (high renin). However, if renin remains suppressed despite these drugs, the result is interpretable. Verapamil, hydralazine and α-blockers are "clean".
- **Confirmation (autonomy):** demonstrate non-suppressible aldosterone —
  - **IV saline infusion test:** 2 L 0.9% saline over 4 h; PAC failing to suppress <5–6 ng/dL (or <170 pmol/L seated) confirms PA (5–10 ng/dL indeterminate).
  - **Oral sodium loading:** high-salt diet 3 days → 24-h urinary aldosterone >12 µg/24 h.
  - **Fludrocortisone suppression test** (0.1 mg q6h + NaCl × 4 days; PAC not suppressing <6 ng/dL) — sensitive but cumbersome, now seldom used.
  - **Captopril challenge** — alternative (contraindicated in pregnancy).
  - Confirmation may be **omitted** with overt hypokalaemic hypertension + strongly positive ARR + clearly raised PAC.
- **Subtyping (unilateral vs bilateral):**
  - **Fine-cut adrenal CT** — first step; identifies adenomas and excludes carcinoma, but **cannot reliably distinguish** APA from IHA (may miss micro-adenomas, or mislabel a non-functioning incidentaloma).
  - **Adrenal vein sampling (AVS)** — the **gold standard** for lateralisation in surgical candidates. Correct catheter placement is confirmed by an **adrenal-vein-to-IVC cortisol gradient** (>2–3 unstimulated; >5:1 with cosyntropin). **Lateralisation** = cortisol-corrected aldosterone ratio (dominant:non-dominant side) **>4** (sensitivity ~95%, specificity ~100%); a **contralateral suppression index <1** is supportive. Technically demanding (difficult right adrenal vein).
  - **Selective use:** patients <35 yr with spontaneous hypokalaemia, marked PA and a clear unilateral adenoma on CT may proceed to surgery without AVS; older patients need AVS because of frequent coincidental non-functioning adenomas.
  - **[11C]-metomidate PET-CT** (with dexamethasone pre-treatment) — emerging non-invasive alternative to AVS.
- **Non-aldosterone (low-renin, low-aldosterone) mineralocorticoid excess** is confirmed by **urinary steroid metabolite profiling (GC/MS)**, identifying AME (HSD11B2 deficiency, raised

cortisol:cortisone), CAH (CYP11B1/CYP17A1), DOC excess; a normal profile suggests **Liddle syndrome** (amiloride-responsive).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Renin-Angiotensin-Aldosterone axis (with feedback):** label *Renal juxtaglomerular cells → Renin*; *Angiotensinogen → Angiotensin I (via renin) → Angiotensin II (via ACE)*; *Adrenal zona glomerulosa → Aldosterone (CYP11B2)*; stimuli ↓*BP*/↓Na^+/↑K^+; target *Distal nephron MR → ENaC → Na^+ reabsorption, K^+/H^+ excretion*; negative-feedback arrow *Volume expansion* ⟶ ↓*Renin*. Mark the "block" in primary aldosteronism (autonomous aldosterone, suppressed renin).
- **Diagram 2 — Diagnostic algorithm flowchart:** boxes — *Screen high-risk hypertensive → ARR (PAC + PRA) → if positive → Confirmatory test (saline infusion/oral salt load) → Adrenal CT → if surgical candidate, Adrenal Vein Sampling → Lateralised = unilateral adrenalectomy / Non-lateralised = MR antagonist*. Side branch: *normal adrenals + family history → consider GRA / genetic testing*.

Clinical / Diagnostic significance

- **Differentiate primary vs secondary** by renin: PA = **low renin, high aldosterone**; secondary = **high renin, high aldosterone** (PAC:PRA <10). Pseudo-aldosteronism (Liddle, AME, liquorice, CAH) = **low renin, low aldosterone**.
- **Treatment of unilateral PA (APA/unilateral hyperplasia): laparoscopic (total) adrenalectomy** — cures hypokalaemia in nearly all, cures/improves hypertension in ~30–60% (residual essential hypertension common). Correct K^+ pre-operatively; anticipate **transient post-operative hypoaldosteronism** (hyperkalaemia, hypotension) from chronic contralateral suppression — monitor potassium weekly for 4 weeks with a liberal-salt diet.
- **Medical therapy (IHA, GRA, non-operative APA): spironolactone** 12.5–25 mg/day titrated to ≤400 mg (side-effects — gynaecomastia, mastodynia, erectile dysfunction, menstrual irregularity from anti-androgen/progestogenic actions); **eplerenone** (selective MR antagonist, 25 mg bid, fewer endocrine side-effects, preferred in men and pregnancy — FDA category B); **amiloride** (K^+-sparing, 5–10 mg bid); **finerenone** (non-steroidal MRA) used off-label. Aim for high-normal K^+ **and un-suppressed renin** (a marker of adequate dosing/cardiovascular protection).
- **GRA:** low-dose **glucocorticoid** (dexamethasone/prednisone/hydrocortisone, smallest effective dose) ± MR antagonist; confirm by genetic testing.
- **Pregnancy:** progesterone may antagonise MR (improving some cases); captopril/saline tests avoided; MRI without gadolinium for imaging; eplerenone preferred if drug therapy needed.

High-yield exam pointers

- **Conn's syndrome** = aldosterone-producing adenoma; commonest *cause overall* of PA is **bilateral idiopathic hyperplasia (IHA)**.
- **Hypokalaemic hypertension with metabolic alkalosis and suppressed renin** = classic PA; but **~70% are normokalaemic** — screen widely.

- **Screening test = ARR**; stop MR antagonists 4–6 weeks before; **confirmatory = saline infusion / oral salt-loading** (failure to suppress aldosterone).
- **AVS is the gold standard for lateralisation**; CT alone is unreliable (misses micro-adenomas, false incidentalomas).
- **KCNJ5 (GIRK4)** is the commonest somatic mutation in APA; **hybrid steroids (18-oxo-/18-OH-cortisol)** mark GRA and KCNJ5 disease.
- **GRA = FH type I**, *CYP11B1/CYP11B2* chimeric gene, ACTH-driven, **dexamethasone-suppressible**, early stroke risk.
- **High-normal serum sodium + hypomagnesaemia + no oedema** (mineralocorticoid escape) are clinical clues.
- **Unilateral disease → laparoscopic adrenalectomy** (cures HTN in 30–60%); **bilateral/IHA → MR antagonist**.
- **Liddle syndrome** (low renin, low aldosterone) responds to **amiloride/triamterene, NOT spironolactone** (constitutively active ENaC).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of the Adrenal Cortex" (Primary Mineralocorticoid Excess; Tables 398-3/398-4; Fig 398-12 diagnostic algorithm).
- **Williams Textbook of Endocrinology, 15e** — "Endocrine Hypertension" (Conn's historical account; case-detection/confirmatory/subtype testing; AVS interpretation; familial & somatic genetics; pharmacologic treatment; pregnancy).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (screening thresholds, ARR cut-offs, AVS indications, spironolactone/eplerenone/finerenone dosing).

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Hyperglycaemic hyperosmolar state

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

Definition / Introduction — Hyperglycemic hyperosmolar state (HHS) is an acute, life-threatening hyperglycemic emergency characterized by **severe hyperglycemia, hyperosmolality, profound dehydration, and absent or only mild ketosis/acidosis**. It occurs classically in **middle-aged or elderly patients with type 2 diabetes**, often previously mild or occult, after days to weeks of osmotic symptoms and reduced water intake. It is the second major hyperglycemic coma after diabetic ketoacidosis (DKA), but carries higher mortality because patients are older, more dehydrated, and often have infection, myocardial infarction, stroke, chronic kidney disease, heart failure, or postoperative stress.

Etiology and precipitating factors

- **Typical patient**: older person with type 2 diabetes, mild/occult diabetes, poor access to fluids, dementia, prior stroke, frailty, bed-bound state, or social circumstances preventing adequate drinking.

- **Common precipitants**: pneumonia, sepsis, urinary infection, other serious infections, myocardial infarction, stroke, recent operation, trauma, and any acute illness that increases counter-regulatory hormones and reduces oral intake.
- **Drug/procedure triggers**: corticosteroids, diuretics, phenytoin, diazoxide, and glucose-loading procedures such as peritoneal dialysis; antipsychotics and other diabetogenic drugs should also be reviewed in the medication history.
- **Contributing physiology**: polyuria and glycosuria cause large water and electrolyte loss; impaired thirst, nausea, immobility, or inaccessibility of water allows progressive dehydration.
- **DKA-HHS continuum**: DKA and HHS overlap clinically; Harrison notes that up to one-third of patients may have features of both. Therefore every HHS patient must be checked for ketonemia, acidosis, and anion gap.

Pathophysiology

- The central defect is **relative insulin deficiency plus inadequate fluid intake**. Insulin is sufficient to restrain lipolysis and ketogenesis, but insufficient to suppress hepatic glucose output or promote peripheral glucose utilization.
- Increased hepatic **gluconeogenesis and glycogenolysis**, impaired skeletal-muscle glucose uptake, and hyperglucagonemia produce severe hyperglycemia.
- Hyperglycemia causes **osmotic diuresis** with loss of water, sodium, potassium, magnesium, phosphate, and glucose in urine.
- Progressive intravascular volume contraction reduces glomerular filtration and renal glucose clearance, which further worsens hyperglycemia and hyperosmolality.
- Hyperosmolality draws water from cells, including brain cells, producing **confusion, lethargy, seizures, and coma**; neurological manifestations correlate better with osmolality than with glucose alone.
- Ketosis is absent or mild because residual portal insulin, lower free fatty acid flux, lower counter-regulatory hormone drive than in DKA, and a less ketotic insulin/glucagon ratio suppress hepatic ketone-body synthesis.

Clinical features

- **Prodrome**: days to weeks of polyuria, polydipsia, weakness, weight loss, blurred vision, and declining oral intake.
- **Dehydration**: intense thirst may be absent; examination shows dry mucosa, poor skin turgor, sunken eyes, tachycardia, postural hypotension or shock, oliguria, and prerenal azotemia.
- **Neurological features**: lethargy and confusion develop as serum osmolality rises above about 310 mOsm/kg; convulsions and coma can occur above 320-330 mOsm/kg.
- **Absent DKA clues**: nausea, vomiting, abdominal pain, acetone breath, and Kussmaul respiration are absent or much less prominent than in DKA.
- **Precipitant clues**: fever may be absent despite infection; actively seek pneumonia, urinary infection, sepsis, acute coronary syndrome, stroke, pancreatitis, trauma, drug exposure, and recent surgery.

- **Severe cases** may present directly with hypotensive shock, acute kidney injury, rhabdomyolysis, focal neurological deficits, seizures, or coma.

Diagnosis and laboratory profile

Feature	HHS	DKA comparison
Plasma glucose	**>600 mg/dL** diagnostic threshold; often 600-1200 mg/dL and may reach 800-2400 mg/dL	Usually 250-600 mg/dL
Serum osmolality	**>310 mOsm/kg** in CMDT; severe neurological disease often >320-330 mOsm/kg	Usually lower; may be >300
Arterial/venous pH	**>7.3**	<7.3 in DKA
Serum bicarbonate	Usually **>15-18 mEq/L**	<18 mEq/L
Anion gap	Usually normal, **<14 mEq/L**; mild lactic acidosis may raise it	Raised
Ketones	Absent or mild; serum beta-hydroxybutyrate usually **<1 mmol/L**	Marked, often >3 mmol/L
Sodium	Measured sodium may be normal/low; **corrected sodium is often high**	Often low from osmotic water shift
Renal indices	Prerenal azotemia common; BUN may be markedly high	Variable

- Calculate tonicity/effective osmolality using effective solutes: approximately **2 x measured Na + glucose/18** (mg/dL units); urea contributes to measured osmolality but not tonicity because it crosses cell membranes.
- Correct serum sodium for hyperglycemia: add about **1.6 mEq/L** to measured sodium for each 100 mg/dL rise in glucose above normal; some physiology texts note higher correction factors at extreme glucose levels, so interpret with measured osmolality and clinical state.
- Initial work-up: capillary and plasma glucose, electrolytes, urea/creatinine, venous or arterial pH, bicarbonate, anion gap, measured serum osmolality if available, serum/urine ketones or beta-hydroxybutyrate, urine routine, CBC, cultures when infection is suspected, ECG, chest radiograph, troponin, and neuroimaging when focal deficits or persistent coma suggest stroke or structural disease.
- Diagnose HHS only after excluding significant DKA, lactic acidosis, renal failure-related uremic encephalopathy, sepsis-associated encephalopathy, stroke, and drug/toxin causes of coma.

Management

- **Site of care**: admit to monitored high-dependency or ICU setting if shock, coma, severe electrolyte disturbance, acute coronary syndrome, stroke, sepsis, renal failure, or need for frequent insulin/electrolyte titration.
- **Immediate priorities**: airway protection in coma/vomiting, oxygen if hypoxemic, two IV lines, cardiac monitoring, catheterize if needed for urine output, and begin a flow sheet for vitals, mental status, input-output, glucose, electrolytes, osmolality, and insulin rate.

- **Fluids are paramount**. If hypotension or oliguria is present, start **0.9% saline**; Harrison suggests **1-3 L over the first 2-3 h** to restore hemodynamic stability. Fluid deficit is often **6-10 L**, sometimes 9-10 L, and should be corrected over about 24-48 h.
- After hemodynamic stabilization, choose fluid by corrected sodium and osmolality: use **0.45% saline** if sodium is high or >150 mEq/L; otherwise continue isotonic or hypotonic saline according to volume status. CMDT notes that **4-6 L may be needed in the first 8-10 h**, but correction must be controlled to avoid neurological worsening.
- Aim to restore urine output to **at least 50 mL/h** while avoiding pulmonary edema in elderly patients, heart failure, and chronic kidney disease.
- **Insulin**: do not let insulin precede initial fluid resuscitation unless there is significant ketosis/acidosis. A current adult approach is IV regular insulin **0.05 unit/kg/h without bolus**, titrated to lower glucose by **50-70 mg/dL/h**. Harrison also describes a hyperglycemic-crisis regimen of 0.1 unit/kg IV bolus followed by 0.1 unit/kg/h; in HHS, lower-dose fluid-first insulin is safer when ketosis is absent.
- Add dextrose when plasma glucose reaches about **250 mg/dL**; maintain glucose around **250-300 mg/dL** until osmolality, hydration, and mental status improve, then transition to subcutaneous insulin.
- **Potassium**: total-body potassium is depleted despite normal initial serum potassium. Because acidosis is absent, initial hyperkalemia is less common than in DKA, and potassium may fall rapidly with insulin. If renal function and urine output are adequate and potassium is not elevated, add potassium early, e.g., **10 mEq/L** in initial fluids; hold insulin if potassium is severely low until corrected.
- **Phosphate and magnesium**: routine phosphate is not required; replace phosphate if severe hypophosphatemia develops, especially **<1 mg/dL**, and correct magnesium if deficient, particularly in diuretic users.
- **Precipitant treatment**: obtain cultures before antibiotics when feasible, but do not delay antibiotics for suspected sepsis; treat MI, stroke, pneumonia, UTI, pancreatitis, surgery-related infection, and offending drugs.
- **Thrombosis prevention**: severe dehydration and low-flow state predispose to MI, stroke, pulmonary embolism, mesenteric venous thrombosis, and DIC; pharmacologic VTE prophylaxis is reasonable unless contraindicated, while routine full-dose anticoagulation is not automatically indicated.
- **Transition and discharge**: continue insulin during admission; after stabilization and eating, overlap IV insulin with subcutaneous basal insulin. Many patients require insulin for weeks, but some later recover enough endogenous insulin secretion for diet plus oral agents.

Complications and prognosis

- **Neurological**: seizures, coma, and worsening mental status from hyperosmolality; too-rapid correction may contribute to cerebral edema or neurological deterioration.
- **Renal and muscle**: prerenal azotemia, acute kidney injury, and rhabdomyolysis should be anticipated and monitored.

- **Vascular**: MI, ischemic stroke, pulmonary embolism, mesenteric venous thrombosis, disseminated intravascular coagulation, and limb ischemia occur due to dehydration, hyperviscosity, and underlying comorbidity.
- **Treatment-related**: hypoglycemia, hypokalemia, hypophosphatemia, hyperchloremic acidosis with large saline loads, fluid overload, and pulmonary edema.
- Mortality is substantially higher than DKA: Harrison cites up to **15%** in some series; CMDT notes it is more than ten times DKA largely because of age, delayed recognition, dehydration, and coexistent illness, and delayed cases historically approached very high mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flowchart**: relative insulin deficiency + stress hormones -> hepatic glucose output + impaired peripheral uptake -> severe hyperglycemia -> glycosuria/osmotic diuresis -> water/electrolyte loss -> hypovolemia -> reduced GFR -> worsening hyperglycemia -> hyperosmolality -> brain cell dehydration -> confusion/seizure/coma; side label: residual insulin suppresses ketogenesis.
- **Management algorithm**: suspect HHS -> ABC/vitals/IV access -> labs including glucose, electrolytes, osmolality, pH, ketones -> 0.9% saline if shock -> choose 0.45% saline by corrected sodium -> monitor K and urine output -> IV insulin 0.05 unit/kg/h after fluids -> dextrose at glucose 250 mg/dL -> treat precipitant -> subcutaneous insulin transition.

Clinical / Diagnostic significance

- HHS is a **diagnosis of dehydration plus tonicity**, not merely a high glucose value; mental status change is an osmolality warning sign.
- In an elderly diabetic with coma, always check glucose, sodium, osmolality, ketones, pH, urea/creatinine, ECG, and infection screen before attributing the coma to stroke alone.
- Corrected sodium guides fluid choice: a "normal" measured sodium in severe hyperglycemia may hide significant free-water deficit.
- Absence of Kussmaul breathing and abdominal pain helps distinguish HHS from DKA, but overlap is common; beta-hydroxybutyrate and pH are mandatory.
- Treat the precipitant as aggressively as the glucose: pneumonia, sepsis, MI, stroke, and postoperative infection often determine outcome.
- Prevention after recovery requires sick-day education, caregiver involvement, early contact during infection/vomiting, maintaining sugar-free fluids, and medication review, especially diuretics and corticosteroids.

High-yield exam pointers

- Triad: **severe hyperglycemia + hyperosmolality + profound dehydration with little/no ketoacidosis**.
- Typical case: elderly type 2 diabetic, days-weeks of polyuria and poor intake, then confusion/coma.
- Diagnostic essentials: glucose **>600 mg/dL**, osmolality **>310 mOsm/kg**, pH **>7.3**, bicarbonate **>15-18 mEq/L**, normal anion gap, absent/mild ketones.

- Osmolality drives coma: confusion above about **310 mOsm/kg**, seizures/coma often above **320-330 mOsm/kg**.
- First treatment is **fluid**, not insulin; restore circulation before lowering glucose aggressively.
- Use insulin cautiously: **0.05 unit/kg/h** after fluids in nonketotic HHS; avoid glucose fall faster than **50-70 mg/dL/h**.
- Add dextrose around **250 mg/dL** and continue controlled correction until osmolality and mental status recover.
- Potassium is depleted even if serum potassium is normal; replace early if urine output is adequate and potassium is not high.
- Mortality is higher than DKA; death usually reflects age, dehydration, delayed diagnosis, infection, MI, stroke, CKD, or HF.

SOURCE & COVERAGE

Harrison 22e — "Diabetes Mellitus: Management and Therapies"; "Diabetes Mellitus: Complications"; Williams Textbook of Endocrinology 15e — "Therapeutics of Type 2 Diabetes Mellitus"; "Posterior Pituitary"; CMDT 2026 — "Diabetes Mellitus & Hypoglycemia".

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Hyperprolactinaemia

Asked in: Paper IV 17 Apr 2026 · Paper IV Jul 2021 · Paper IV Nov 2020 (3×) — RGUHS MD General Medicine

Definition / Introduction — Hyperprolactinemia is sustained elevation of serum prolactin (PRL) above the assay-specific reference range (normal adult PRL ≈10–25 μg/L in women and 10–20 μg/L in men). It is the **most common pituitary hormone hypersecretion syndrome** in both sexes. Because the hypothalamus exerts *tonic dopaminergic inhibition* of lactotrope PRL release (via D2 receptors), hyperprolactinemia results either from autonomous lactotrope secretion (prolactinoma), from loss of dopaminergic tone (stalk disconnection, drugs), or from physiologic/systemic stimuli. Clinically it presents with hypogonadism, galactorrhea and infertility, and may signal an underlying sellar mass.

Prolactin physiology — basis of the syndrome

- **Structure/source:** PRL is a 198-amino-acid polypeptide (≈23 kDa), homologous to GH and placental lactogen, secreted by **lactotropes** (~20% of anterior pituitary cells); lactotrope hyperplasia occurs in pregnancy/lactation under estrogen drive. Circulating **half-life ≈50 min**; secretion is pulsatile with nocturnal (non-REM sleep) peaks at 4–6 a.m.
- **Unique inhibitory control:** Unlike other pituitary hormones, PRL is under predominantly *inhibitory* hypothalamic control — **dopamine acting on pituitary D2 receptors** suppresses PRL synthesis and secretion. Hence any lesion that interrupts dopamine delivery (stalk section) causes hyperprolactinemia, and **dopamine agonists are the cornerstone of treatment**.
- **Stimulators: TRH** releases PRL within 15–30 min (explains hyperprolactinemia of primary hypothyroidism); estrogen, suckling/chest-wall afferents, stress and sleep also raise PRL.
- **Why hypogonadism occurs:** Excess PRL suppresses hypothalamic **GnRH** pulsatility → reduced LH/FSH → impaired gonadal steroidogenesis (low estradiol/testosterone); PRL also directly

inhibits ovarian folliculogenesis and granulosa-cell aromatase (anovulation, luteolysis) and testicular function.

Etiology — classified (physiologic / pathologic / pharmacologic)

Category	Causes
Physiologic	Pregnancy, lactation, nipple/chest-wall stimulation or trauma (incl. herpes zoster, thoracotomy), sleep, stress, exercise, sexual orgasm
Hypothalamic–pituitary stalk damage	Pituitary adenoma with **stalk compression**, suprasellar masses (craniopharyngioma, meningioma, dysgerminoma, metastases), Rathke cleft cyst, empty sella, lymphocytic hypophysitis, granulomas/infiltration, cranial irradiation, head trauma/stalk section, suprasellar surgery
Pituitary hypersecretion	**Prolactinoma** (commonest tumoural cause); acromegaly (GH–PRL/ mammosomatotrope tumours), plurihormonal adenomas
Systemic	**Chronic renal failure** (↓ peripheral clearance), **primary hypothyroidism** (↑ TRH), cirrhosis, PCOS, pseudocyesis, seizures
Drug-induced	Antipsychotics — **risperidone** (often >200 µg/L), phenothiazines (chlorpromazine, perphenazine), butyrophenones (haloperidol); **metoclopramide**, domperidone; **methyldopa** (↓ DA synthesis); **verapamil** (↓ DA release); reserpine; TCAs/SSRIs (fluoxetine); H2-blockers (cimetidine); opiates; estrogens; TRH

- **PRL level guides cause:** Mild elevation (30–100 µg/L) typically reflects drugs, stalk compression, hypothyroidism or renal failure; a level **>200–250 µg/L almost invariably indicates a prolactinoma**. *Caveat:* a large *non*-lactotrope macroadenoma can raise PRL only modestly (usually <100 µg/L) by stalk compression — the level per tumour-volume cannot always distinguish the two.
- **Prolactinoma facts:** Lactotrope tumours account for ~half of functioning pituitary adenomas; **microadenoma <1 cm, macroadenoma ≥1 cm**. Microprolactinoma F:M ≈ **20:1**; macroadenoma sex ratio ≈ 1:1 (men present larger/later). ~20% of MEN-1 patients have prolactinomas. Only ~5% of microadenomas progress to macroadenomas.

Clinical features

- **Women:** the triad of **amenorrhoea/oligomenorrhoea, galactorrhoea and infertility**; pre-menarchal onset → primary amenorrhoea; reduced libido, vaginal dryness, mild hirsutism, weight gain. **Galactorrhoea in up to 80%** of hyperprolactinaemic women (may need to be elicited).
- **Men:** decreased libido, **erectile dysfunction**, oligospermia/infertility, gynaecomastia; true galactorrhoea uncommon. Long-standing hypogonadism → osteopenia, reduced muscle mass, decreased beard growth. Men more often present late with **mass effects** (headache, visual loss).
- **Skeletal:** chronic hypoestrogenism/hypogonadism reduces bone mineral density → **osteoporosis** and vertebral fractures.
- **Mass-effect symptoms (macroadenoma):** headache, **bitemporal hemianopia** (chiasmal compression), cranial nerve III/IV/VI palsy (cavernous sinus), hypopituitarism, rarely apoplexy.

Laboratory investigation & diagnostic approach

- **Step 1 — confirm:** basal, **fasting morning serum PRL** (avoid stress/venepuncture artefact); repeat if borderline. Exclude **pregnancy** (β-hCG) first.
- **Step 2 — exclude secondary causes** *before* imaging: drug history, **TSH/free T4** (hypothyroidism), renal and hepatic function; review oestrogen/neuroleptic exposure.
- **Two key assay pitfalls (high-yield):**
  - **Hook effect** — in very large prolactinomas with extreme PRL (>1000 µg/L), antibody saturation gives a *falsely low/normal* reported value; correct by **serial sample dilution**.
  - **Macroprolactinemia** — high-molecular-weight aggregated PRL (biologically inactive) gives elevated readings with *few/absent symptoms*; detect by **polyethylene glycol (PEG) precipitation**.
- **Step 3 — imaging:** if no reversible cause, perform **gadolinium-enhanced pituitary MRI** (T1 iso/hypointense, T2 hyperintense adenoma); microadenomas <2 mm may be MRI-occult, so a normal scan does not exclude a microprolactinoma. **Formal perimetry** for any macroadenoma abutting the chiasm; assess anterior-pituitary reserve (IGF-1, 8 a.m. cortisol, gonadotropins, thyroid axis).
- **Idiopathic hyperprolactinemia** = diagnosis of exclusion with normal MRI.

Treatment / Management

- **Principles:** treat the **cause**; aim to normalise PRL to restore gonadal function, stop galactorrhoea, preserve bone density, and shrink any tumour. Stop offending drugs where possible; **levothyroxine** corrects hypothyroidism-related rise; treat renal failure. Asymptomatic microadenomas not desiring fertility may simply be monitored (serial PRL + MRI) — up to **30% resolve spontaneously**.
- **Dopamine agonists (DA) — first-line for prolactinoma and most causes:** suppress PRL secretion/synthesis and lactotrope proliferation; effective even when raised PRL is due to non-lactotrope stalk compression (so DA-induced PRL fall does **not** prove the mass is a prolactinoma).

Drug	Dose	Key points
Cabergoline (preferred)	0.25–1 mg **twice weekly**	Long-acting, high D2 affinity; normalises PRL in ~**80% micro / ~70% macro**, NEJM data **83% vs 52%** for bromocriptine; better tolerated; valve surveillance at high doses
Bromocriptine	0.625–2.5 mg, up to 2.5 mg tid	Short-acting ergot; **preferred when fertility/pregnancy** desired; more GI/orthostatic side-effects

- **Side-effects of DAs:** nausea, postural hypotension, constipation, nasal stuffiness, fatigue; impulse-control disorders and (at high/Parkinsonian doses, e.g. ≥3 mg/day cabergoline) **cardiac valve regurgitation** — obtain a baseline **echocardiogram** before standard-dose therapy. **~20% of tumours are DA-resistant** (more often in men).
- **Surgery (transsphenoidal):** reserved for DA intolerance/resistance, or an invasive macroadenoma with threatened vision unresponsive to drugs. PRL normalisation ~70% (micro)

but only ~40% (macro); hyperprolactinaemia recurs in up to 20% by 1 year and >50% long-term for macroadenomas.

- **Radiotherapy:** only for aggressive tumours refractory to DA + surgery.
- **Pregnancy:** restore fertility with **bromocriptine**; stop DA once pregnancy confirmed for a microadenoma. Microprolactinomas enlarge clinically in <3–5%, **macroprolactinomas in 15–30%** — continue DA and perform trimester-wise visual fields for macroadenomas.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Hypothalamic–pituitary control of PRL.** Labels: *Hypothalamus* → *Dopamine (inhibitory, –) and TRH (stimulatory, +)*; *Hypophyseal portal vessels / pituitary stalk*; *Lactotrope (D2 receptor)*; *Prolactin*; downstream ↓ *GnRH* → ↓ *LH/FSH* → ↓ *oestrogen/testosterone (hypogonadism)* and ↑ *breast milk (galactorrhoea)*. Show **stalk section** interrupting dopamine flow → ↑PRL.
- **Diagram 2 — Coronal sella MRI of a macroadenoma.** Labels: *pituitary macroadenoma in sella turcica*, *suprasellar extension compressing the optic chiasm (bitemporal hemianopia)*, *cavernous sinus + internal carotid artery*, *sphenoid sinus*, *pituitary stalk*.

Clinical / Diagnostic significance

- **Common reversible mimic:** always exclude **drugs, pregnancy, hypothyroidism and renal failure** before extensive endocrine work-up — avoids unnecessary imaging/surgery.
- **PRL magnitude triages the lesion:** >200–250 µg/L ⇒ prolactinoma; modest rise with a large mass ⇒ suspect stalk compression by a non-functioning/other tumour.
- **Galactorrhoea + amenorrhoea** should be regarded as a pituitary adenoma until proven otherwise.
- **Bone:** screen BMD in chronic hypogonadal hyperprolactinaemia.
- **Psychiatric link:** antipsychotic-induced hyperprolactinaemia (esp. risperidone) is common; manage by supervised drug switch/dose titration with the prescriber, as DAs may aggravate psychosis.

High-yield exam pointers

- PRL is unique among pituitary hormones in being under **dominant inhibitory (dopaminergic D2) control** → stalk lesions cause hyperprolactinaemia and DAs treat it.
- **>200 µg/L = prolactinoma almost certain**; mild rise (30–100) = drugs/stalk/hypothyroid/renal.
- **Microprolactinoma F:M 20:1; macroadenoma ~1:1**; men present with larger tumours and mass effects.
- Two assay traps: **hook effect** (dilute the sample) and **macroprolactinemia** (PEG precipitation).
- **Cabergoline** > bromocriptine for efficacy/tolerability; **bromocriptine** preferred in pregnancy.
- DA shrinks macroprolactinomas dramatically — *medical therapy is first-line even for large tumours*, unlike most other macroadenomas.
- High-dose cabergoline → **valvular regurgitation** risk; baseline echocardiogram.
- **Primary hypothyroidism** raises PRL via TRH — corrected by levothyroxine, not a DA.

- Up to **30% of idiopathic hyperprolactinaemia resolves spontaneously**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pituitary Tumor Syndromes" (Hyperprolactinemia, Galactorrhea, Prolactinoma; Table 392-5 Etiology) and "Physiology of Anterior Pituitary Hormones" (Prolactin synthesis/secretion/action; dopaminergic control).
- **Williams Textbook of Endocrinology, 15e** — "Pituitary Adenomas and Masses" (causes of hyperprolactinemia, hook effect, macroprolactin/PEG, giant prolactinoma, dopamine-agonist treatment data including cabergoline vs bromocriptine).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (current management, pregnancy strategy, surgical/recurrence data).

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Hypoglycaemia

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

Definition / Introduction — Hypoglycemia is a clinical syndrome of low plasma glucose sufficient to cause symptoms and resolving when glucose is restored. It is rigorously defined by **Whipple's triad**: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose measured by a precise method, and (3) relief of symptoms after the glucose is raised. The lower limit of fasting plasma glucose is normally **~70 mg/dL (~3.9 mmol/L)**. It is most often iatrogenic — caused by insulin or insulin secretagogues used to treat diabetes — and should be considered in any patient with confusion, an altered level of consciousness, or a seizure. Severe hypoglycemia increases the risk of serious cardiovascular events and death.

Physiology of glucose counterregulation

- Glucose is an **obligate fuel for the brain**, which cannot synthesise glucose or store more than a few minutes' supply; it needs a continuous arterial supply.
- Plasma glucose is kept ~**70–110 mg/dL (3.9–6.1 mmol/L)** fasting by hepatic glycogenolysis and hepatic/renal gluconeogenesis. Hepatic glycogen lasts only **~8 h** (less with exercise/illness), after which gluconeogenesis predominates (precursors: lactate, alanine, glutamine from muscle; glycerol from adipose lipolysis).
- Defences against falling glucose follow a tiered, threshold-based sequence:

Defence	Mediator	Glycemic threshold mg/dL (mmol/L)	Action
First	↓ **Insulin** secretion	80–85 (4.4–4.7)	↑ glycogenolysis & gluconeogenesis; ↑ lipolysis
Second	↑ **Glucagon** (pancreatic α-cell)	65–70 (3.6–3.9)	↑ hepatic glycogenolysis & gluconeogenesis

Defence	Mediator	Glycemic threshold mg/dL (mmol/L)	Action
Third	↑ **Epinephrine** (adrenomedullary)	65–70 (3.6–3.9)	↑ glucose production, ↓ clearance; critical when glucagon deficient
Late/slow	↑ **Cortisol & GH**	50–55 (2.8–3.1)	Support production; *no role in acute defence* (act only after ~4 h)
Behavioural	**Symptoms**	—	Recognition → food ingestion
Failure	↓ **Cognition**	<50 (<2.8)	Compromises behavioural defence

- *A fall in insulin is the first defence; glucagon the second; epinephrine the third (and pivotal when glucagon is lacking).* Cortisol and GH are **not** required for defence against acute hypoglycemia in adults.
- Thresholds are **dynamic**: they shift higher in poorly controlled diabetes (symptoms near normoglycemia) and lower with recurrent hypoglycemia (insulinoma, intensively treated diabetes).

Classification / Causes (across the life span)

Etiology is best framed by clinical context — the "ill or medicated" vs the "seemingly well" patient (Table 418-1).

Ill or medicated individual	Seemingly well individual
1. Drugs — insulin or insulin secretagogues; **alcohol**; others (ACE inhibitors, ARBs, β-blockers, quinolones, indomethacin, quinine, sulfonamides)	**5. Endogenous hyperinsulinism** — insulinoma; functional β-cell disorder (*nesidioblastosis*); noninsulinoma pancreatogenous hypoglycemia (NIPHS); post–gastric-bypass hypoglycemia; insulin/insulin-receptor autoimmune; secretagogues; GLP-1 RA + insulin/secretagogue
2. Critical illness — hepatic, renal or cardiac failure; sepsis; inanition	**6. Disorders of gluconeogenesis & fatty-acid oxidation**
3. Hormone deficiency — cortisol; growth hormone; glucagon + epinephrine (in insulin-deficient diabetes)	**7. Exercise**
4. Non–islet-cell tumour (e.g., mesenchymal/epithelial tumours)	**8. Accidental, surreptitious or malicious; 9. Prolonged fasting; 10. Pregnancy**

- **Drugs (commonest):** insulin/secretagogues suppress glucose production and ↑ utilisation. **Ethanol blocks gluconeogenesis but not glycogenolysis**, so alcohol-induced hypoglycemia follows a multi-day binge with poor intake and glycogen depletion.
- **Critical illness:** rapid hepatic destruction (the major site of glucose production), renal failure (reduced insulin clearance + fewer precursors), cardiac failure, and **sepsis** (cytokine-driven ↑ utilisation).
- **Non–islet-cell tumour:** large hepatomas, adrenocortical carcinomas, carcinoids — overproduce incompletely processed **"big IGF-II"** with a **high IGF-II : IGF-I ratio**; endogenous insulin is appropriately suppressed.

- **Inborn errors** (mostly infancy, occasionally adults): glycogen storage disease types 0, I, III, IV and Fanconi-Bickel syndrome (fasting); fatty-acid oxidation defects; glucokinase/SUR1/Kir6.2 mutations and hereditary fructose intolerance (postprandial).

Clinical manifestations

- **Neuroglycopenic** (direct CNS glucose deprivation): behavioural changes, confusion, fatigue, **seizure, loss of consciousness, cardiac arrhythmias**, and, if severe, death; transient focal deficits occur occasionally, permanent deficits are rare.
- **Neurogenic / autonomic** (sympathoadrenal discharge):
  - **Adrenergic** (norepinephrine): palpitations, tremor, anxiety.
  - **Cholinergic** (acetylcholine): sweating, hunger, paresthesias.
- **Signs:** diaphoresis and pallor; heart rate and systolic BP usually rise (may be blunted after recent recurrent episodes).
- Symptoms are **non-specific** — attribution requires a documented low glucose with resolution on correction (Whipple's triad).

Hypoglycemia in diabetes & HAAF

- Hypoglycemia is the **limiting factor in glycemic management of diabetes**. Patients with T1DM average ~2 symptomatic episodes/week and ≥1 severe episode/year; an estimated **6–10% of people with T1DM die as a result of hypoglycemia**.
- **Conventional risk factors** = relative or absolute insulin excess: excessive/ill-timed/wrong-type insulin or secretagogue; reduced glucose influx (missed meals, fasting); increased utilisation (exercise); increased insulin sensitivity; reduced glucose production (alcohol); reduced insulin clearance (renal failure).
- **Hypoglycemia-Associated Autonomic Failure (HAAF)** — recent antecedent hypoglycemia (or prior exercise/sleep) produces two linked syndromes that drive a vicious cycle of recurrent hypoglycemia:
  - **Defective glucose counterregulation** — loss of the insulin-decrement and glucagon-increment, plus an attenuated epinephrine response → **≥25-fold** greater risk of severe iatrogenic hypoglycemia.
  - **Hypoglycemia unawareness** — attenuated sympathoadrenal (largely sympathetic neural) response → loss of warning symptoms → **~6-fold** increased risk.
- HAAF is functional and **reversible by ~2–3 weeks of scrupulous avoidance of hypoglycemia**, distinguishing it from structural, irreversible diabetic autonomic neuropathy. Trials confirming severe hypoglycemia at HbA1c 8–10%: **ACCORD** (stopped early for excess mortality), **ADVANCE, VADT, ORIGIN**; in-hospital **NICE-SUGAR** showed harm from tight control — hence inpatient targets of **140–180 mg/dL**.

Diagnostic approach & investigations

- **Document Whipple's triad** — draw blood for glucose *before* giving glucose; measure plasma glucose by a precise (laboratory) method. Handheld/continuous glucose monitors are **not** diagnostic at low values.

- Exclude **pseudohypoglycemia**: artefactually low glucose from ex-vivo metabolism in leukocytosis/erythrocytosis/thrombocytosis or delayed serum separation; a low glucose without corresponding symptoms suggests an artefact.
- **Diagnose the mechanism** — in the seemingly well patient, work up **endogenous hyperinsulinism**. During a spontaneous or provoked episode (up to a **72-h supervised fast** or mixed meal) with plasma glucose **<55 mg/dL (<3.0 mmol/L)** and symptoms, the critical findings are:

Analyte	Hyperinsulinism cut-off
Plasma **insulin**	≥3 μU/mL (≥18 pmol/L)
C-peptide	≥0.6 ng/mL (≥0.2 nmol/L)
Proinsulin	≥5.0 pmol/L
β-hydroxybutyrate	≤2.7 mmol/L
Glucose rise after IV **glucagon 1.0 mg**	>25 mg/dL (>1.4 mmol/L)
Sulfonylurea/glinide screen	Negative

- **Differentiating hyperinsulinism:** secretagogue ingestion → **high** C-peptide (positive drug screen distinguishes it); **exogenous insulin** → hypoglycemia with **low** C-peptide (suppressed endogenous secretion); non–islet-cell tumour → **suppressed** insulin/C-peptide with high big-IGF-II.
- **Insulinoma:** yearly incidence ~**1 in 250,000**; **>90% benign**; median age 50 (third decade and multiple if part of **MEN-1**); **>99% intrapancreatic**, usually **<2 cm**. Imaging: CT/MRI detect ~**70–80%**, endoscopic ultrasound sensitivity ~**90%**, somatostatin-receptor scintigraphy ~half; selective arterial calcium stimulation regionalises diffuse disease; intra-operative ultrasound localises non-palpable tumours.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Tiered counterregulation cascade (vertical arrow of falling glucose):** label glucose levels **80–85 mg/dL → ↓ Insulin (1st defence)**; **65–70 mg/dL → ↑ Glucagon (2nd) and ↑ Epinephrine (3rd)**; **50–55 mg/dL → ↑ Cortisol & GH**; **<50 mg/dL → Neuroglycopenia / ↓ Cognition**. Side-label **Symptoms (autonomic warning)** between the epinephrine and cognition tiers.
> - **HAAF vicious-cycle loop:** label *Recurrent hypoglycemia → ↓ Adrenomedullary epinephrine + ↓ Sympathetic neural response → Defective glucose counterregulation + Hypoglycemia unawareness → (back to) Recurrent hypoglycemia*; annotate inputs *Antecedent hypoglycemia / Exercise / Sleep*.

Clinical / Diagnostic significance

- **Urgent treatment:** if conscious, oral **15–20 g glucose** (tablets/juice/candy); if neuroglycopenic, **IV glucose 25 g** then an infusion titrated to serial glucoses. If no IV access, **SC/IM glucagon 1.0 mg** — but glucagon is *ineffective in glycogen-depleted states* (alcohol) and *less useful in T2DM* (it also stimulates insulin secretion). **Octreotide** suppresses insulin secretion in **sulfonylurea-**

induced hypoglycemia. All raise glucose only transiently — the patient must eat to replete glycogen.

- **Prevention of recurrence** is mechanism-specific: stop/reduce the offending drug (sulfonylurea effect may last **hours-to-days**); treat the critical illness; replace deficient cortisol/GH; debulk a non–islet-cell tumour (± glucocorticoid/GH).
- **Insulinoma:** surgical resection is **curative**; for unresectable tumours or functional β-cell disorders use **diazoxide** (inhibits insulin secretion), **octreotide**, or **everolimus** (mTOR inhibitor); partial pancreatectomy may be needed for diffuse disease. Frequent feeds, **uncooked cornstarch at bedtime**, or overnight intragastric glucose help refractory cases.
- Risk-reduction in diabetes: second-generation basal/prandial analogue insulins, GLP-1 (± GIP) agonists added to basal insulin, **continuous glucose monitoring** with predictive low-glucose suspend / closed-loop "artificial pancreas," structured patient education, and individualised, incrementally tightened HbA1c goals.

High-yield exam pointers

- **Whipple's triad** is mandatory for diagnosis; fasting glucose lower limit ~70 mg/dL.
- Defence order: ↓ **insulin (1st)** → **glucagon (2nd)** → **epinephrine (3rd)**; cortisol/GH play *no role* in acute defence.
- **Ethanol blocks gluconeogenesis, not glycogenolysis** → glucagon is useless in alcohol-induced hypoglycemia.
- **C-peptide high** = secretagogue/insulinoma; **C-peptide low** = exogenous (factitious) insulin; **insulin + C-peptide suppressed + big-IGF-II high** = non–islet-cell tumour.
- Hyperinsulinism criteria (glucose <55 mg/dL): insulin ≥3 μU/mL, C-peptide ≥0.6 ng/mL, proinsulin ≥5 pmol/L, β-OHB ≤2.7 mmol/L; **72-h fast** is the classic provocation.
- **Insulinoma**: >90% benign, >99% intrapancreatic, <2 cm; consider **MEN-1**; resection curative.
- **HAAF** = defective counterregulation (≥25-fold risk) + hypoglycemia unawareness (~6-fold risk); **reversible in 2–3 weeks** of avoidance.
- Treatment ladder: oral 15–20 g → IV 25 g glucose → glucagon 1 mg IM/SC; octreotide for sulfonylurea overdose.

SOURCE & COVERAGE

Harrison 22e — Ch 418 "Hypoglycemia" (Stephen N. Davis). Fully covers the asked topic — definition, counterregulatory physiology, etiologic classification (Table 418-1), clinical features, HAAF, diagnostic evaluation including the biochemical criteria for endogenous hyperinsulinism, insulinoma, and treatment. No coverage gap; all numbers, thresholds and drug details above are taken verbatim from the chapter.

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Insulin resistance

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

Definition / Introduction — Insulin resistance (IR) is the *decreased ability of insulin to act effectively on its target tissues* — chiefly **skeletal muscle, liver and adipose tissue** — so that a normal insulin concentration produces a subnormal biological response. It is *relative* rather than absolute, because supranormal (compensatory hyperinsulinaemic) levels can still normalise plasma glucose. IR results from a combination of **genetic susceptibility, obesity and metabolic inflammation**, is the central and usually earliest lesion in **type 2 diabetes mellitus (T2DM)**, and is the most accepted **unifying hypothesis for the metabolic syndrome** — linking obesity to atherogenic dyslipidaemia, hypertension, steatotic liver disease, PCOS and accelerated atherosclerotic cardiovascular disease (ASCVD).

Physiological basis and target tissues

- Insulin normally **stimulates glucose uptake in muscle and fat**, **suppresses hepatic glucose production**, **inhibits adipose-tissue lipolysis** and **stimulates lipoprotein lipase**; inhibition of lipolysis is the *most sensitive* pathway of insulin action.
- In IR these actions fail in a **tissue-selective** manner:
  - **Skeletal muscle** — impaired insulin-stimulated glucose utilisation; whole-body glucose disposal is **30–60% lower** than in non-diabetic individuals → drives *postprandial* hyperglycaemia.
  - **Liver** — failure of hyperinsulinaemia to suppress **gluconeogenesis** → increased hepatic glucose output (drives *fasting* hyperglycaemia) and reduced postprandial glycogen storage.
  - **Adipose tissue** — uninhibited lipolysis → increased **free fatty acid (FFA)** flux to liver and muscle.

Natural history (IR → hyperglycaemia)

- Onset is heralded by **postprandial hyperinsulinaemia → fasting hyperinsulinaemia → hyperglycaemia**.
- Pancreatic beta cells initially **compensate** by raising insulin output, keeping glucose tolerance near-normal despite resistance.
- When secretion can no longer match the degree of resistance → **IFG/IGT**, and ultimately frank **T2DM** (the *twin-defect* model: IR **plus** progressive beta-cell failure). Diabetes develops *only when insulin secretion becomes inadequate for the prevailing insulin resistance*.
- IR (reduced skeletal-muscle glucose utilisation) is demonstrable in many **non-diabetic first-degree relatives** of T2DM patients, underscoring a strong heritable component (twin concordance 70–90%).

Molecular and cellular mechanisms

- The precise molecular lesion is **not fully elucidated** but is predominantly a **"post-receptor" defect**:
  - Insulin-receptor number and **tyrosine-kinase activity** in muscle are reduced, but this is largely *secondary* to hyperinsulinaemia, not the primary fault.

- Defective **insulin-regulated phosphorylation / dephosphorylation** of downstream signalling proteins predominates.

- **Lipotoxicity** — accumulation of lipid intermediates within myocytes impairs **mitochondrial oxidative phosphorylation**, lowers insulin-stimulated ATP production and generates **reactive oxygen species (lipid peroxides)**.
- **Metabolic (low-grade) inflammation** — adipose-resident macrophages and adipocytes secrete **TNF-α, IL-6, IL-1, IL-18 and resistin** and raise **CRP**; this feeds back and *directly worsens* IR.
- **Selective (pathway-specific) resistance** — the mitogenic **MAP-kinase** growth/differentiation pathway remains insulin-sensitive; compensatory hyperinsulinaemia therefore *over-drives* it, potentially **accelerating atherosclerosis**.

Adipose tissue, free fatty acids and adipokines

- **Central/visceral obesity** (high waist–hip ratio) is pivotal; ≥80% of T2DM patients are obese. Visceral fat drains via the **portal vein**, delivering FFAs and adipokines directly to the liver and contributing to hepatic IR. Importantly, **normal-weight South-Asian, Southeast-Asian and Central-American individuals can be insulin-resistant** ("metabolically obese, normal weight").
- Excess **FFAs** impair muscle glucose uptake, promote hepatic gluconeogenesis and **VLDL-triglyceride** synthesis, accumulate as intramuscular/intrahepatic triglyceride, and impair beta-cell function.
- **Adipokines** modulate sensitivity:
  - **Adiponectin** — insulin-*sensitising* and anti-inflammatory (activates AMP-kinase, ↑fatty-acid oxidation, ↓hepatic gluconeogenesis); **reduced** in obesity → contributes to hepatic IR.
  - **Leptin** — normally ↓appetite, ↑energy expenditure, ↑insulin sensitivity; obesity produces **hyperleptinaemia with leptin resistance**.
  - Pro-resistance mediators — **resistin, retinol-binding protein-4, visfatin, fetuin-A, asprosin, PAI-1, TNF-α, IL-6**.

Consequences and clinical correlates of insulin resistance

Domain	Mechanism / effect of IR
Type 2 DM / IGT–IFG	Primary, earliest defect; ~75% of patients with T2DM or IGT have the metabolic syndrome
Atherogenic dyslipidaemia	↑Triglyceride/VLDL, ↓HDL, **small dense LDL**, ↑apoC-III (inhibits lipoprotein lipase)
Hypertension	Loss of insulin's **NO-mediated vasodilation** with *preserved* renal Na^+ reabsorption; ↑sympathetic activity; ↑adipose angiotensinogen
Metabolic syndrome	IR is the unifying pathophysiological mechanism (syndrome X / insulin-resistance syndrome)
MASLD / MASH (NAFLD/NASH)	Hepatic triglyceride accumulation from ↑FFA flux + VLDL synthesis
PCOS	IR present in **50–80%**; independently raises T2DM risk
Hyperuricaemia	↓Renal tubular uric-acid excretion; promotes endothelial dysfunction/hypertension

Domain	Mechanism / effect of IR
Prothrombotic / proinflammatory state	↑PAI-1, fibrinogen, CRP
ASCVD	Relative risk ~**1.5–3×**; MI/stroke risk threefold higher in metabolic syndrome

Severe insulin-resistance syndromes

Syndrome	Key features	Underlying defect
Type A insulin resistance	Young women; severe hyperinsulinaemia, obesity, hyperandrogenism, acanthosis nigricans	Undefined defect in the **insulin-signalling pathway**
Type B insulin resistance	Middle-aged women; severe hyperinsulinaemia, hyperandrogenism, autoimmune disease	**Autoantibodies to the insulin receptor** (block → hyperglycaemia; stimulate → intermittent hypoglycaemia)
Insulin-receptor mutations	Rare; features of T2DM/IGT	Impaired insulin **binding or signal transduction**
Leprechaunism (Donohue) / Rabson-Mendenhall	Severe congenital IR	Genetic defects in insulin action
Lipodystrophies	Selective loss of adipose tissue → severe IR + hypertriglyceridaemia	Inherited (**Berardinelli-Seip** congenital generalised; **Dunnigan** familial partial) or acquired (**HIV-related**)
PCOS	Chronic anovulation + hyperandrogenism	IR in a major subset; independent T2DM risk

- *Acanthosis nigricans* and signs of hyperandrogenism (hirsutism, acne, oligomenorrhoea) are the physical hallmarks of **severe** IR.
- Secondary IR also accompanies **endocrinopathies** (acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma) and **drugs** (glucocorticoids, calcineurin/mTOR inhibitors, certain antiretrovirals, nicotinic acid, thiazides).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology of IR / metabolic syndrome (central-obesity hub):** draw an expanded **adipocyte** at the centre releasing **FFAs**, **TNF-α / IL-6 / resistin / PAI-1** and *reduced* **adiponectin**; arrows to **Liver** (↑gluconeogenesis, ↑VLDL-triglyceride → fasting hyperglycaemia + dyslipidaemia), **Muscle** (↓glucose uptake → postprandial hyperglycaemia), **Pancreas** (compensatory **hyperinsulinaemia**), **Vessels** (↓NO, ↑Na^+ reabsorption, ↑SNS → hypertension) and **Blood** (↑CRP/fibrinogen → prothrombotic state). Labels: *FFA, adiponectin↓, TNF-α, IL-6, PAI-1, VLDL/TG, small dense LDL, HDL↓, hyperinsulinaemia, NO↓, ASCVD.*
- **Beta-cell compensation curve (insulin secretion vs insulin sensitivity):** hyperbolic curve with points **A (normal) → B (insulin-resistant, ↑secretion) → C (IGT) → D (Type 2 DM)**. Labels: *insulin sensitivity (M value), insulin secretion, NGT, IGT, Type 2 DM.*

Clinical / Diagnostic significance

- **Clinical clues** — **acanthosis nigricans**, skin tags, central obesity (↑waist circumference), and hyperandrogenism (hirsutism, acne, oligomenorrhoea) flag significant IR.
- **Assessment of IR:**
  - *Surrogate indices* — fasting insulin and **HOMA-IR** (homeostasis model assessment) are the practical clinical surrogates; the chapter notes that fasting insulin / HOMA only *partially* capture IR.
  - *Quantitative gold standard* — the **hyperinsulinaemic-euglycaemic clamp**, expressing whole-body glucose disposal as the **"M value" (μmol/min per kg)** = insulin sensitivity.
  - *Clinical surrogate* — meeting **metabolic-syndrome criteria** (NCEP:ATP III 2001 / Harmonizing definition: central obesity + ≥2 of ↑TG ≥150 mg/dL, HDL <40/<50 mg/dL, BP ≥130/85 mmHg, FPG ≥100 mg/dL).
- **Management — reduce/reverse IR (insulin sensitisation):**
  - **Lifestyle is first-line** — weight loss (target ≥5–7% body weight), saturated-fat restriction and ≥150 min/week physical activity. The **Diabetes Prevention Program (DPP)** showed intensive lifestyle change reduced incident T2DM by **58%**.
  - **Metformin (biguanide)** — enhances hepatic insulin action and suppresses endogenous glucose production; DPP reduction **31%**; benefits IR in PCOS.
  - **Thiazolidinedione (pioglitazone)** — improves insulin-mediated glucose uptake in muscle/adipose tissue *and* hepatic action; a meta-analysis (9 trials, 12,026 participants) showed **↓ASCVD events**; caution — weight gain, oedema/CHF, fractures.
  - **GLP-1 receptor agonists / tirzepatide** — improve insulin sensitivity largely via weight loss.
  - Treat the clustered components — statins/fibrates for dyslipidaemia, antihypertensives, and urate-lowering where indicated.

High-yield exam pointers

- IR = **reduced insulin action on muscle, liver and fat**; *relative* (overcome by hyperinsulinaemia); central lesion of **T2DM** and **unifying mechanism of metabolic syndrome**.

- Sequence: **postprandial → fasting hyperinsulinaemia → hyperglycaemia**; T2DM only when **beta-cell compensation fails**.
- Predominantly a **post-receptor signalling defect**; lipotoxicity + ROS + metabolic inflammation; **MAP-kinase pathway spared** → hyperinsulinaemia promotes atherosclerosis.
- **FFA excess** and **low adiponectin / high resistin, TNF-α, IL-6, leptin resistance** drive IR.
- **Type A** = insulin-signalling defect (young women); **Type B** = **anti-insulin-receptor antibodies** (autoimmune, middle-aged women).
- **Acanthosis nigricans + hyperandrogenism** = clinical markers of severe IR; lipodystrophy (Berardinelli-Seip, Dunnigan) causes severe IR with hypertriglyceridaemia.
- **PCOS**: IR in 50–80%, independent T2DM risk.
- Best quantified by **hyperinsulinaemic-euglycaemic clamp**; HOMA-IR is the practical surrogate.
- Sensitisers = **metformin and pioglitazone**; lifestyle/weight loss is most effective (DPP 58% vs metformin 31%).

> **SOURCE & COVERAGE**
>
> Harrison 22e — Ch 415 "Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology" + Ch 420 "The Metabolic Syndrome". Coverage note: The HOMA-IR formula (fasting insulin × fasting glucose ÷ 22.5) and the use of the hyperinsulinaemic-euglycaemic clamp as the quantitative gold standard are universally accepted standard internal medicine; the provided chapters reference "homeostasis model assessment", fasting insulin, and the clamp-derived **"M value" (insulin sensitivity)** but do not print the HOMA-IR formula explicitly. Drug doses are deliberately not stated, as the source chapters cite drug classes rather than specific doses (detailed dosing is in Ch 416, not provided).

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Insulin sensitizers

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

Definition / Introduction — *Insulin sensitizers* are glucose-lowering agents that act by enhancing the responsiveness of target tissues (liver, skeletal muscle, adipose) to circulating insulin, thereby reducing insulin resistance, rather than by stimulating insulin secretion. Two oral classes form this group: the **biguanides** (metformin) and the **thiazolidinediones / glitazones** (pioglitazone, rosiglitazone). Because their action is insulin-dependent and does not augment β-cell secretion, they **do not cause hypoglycaemia as monotherapy** and are central to the management of type 2 diabetes mellitus (T2DM), where insulin resistance is a defining lesion.

Classification and rationale

- **Biguanides** — metformin (the only biguanide in current use; *phenformin* and *buformin* were withdrawn from most markets in the 1970s after deaths from lactic acidosis). Acts predominantly on the **liver** to lower hepatic glucose output.

- **Thiazolidinediones (TZDs)** — *pioglitazone* and *rosiglitazone*; the first agent, *troglitazone* (1997), was withdrawn in 2000 because of rare fatal hepatotoxicity. Act predominantly on **adipose tissue** (PPAR-γ) with secondary benefit at liver and muscle.
- Both classes lower glucose without directly raising insulin levels; circulating insulin actually **falls** with effective therapy, confirming improved sensitivity.
- They target the *insulin-resistance* arm of T2DM pathophysiology and so are complementary to secretagogues, incretins and SGLT-2 inhibitors in combination regimens.

Biguanides — Metformin

- **Mechanism (incompletely defined):** principally **reduces hepatic gluconeogenesis** and hepatic insulin resistance; less consistently improves peripheral (muscle) glucose uptake; influences gut function (alters microbiome, increases GLP-1 release). At the molecular level it **activates AMP-activated protein kinase (AMPK)** (a sensor of depleted cellular energy), and more recent work implicates **inhibition of mitochondrial glycerophosphate dehydrogenase** and a direct effect on the intestinal mucosa signalling to brain/liver.
- **Pharmacokinetics:** half-life ~1.5–3 h; **not protein-bound, not metabolised, excreted unchanged by the kidney** (hence the dependence of safety on renal function).
- **Efficacy:** lowers **HbA1c by ~1–2%**; reduces fasting plasma glucose and insulin; modestly improves the lipid profile (↓ LDL, ↓ triglycerides) and procoagulant factors; **weight-neutral to modest weight loss**; no hypoglycaemia; inexpensive — hence the **first-line agent** in most T2DM algorithms (ADA/EASD, IDF, AACE).
- **Dosing:** start low (500 mg once–twice daily *with food*) and titrate every 1–2 weeks; maximally tolerated dose **2000 mg/day** (formal maximum 2550 mg, little extra benefit beyond 2000 mg). IR: 500 mg tid or 850–1000 mg bid; **extended-release (ER)** once daily has fewer upper-GI effects and better adherence.
- **Adverse effects:** GI intolerance (nausea, anorexia, abdominal cramps, diarrhoea, metallic taste) in up to 20–30%, often transient and dose-related; **vitamin B12 deficiency** (interferes with calcium-dependent absorption of the B12–intrinsic-factor complex in the terminal ileum — monitor periodically, especially if neuropathy or macrocytosis); **lactic acidosis** — the major but *very rare* toxicity (incidence <10/10,000 patient-years), almost confined to patients with predisposing illness.
- **Contraindications / cautions: eGFR <30 mL/min/1.73 m² (contraindicated)**; do not *initiate* if eGFR <45, and halve the dose (≈1000 mg/day) if eGFR 30–45; hepatic insufficiency, excess alcohol intake, unstable/decompensated CHF, any acidosis, severe hypoxaemia. **Withhold for iodinated radiographic contrast** (halt on the day in patients with eGFR 30–60, restart after 48 h once renal function is confirmed stable) and in hospitalised/NPO/acutely ill patients (substitute insulin).
- **Cardiovascular / outcome data:** in overweight patients in the **UKPDS (UKPDS 34)**, metformin reduced *any diabetes-related endpoint by 32%*, *myocardial infarction by 39%* and *all-cause mortality by 36%*; benefit persisted at 10-year post-trial follow-up (a "legacy"/metabolic-memory effect). Metformin also **reduces progression from prediabetes to diabetes** (Diabetes Prevention Program). It is the insulin sensitiser with the best long-term outcome record.

Thiazolidinediones (Glitazones)

- **Mechanism:** bind and activate the nuclear transcription factor **peroxisome proliferator-activated receptor-γ (PPAR-γ)**, which forms a **heterodimer with the retinoid X receptor (RXR)**. PPAR-γ is expressed at highest levels in **adipocytes**. Activation regulates many genes → promotes **adipocyte differentiation**, **redistributes fat from central/visceral to peripheral/subcutaneous depots**, reduces hepatic fat, promotes fatty-acid storage and **lowers circulating free fatty acids**, thereby improving whole-body insulin sensitivity. Onset is **slow (weeks–months)**.
- **Efficacy:** HbA1c reduction ~**0.5–1.4%** (up to 1–2%); effective as monotherapy or with metformin/sulfonylurea/insulin. When combined with insulin they **lower insulin requirement by 30–50%**. **No hypoglycaemia** as monotherapy. **Preserve β-cell function** — in *ADOPT*, rosiglitazone gave the slowest rate of secondary glycaemic failure vs metformin and glyburide.
- **Pioglitazone (preferred TZD):** dose 15–45 mg once daily (start 15 mg; 30 mg ≈ 80% of maximal glucose-lowering; 45 mg least well tolerated); **favourable lipid effect** — ↓ triglycerides (~9–20%), ↑ HDL, neutral/↓ LDL; reduces hepatic fat and can **reverse hepatic fibrosis (benefit in NASH/MASH)**; lowers blood pressure and urinary albumin. Metabolised by CYP2C8 / CYP3A4.
- **Rosiglitazone:** raises LDL and triglycerides; embroiled in a still-unresolved controversy over possible increased myocardial-infarction risk (meta-analyses), leading to a **shift away from its use worldwide** (RECORD trial showed no excess CV death/hospitalisation but did not settle the dispute).
- **Cardiovascular data (pioglitazone):** *PROactive* (5238 T2DM with macrovascular disease) — the broad primary endpoint was negative but a tighter secondary composite (death/MI/stroke) fell by **16%**; the *IRIS* study showed pioglitazone reduced recurrent **stroke or MI** in insulin-resistant, non-diabetic patients after stroke/TIA. Overall, **pioglitazone appears to reduce recurrent cardiovascular events**, partly offset by fluid retention/heart failure.
- **Adverse effects: weight gain (2–4 kg)** — from both fluid retention and an increase in subcutaneous fat; **fluid retention / peripheral oedema** (~5–10%, rising to 10–15% with concomitant insulin or sulfonylurea) which may precipitate **congestive heart failure** — TZDs are **contraindicated in NYHA class III/IV heart failure**; **bone fractures** (especially distal long bones in postmenopausal women — PPAR-γ diverts mesenchymal stem cells from osteoblastic to adipocytic lineage and reduces lumbar BMD); **macular oedema**; mild **anaemia** (dilutional, small fall in haematocrit); **hepatotoxicity** caution (check LFTs; contraindicated if ALT >2.5× ULN); possible **bladder-cancer** association with pioglitazone (conflicting data — avoid with active or prior bladder cancer). TZDs **induce ovulation in PCOS** — counsel premenopausal women on contraception as safety in pregnancy is unestablished.

Biguanide vs Thiazolidinedione — comparison

Feature	Biguanide (Metformin)	Thiazolidinedione (Pioglitazone)
Primary site / target	Liver; activates AMPK	Adipose tissue; **PPAR-γ–RXR** heterodimer
Dominant action	↓ Hepatic gluconeogenesis	↑ Peripheral insulin sensitivity, fat redistribution

Feature	Biguanide (Metformin)	Thiazolidinedione (Pioglitazone)
HbA1c reduction	~1–2%	~0.5–1.4% (up to 2%)
Onset	Days	Weeks–months
Effect on weight	Neutral / slight loss	Gain (2–4 kg)
Hypoglycaemia (mono)	No	No
Key adverse effects	GI upset, B12 deficiency, lactic acidosis	Oedema/CHF, fractures, macular oedema, ?bladder Ca
Major contraindication	eGFR <30, acidosis, hypoxia	NYHA class III/IV heart failure, hepatic disease
Outcome highlight	UKPDS 34 ↓ MI & mortality	PROactive/IRIS ↓ recurrent CV events; benefit in NASH

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Sites of action of insulin sensitizers":** a central panel with three organs labelled — **Liver** (arrow "Metformin → AMPK → ↓ gluconeogenesis / ↓ hepatic glucose output"), **Skeletal muscle** ("↑ insulin-stimulated glucose uptake"), and **Adipose tissue** ("Pioglitazone → PPAR-γ → adipocyte differentiation, fat redistributed visceral → subcutaneous, ↓ free fatty acids"). Add a peripheral box: "Net result = ↓ insulin resistance, ↓ circulating insulin, no hypoglycaemia." Labels: *Metformin, AMPK, hepatic gluconeogenesis, PPAR-γ, FFA, insulin resistance.*
- **"TZD molecular mechanism":** *TZD* → binds **PPAR-γ**, which dimerises with **RXR**; the **PPAR-γ–RXR heterodimer** binds the **PPRE (PPAR response element)** on DNA → gene transcription → adipocyte differentiation / insulin-sensitising genes. Labels: *TZD, PPAR-γ, RXR, PPRE, DNA, target genes.*

Clinical / Diagnostic significance

- **Metformin** is the recommended **first-line drug** for T2DM (efficacy, safety, weight neutrality, cardiovascular benefit, low cost) and is continued through combination therapy even after HbA1c falls below target.
- Check **eGFR before starting and at least annually** for metformin; obtain **vitamin B12** periodically, particularly when peripheral neuropathy or macrocytosis appears (do not misattribute to diabetic neuropathy).
- **Pioglitazone** is especially useful where insulin resistance, **NASH/MASH**, or hepatic steatosis coexist, and as an inexpensive generic add-on; screen for and avoid in **heart failure** and assess **fracture risk** (BMD) before prescribing, particularly in postmenopausal women.
- Neither agent causes hypoglycaemia alone, but **dose reduction of insulin/sulfonylurea** is needed when either is added to those drugs.

- In current ADA/EASD practice, when **ASCVD, heart failure or CKD** dominate, a GLP-1 RA or SGLT-2 inhibitor is layered onto metformin; pioglitazone is favoured for the MASH/ASCVD-risk phenotype provided heart failure is absent.

High-yield exam pointers

- Two insulin-sensitiser classes: **biguanides (metformin)** and **thiazolidinediones (pioglitazone, rosiglitazone)** — improve sensitivity, **no hypoglycaemia** as monotherapy.
- **Metformin:** ↓ hepatic gluconeogenesis via **AMPK**; renally excreted unchanged; **B12 deficiency** and **lactic acidosis**; stop if **eGFR <30** and hold for **contrast/surgery**.
- **UKPDS 34:** metformin ↓ MI **39%** and all-cause mortality **36%** in overweight T2DM (legacy effect).
- **TZDs:** activate **PPAR-γ–RXR** heterodimer in adipocytes → fat redistribution and ↓ FFA.
- **Pioglitazone** ↓ triglycerides, ↑ HDL, benefits **NASH/MASH**; **PROactive/IRIS** suggest reduced recurrent CV/stroke events.
- **TZD red flags:** fluid retention → **CHF (contraindicated NYHA III/IV)**, **fractures** in postmenopausal women, macular oedema, possible **bladder cancer** (pioglitazone).
- *Troglitazone* withdrawn (hepatotoxicity); *phenformin* withdrawn (lactic acidosis) — historical safety landmarks.
- TZDs **preserve β-cell function** (slowest secondary failure in ADOPT) and **induce ovulation in PCOS**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Management and Therapies" (Biguanides, Thiazolidinediones; Table of agents used for type 1/type 2 diabetes).
- **Williams Textbook of Endocrinology, 15e** — "Therapeutics of Type 2 Diabetes Mellitus" (mechanisms of metformin/AMPK and mitochondrial glycerophosphate dehydrogenase; PPAR pharmacology; UKPDS 34 outcomes; PROactive/RECORD/ADOPT/IRIS).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycaemia" (current dosing, renal thresholds, TZD safety profile, treatment algorithm).

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Diabetes insipidus

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

Definition / Introduction — Diabetes insipidus (DI) is a hypotonic polyuria–polydipsia syndrome caused by deficient secretion of arginine vasopressin (AVP/antidiuretic hormone) or by renal resistance to its action, producing excretion of abnormally large volumes of dilute urine (24-h urine **>40–50 mL/kg** and/or **>3 L/day**, urine osmolality persistently **<300 mosmol/kg**). In Harrison 22e the terminology has been revised: classical *central/cranial/neurogenic DI* is now **AVP deficiency** and classical *nephrogenic DI* is **AVP resistance**. Because thirst is intact, most patients maintain near-normal serum sodium by compensatory polydipsia; hypernatraemic dehydration supervenes only when thirst or water access is impaired.

Physiology of AVP (background that frames the disease)

- AVP is a **nonapeptide** (six-member disulfide ring + tripeptide tail) synthesised in the **supraoptic and paraventricular magnocellular neurons** as a pre-pro-hormone comprising AVP, **neurophysin II**, and **copeptin**, encoded by a single gene on **chromosome 20**; it is transported down axons and stored in the **posterior pituitary (neurohypophysis)**.
- Secretion is governed by hypothalamic **osmoreceptors**; the AVP osmotic set-point is **~275–280 mosmol/L (plasma Na ~135 meq/L)**, above which plasma AVP rises steeply. The **thirst osmostat is set ~3% higher**, so thirst is the last defence against dehydration. AVP is also released by **>10–20% volume/BP fall** (baroregulated), nausea, and hypoglycaemia.
- AVP acts on **V2 receptors** (Gs–cAMP) on collecting-duct principal cells → trafficking of **aquaporin-2 (AQP2)** water channels to the apical membrane → passive water reabsorption down the medullary osmotic gradient; maximal antidiuresis (urine osm up to **~1200 mosmol/L**) occurs at AVP **1–3 pg/mL**. **~90% of AVP neurons must be lost** before symptomatic AVP deficiency appears.

Aetiological classification (Polyuria–Polydipsia syndromes)

Category (Harrison 22e term)	Defect	Representative acquired causes	Hereditary causes
Central DI — AVP deficiency	Failed AVP synthesis/secretion	Trauma/neurosurgery, tumours (**craniopharyngioma, germinoma, meningioma, metastases**—breast/lung), granulomatous (**Langerhans-cell histiocytosis, sarcoidosis**), infiltrative/autoimmune (**lymphocytic infundibuloneurohypophysitis, IgG4**), infection (TB, meningitis), vascular (anterior communicating artery aneurysm), **idiopathic (~1/3, often autoimmune)**	AD *AVP–neurophysin II (AVP-NPII)* gene mutations; AR; **WFS1 → Wolfram syndrome (DIDMOAD)**; PCSK1; X-linked
Nephrogenic DI — AVP resistance	Renal (V2/AQP2) unresponsiveness	**Lithium** (commonest acquired), demeclocycline, cisplatin, foscarnet; **hypercalcaemia, hypokalaemia**; infiltration (amyloid, myeloma, sarcoid); obstructive uropathy/PCKD; sickle-cell	**X-linked recessive *AVPR2*** (>90%, >200 mutations, 3 types); AR/AD ***AQP2***

Category (Harrison 22e term)	Defect	Representative acquired causes	Hereditary causes
Gestational DI	Accelerated AVP metabolism	Placental **vasopressinase (cysteine aminopeptidase/oxytocinase)**; assoc. pre-eclampsia, acute fatty liver	NA
Primary polydipsia (mimic, not true DI)	Excess intake → suppressed AVP	Psychogenic (schizophrenia, PIP syndrome), dipsogenic (low thirst set-point), "health-enthusiast" overdrinking	NA

- **Wolfram syndrome = DIDMOAD** — autosomal-recessive *WFS1* (wolframin, chromosome 4): **D**iabetes **I**nsipidus, **D**iabetes **M**ellitus, **O**ptic **A**trophy, **D**eafness.
- **Adipsic DI** — coexisting AVP deficiency *and* destroyed osmoreceptor thirst centre (e.g., after anterior communicating artery aneurysm clipping); high risk of severe hypernatraemia.

Clinical features and the post-surgical triphasic response

- Cardinal symptoms: **polyuria, nocturia, and intense thirst with craving for ice-cold water**; daily intake 2.5–20 L; low urine specific gravity (**<1.006**). Hypernatraemia (lethargy, weakness, irritability, obtundation) only if thirst/access impaired.
- **Triphasic response** after pituitary stalk section/trauma:
- **Phase 1 — DI** (onset within 24 h, to ~day 6): axon "shock", failed AVP release.
- **Phase 2 — antidiuresis/SIAD** (~day 7–12): unregulated AVP leak from degenerating neurons → **hyponatraemia**, dangerous if hypotonic IV fluids are given.
- **Phase 3 — permanent DI** (~day 13 onward) after stores depleted and gliosis ensues. (An *isolated second phase* of transient hyponatraemia may occur without flanking DI.)

Differential diagnosis & investigations

- **Step 1 – Confirm hypotonic polyuria:** 24-h urine **>40–50 mL/kg** with urine osm **<800 mosmol/kg**; exclude glucosuria, hypercalcaemia, hypokalaemia, renal failure. Measure **serum Na & plasma osmolality**: Na **<135** suggests primary polydipsia (patients drink into hyponatraemia); Na **>147** with high plasma osmolality (**≥300 mosmol/kg**) indicates central or nephrogenic DI.
- **Indirect water-deprivation test (Miller–Moses):** dehydrate until plasma osm >295 mosmol/kg, then give **desmopressin 2 µg**. *Primary polydipsia* concentrates urine during deprivation (>800 mosmol/kg); in DI urine stays dilute, and after desmopressin **central DI shows a >50% rise** in urine osmolality whereas **nephrogenic DI shows little/no rise (<50%)**. Overall accuracy is only ~70% (41% for primary polydipsia), hence newer copeptin testing.
- **Copeptin (stable AVP surrogate) algorithm (preferred):**
  - **Baseline copeptin >21.4 pmol/L** (no prior thirsting) → **nephrogenic DI / AVP resistance** (sens/spec ~100%).
  - **Hypertonic (3%) saline stimulation** to plasma Na **≥150 mmol/L**: stimulated **copeptin ≤4.9 pmol/L → central DI (AVP deficiency)**; **>4.9 pmol/L → primary polydipsia** (accuracy ~96.5%). Requires close Na monitoring.

- **Arginine-stimulated copeptin** (less cumbersome): <2.4 pmol/L = severe AVP deficiency; 2.4 –3.8 = partial; >3.8 = primary polydipsia.

- **MRI sella/suprasellar:** loss of the normal **posterior-pituitary "bright spot"** (T1 hyperintensity, present in >80% normals) supports AVP deficiency; assess **pituitary stalk thickening** (germinoma—check serum/CSF β-hCG & AFP; histiocytosis; sarcoid; hypophysitis). Repeat MRI 3–6 monthly for 2 years if stalk thickened and "idiopathic".

Feature	Central DI (AVP deficiency)	Nephrogenic DI (AVP resistance)	Primary polydipsia
Plasma AVP/copeptin (basal)	Low	Normal/high (copeptin >21.4)	Normal/low
Response to desmopressin	Urine concentrates (>50%)	No response	Concentrates
Plasma Na tendency	High-normal/high	High-normal/high	Low-normal/low
Bright spot on MRI	Absent	Usually present (may deplete)	Present

Treatment

- **Central DI (AVP deficiency): Desmopressin (DDAVP)** — V2-selective AVP analogue (d-arginine + deaminated terminal, ~2000× more antidiuretic-selective, longer t½). Adult doses: **1–2 µg SC/IV od–bid**, **10–20 µg intranasal bid–tid**, or **100–400 µg oral bid–tid** (tablets 0.1/0.2 mg; melt 60/120/240 µg). **Hyponatraemia is the commonest complication** (~1/4 of patients mildly, ~15% Na <130) — minimise by a periodic "**desmopressin escape**" (delaying/omitting a dose to permit aquaresis). Mild partial DI may need only fluids ± a bedtime dose.
- **Nephrogenic DI (AVP resistance):** ensure adequate water; **thiazide diuretic** (induces mild volume contraction → ↑proximal Na/water reabsorption, paradoxically reduces urine output and raises AQP2) **+ low-sodium diet ± NSAID (indomethacin)** [combination is nephrotoxic—monitor renal function]. **Amiloride** is specifically useful in **lithium-induced NDI** (blocks collecting-duct ENaC, reducing lithium entry); stop the offending drug where possible. Correct **hypokalaemia/hypercalcaemia**.
- **Gestational DI: desmopressin** is the treatment of choice — it resists placental vasopressinase and has negligible oxytocic activity; usually remits weeks after delivery.
- **Adipsic DI:** fixed desmopressin dose + a **prescribed daily fluid volume**, daily weights and frequent serum-Na checks (Table 393-2 approach); high thrombotic/hypernatraemia risk.
- **Acute hypernatraemia:** replace the calculated free-water deficit slowly (oral water, or 0.45% saline / 5% dextrose) over 24–48 h with serial Na monitoring to avoid over-rapid correction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — AVP physiology / V2-AQP2 axis:** Hypothalamus (supraoptic + paraventricular nuclei) → axons → posterior pituitary → AVP release → renal collecting-duct principal cell. Label: *osmoreceptor*, *AVP*, *V2 receptor*, *Gs–adenylyl cyclase–cAMP*, *AQP2 (apical, inserted)*, *AQP3/AQP4 (basolateral)*, *water reabsorption*, *concentrated urine*.
- **Diagram 2 — Polyuria–polydipsia diagnostic algorithm:** Confirm polyuria (>40–50 mL/kg/24 h) → serum Na/osmolality → branch by baseline copeptin (>21.4 = nephrogenic) and hypertonic-saline-stimulated copeptin (≤4.9 = central DI; >4.9 = primary polydipsia). Label the three endpoints: *Central DI*, *Nephrogenic DI*, *Primary polydipsia*. (Optionally the **triphasic response curve**: urine volume vs days, phases DI → antidiuresis → DI.)

Clinical / Diagnostic significance

- Distinguishing the three polyuric states is essential because treatment diverges sharply (desmopressin helps central and gestational DI but **not** nephrogenic DI or primary polydipsia, where it risks water intoxication).
- **Stalk thickening + central DI** mandates a search for germinoma, Langerhans-cell histiocytosis, sarcoidosis, IgG4 disease, and metastases (breast/lung) — DI from intrasellar adenomas is rare.
- Post-neurosurgical and post-TBI patients need **anticipation of the triphasic response**: use intermittent parenteral desmopressin and allow each dose to wane before re-dosing to avoid precipitating phase-2 hyponatraemia.
- **Cortisol deficiency masks DI** (cortisol is required for free-water excretion); apparent "resolution" of polyuria after pituitary insult may unmask coexisting ACTH deficiency — check the HPA axis.

High-yield exam pointers

- Two mechanisms: **AVP deficiency (central)** vs **AVP resistance (nephrogenic)**; commonest *acquired* nephrogenic cause = **lithium**; commonest central genetic form = **AD *AVP-NPII* mutation**; **X-linked *AVPR2*** = commonest hereditary nephrogenic (>90%).
- **Copeptin** has largely replaced AVP assay: **baseline >21.4 pmol/L = nephrogenic**; **saline-stimulated ≤4.9 pmol/L at Na ≥150 = central DI**.
- Urine osm **>800 mosmol/kg** essentially **excludes DI** (points to primary polydipsia).
- **Wolfram = DIDMOAD** (DI + DM + Optic atrophy + Deafness), *WFS1*/wolframin, chromosome 4.
- **Desmopressin (DDAVP)** = drug of choice for central & gestational DI; **hyponatraemia** is its chief hazard.
- **Nephrogenic DI:** thiazide + low-salt diet ± NSAID; **amiloride for lithium-induced** NDI.
- **Triphasic response**: DI → antidiuresis (SIAD/hyponatraemia ~day 7–12) → permanent DI.
- **Adipsic DI** (osmoreceptor + AVP loss) carries the highest hypernatraemia/mortality risk.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of the Neurohypophysis" (vasopressin physiology, Table 393-1 aetiology, copeptin-based diagnostic algorithm Fig 393-4, treatment, adipsic AVP deficiency).
- **Williams Textbook of Endocrinology, 15e** — "Posterior Pituitary" (genetics of central & nephrogenic DI, triphasic response, water-deprivation vs copeptin/hypertonic-saline & arginine-stimulation testing, treatment of nephrogenic DI and DI of pregnancy, stalk-lesion differential).
- **CMDT 2026** — "Disorders of the Pituitary… (ADH Deficiency / Central Diabetes Insipidus)" (essentials of diagnosis, ADH levels, hypertonic-saline and arginine copeptin cut-offs, vasopressin challenge test, desmopressin dosing, nephrogenic causes and drugs).

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Maturity-onset diabetes of the young

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

Definition / Introduction — MODY is a clinically and genetically heterogeneous group of **monogenic** (single-gene) forms of diabetes characterised by **autosomal-dominant inheritance**, **young age at onset** (typically diagnosed before 30 years, often ≤25 years), a **primary β-cell secretory defect** (impaired glucose-induced insulin secretion) rather than insulin resistance, **absence of obesity**, and **absence of islet autoimmunity and ketosis**. It belongs to the "other specific types" category of the ADA classification and accounts for roughly **1–2% of all diabetes**. It is the prototype of **precision (genotype-directed) diabetes medicine** — accurate molecular diagnosis changes treatment, prognosis and family screening.

Historical note & nomenclature

- The term was coined by **Fajans and Tattersall (1974)** after study of the multigenerational Michigan **"R-W pedigree"** (Fajans, from 1958) and Tattersall's description of *mild familial diabetes with dominant inheritance*, distinguishing it from classic juvenile-onset (type 1) diabetes.
- "MODY" historically refers to autosomal-dominant β-cell diabetes; with **>30 causative genes** now known, the older numerical **"MODY-X"** nomenclature (MODY 1–14) is being replaced by **gene-based names** (e.g., *HNF1A*-MODY rather than MODY 3).
- *Monogenic diabetes* is the umbrella term encompassing both **MODY** and **neonatal diabetes** (onset generally <6 months), plus rarer **syndromic** forms.

When to suspect MODY — clinical clues

MODY is frequently **misclassified as type 1 or type 2 diabetes**; suspect it when atypical features are present.

- **Atypical for type 1 DM:** absence of pancreatic islet autoantibodies; persistent endogenous insulin production **beyond the honeymoon period**; **measurable C-peptide (≥0.60 ng/mL [≥0.2**

nmol/L]) in the presence of hyperglycaemia; low insulin requirement; **no ketoacidosis when insulin is withheld**.

- **Atypical for type 2 DM:** onset **<45 years**; **lack of significant obesity**; absence of acanthosis nigricans; normal triglycerides and/or normal-to-high HDL cholesterol.
- **Strong multigenerational family history** of diabetes (parent affected; 2–3 generations) with an autosomal-dominant pattern.
- The **Exeter MODY probability calculator** (uses age at diagnosis, sex, BMI, HbA1c, treatment, family history; valid for diagnosis <35 years) and **type 1 genetic risk scores (T1D-GRS)** help select patients for genetic testing.

Classification of the main MODY subtypes

The four classic genes — **GCK, HNF1A, HNF4A, HNF1B** — account for the great majority of cases (relative frequencies vary geographically: *HNF1A* predominates in many UK/European registries, while *GCK* predominates in others and in paediatric/incidental cohorts).

Gene (locus) — old name	Protein / defect	Approx. share *	Hallmark clinical features	Precision treatment
GCK (7p) — MODY 2	Glucokinase = β-cell "glucose sensor"; glucose-sensing defect	>70% (of suspected)	**Mild, stable, non-progressive fasting hyperglycaemia (≈99–144 mg/dL) present from birth**; small OGTT rise (<90 mg/dL); HbA1c usually <7.5%; essentially **no micro-/macrovascular complications**	**None** — diet only; oral agents/insulin **not recommended (contraindicated)**; treat only in pregnancy if fetus unaffected
HNF1A (12q24.2) — MODY 3	Hepatocyte nuclear factor-1α; transcription factor → progressive β-cell dysfunction	20–30%	**Progressive** hyperglycaemia; **glycosuria at low renal threshold** (reduced SGLT2 expression); hepatic adenomas; **increased cardiovascular mortality**	**Low-dose sulfonylurea** (markedly sensitive — can cause hypoglycaemia); insulin later as β-cells fail
HNF4A (20q12–13.1) — MODY 1	Hepatocyte nuclear factor-4α; transcription factor	~5%	**Fetal macrosomia + transient neonatal hyperinsulinaemic hypoglycaemia**; progressive hyperglycaemia; low HDL/apoA2	**Low-dose sulfonylurea**, insulin later
HNF1B (17q12) — MODY 5	Hepatocyte nuclear factor-1β; transcription factor	<2%	**Renal cysts and diabetes (RCAD)** syndrome; pancreatic hypoplasia + exocrine insufficiency; **hypomagnesaemia, hyperuricaemia**, genital-tract anomalies, abnormal LFTs; **50–60% de novo** (17q12 deletions)	**Insulin** (sulfonylurea-**unresponsive**)

*Relative incidence among patients suspected to have MODY (Williams Table 37.3).

- **Rarer / disputed subtypes (<1% each):** *IPF1/PDX1* (MODY 4), *NEUROD1* (MODY 6), *INS*, *CEL* (MODY 8), *ABCC8*, *KCNJ11*, *APPL1*; refuted/disputed: *KLF11* (MODY 7), *PAX4* (MODY 9), *BLK* (MODY 11).

Pathophysiology in brief

- All classic MODY genes converge on **defective glucose-stimulated insulin secretion** by the pancreatic β-cell.
- **GCK** raises the glucose threshold for insulin release (a regulatory "reset"), giving lifelong **mild, stable** hyperglycaemia.
- **HNF1A, HNF4A, HNF1B** are interacting **transcription factors** controlling β-cell development and gene expression; haploinsufficiency causes **progressive** β-cell failure (hence the deteriorating course and eventual insulin need in *HNF1A/HNF4A*).
- *HNF1A* also drives renal **SGLT2** expression — its loss explains glycosuria at a low renal threshold, often **preceding** frank hyperglycaemia.

Diagnostic approach (biomarker-led pathway to genetic testing)

A stepwise strategy avoids unnecessary, costly sequencing:

- **Endogenous insulin secretion** — serum C-peptide or **urinary C-peptide/creatinine ratio (UCPCR)**.
- If **C-peptide ≥0.60 ng/mL (0.2 nmol/L)** or **UCPCR ≥0.2 nmol/mmol** → measure **islet autoantibodies (GAD-65 and IA-2)**.
- If **autoantibody-negative** → proceed to **molecular genetic testing** (targeted **next-generation sequencing gene panel** including GCK, HNF1A, HNF4A, HNF1B ± others).
- **GCK-MODY** has a distinctive, near-pathognomonic biochemical signature (mild stable fasting hyperglycaemia, tiny OGTT increment) and can often be recognised clinically before sequencing.
- Confirming the variant enables **cascade (predictive) genetic screening of first-degree relatives**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Diagnostic algorithm for monogenic diabetes:** boxes labelled *"Diabetes"* → branch on **autoantibodies +/– and C-peptide**; left arm *autoantibody-positive / low C-peptide → Type 1 DM*; *high BMI, acanthosis nigricans, metabolic syndrome → Type 2 DM*; right arm *autoantibody-negative, C-peptide ≥0.2 nmol/L, family history* → MODY testing, splitting to **GCK** (mild fasting hyperglycaemia, HbA1c <8%, no microvascular complications), **HNF1A** (glycosuria, high HDL), **HNF4A** (low HDL, neonatal hypoglycaemia/macrosomia history), **HNF1B** (renal cysts, hypomagnesaemia, pancreatic/genital anomalies). Add a side box: *diagnosis <6 months → test neonatal-diabetes genes KCNJ11, ABCC8, INS*.
- **Diagram 2 — β-cell glucose-stimulated insulin secretion:** label **GLUT2 (SLC2A2)** glucose entry → **glucokinase (GCK)** → glycolysis/Krebs → **↑ATP** → closure of **K-ATP channel (KCNJ11/ABCC8 subunits)** → membrane **depolarisation** → opening of **voltage-gated Ca^{2+} channel** → Ca^{2+} influx → **insulin granule exocytosis**; nucleus labelled with transcription factors **HNF1A, HNF4A, HNF1B, NEUROD1, PDX1**.

Clinical / Diagnostic significance

- **Treatment is genotype-specific:** *GCK*-MODY needs **no pharmacotherapy** (and is harmed by it); *HNF1A/HNF4A*-MODY respond dramatically to **low-dose sulfonylureas** (often allowing patients on insulin to be switched off it); *HNF1B*-MODY requires **insulin**.
- **Avoids lifelong mislabelling** — many MODY patients are wrongly on insulin as "type 1," or chased with intensifying type 2 regimens; a molecular diagnosis can de-escalate therapy.
- **Prognostic / surveillance value:** *HNF1A* carries excess **cardiovascular mortality** (warrants statin) and risk of **hepatic adenomas**; *HNF1B* mandates renal, electrolyte (magnesium), hepatic, urogenital and (in 17q12 deletions) neurodevelopmental surveillance — multidisciplinary care.
- **Pregnancy** is a special situation: in **GCK-MODY**, management depends on whether the fetus inherited the mutation — if the fetus is **unaffected**, maternal hyperglycaemia drives fetal hyperinsulinism and **macrosomia**, so **insulin** is given (often >1 IU/kg/day) with delivery considered at ~38 weeks; if the fetus is affected, no treatment is needed. *HNF1A/HNF4A* carriers are usually switched from sulfonylurea to **insulin** during pregnancy (glyburide crosses the placenta); *HNF4A* fetuses need monitoring for macrosomia and **neonatal hypoglycaemia**.
- **GCK-MODY** is a frequent cause of apparent "gestational diabetes" that fails to resolve postpartum (≈2% of GDM).

High-yield exam pointers

- MODY = **autosomal-dominant, young-onset (<25–30 yr), non-obese, autoantibody-negative, ketosis-resistant, C-peptide–positive** diabetes; ~1–2% of all diabetes.
- **Four classic genes: GCK, HNF1A, HNF4A, HNF1B** — know each gene's phenotype and treatment.
- **GCK (MODY 2)** = mild **stable** fasting hyperglycaemia from birth, **no complications, no treatment** (except pregnancy).

- **HNF1A (MODY 3)** = commonest *symptomatic* MODY in many populations; **glycosuria, sulfonylurea-sensitive**, hepatic adenomas, ↑CV risk.
- **HNF4A (MODY 1)** = **macrosomia + neonatal hypoglycaemia**, sulfonylurea-responsive.
- **HNF1B (MODY 5)** = **renal cysts and diabetes (RCAD)**, hypomagnesaemia, pancreatic/genital anomalies, **insulin-requiring**, often **de novo**.
- Diagnostic gateway: **C-peptide/UCPCR → islet autoantibodies → gene panel**; use the **Exeter MODY calculator** to triage.
- It is the **flagship example of precision medicine** in diabetes; molecular diagnosis enables **cascade family screening**.
- Do not confuse with **neonatal diabetes** (<6 months; *KCNJ11/ABCC8* K-ATP channel mutations → high-dose sulfonylureas; *INS* mutations → insulin) or **MIDD** (m.3243A>G, maternally inherited diabetes + deafness; avoid metformin).

SOURCE & COVERAGE

- **Williams Textbook of Endocrinology (15e) — "Monogenic Diabetes"** (dedicated chapter; subtype classification, biomarker pathway, gene/phenotype/treatment table, pregnancy management — primary source for depth).
- **Harrison's Principles of Internal Medicine, 22e — "Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology"** (ADA aetiologic classification of monogenic/MODY).
- **CMDT 2026 — "Diabetes Mellitus & Hypoglycemia"** (definition, autosomal-dominant onset ≤25 yr, genetic-screening candidacy, current management framing).

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Metabolic syndrome

Asked in: Paper IV 17 Apr 2026 · Paper I Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — The **metabolic syndrome** (*syndrome X, insulin-resistance syndrome*) is a constellation of inter-related metabolic abnormalities — **central (visceral) obesity, atherogenic dyslipidaemia (high triglycerides, low HDL-cholesterol), raised blood pressure and hyperglycaemia** — that together confer a markedly increased risk of **atherosclerotic cardiovascular disease (ASCVD)** and **type 2 diabetes mellitus**. The unifying pathophysiological substrate is **insulin resistance** driven by an expanded, dysfunctional visceral adipose mass. It is a clustering construct, not a single disease, and is diagnosed by meeting an agreed set of cut-point criteria.

Definitions and diagnostic criteria (evolution)

- The criteria have evolved since the first **WHO definition (1998)**, which required *demonstrable insulin resistance* (type 2 diabetes, impaired glucose tolerance/fasting glucose, or low insulin-mediated glucose uptake) as an obligatory anchor plus additional components.
- The **NCEP:ATP III (2001)** definition popularised a simple, non-glucose-clamp, "any 3 of 5" approach. The **IDF (2005)** definition made *central obesity (ethnicity-specific waist) mandatory* plus 2 others. The **2009 Harmonized joint statement** (IDF, AHA/NHLBI, World Heart

Federation, International Atherosclerosis Society, International Association for the Study of Obesity) requires *any 3 of 5* components with **population/ethnicity-specific waist thresholds**.

Component	NCEP:ATP III 2001 (any 3 of 5)	Harmonized / IDF (any 3 of 5; ethnicity-specific waist)
Central obesity (waist)	>102 cm men, >88 cm women	Europid / sub-Saharan African / Eastern & Middle Eastern: ≥94 men, ≥80 women · South Asian, Chinese, ethnic South & Central American: ≥90 men, ≥80 women · Japanese: ≥85 men, ≥90 women
Triglycerides	≥150 mg/dL (or on Rx)	>150 mg/dL (or on specific Rx)
HDL cholesterol	<40 mg/dL (men), <50 mg/dL (women), or on Rx	<40 mg/dL (men), <50 mg/dL (women), or on Rx
Blood pressure	≥130 systolic or ≥85 diastolic (or on Rx)	>130 systolic or >85 diastolic, or prior Dx / specific Rx
Fasting glucose	≥100 mg/dL (or on Rx / known T2DM)	≥100 mg/dL (or drug Rx of raised glucose)

- The **AHA/NHLBI (2005)** statement is essentially identical (3 of 5), applying Asian waist cut-points of ≥35 in. (men) / ≥32 in. (women) versus ≥40 in. / ≥35 in. for other groups — important because *normal-weight individuals from India, South-East Asia and Central America may be insulin-resistant* with metabolic syndrome at lower waist values.

Epidemiology and risk factors

- **Prevalence ~33–35%** of US adults (NCEP:ATP III); NHANES 1999–2018 (n = 28,049) showed **33.4%**, rising with age from **19.5% (20–39 y) to 48.6% (≥60 y)**; nearly **50% of those >60 y** are affected, with women predominating beyond 60.
- **Overweight/obesity** (especially central adiposity) is the principal driver; the global obesity epidemic underlies its rising recognition, including in children (~12–30% of obese/overweight children show features).
- **Sedentary lifestyle / low cardiorespiratory fitness** — >4 h/day of screen time carries a *twofold* increased risk versus <1 h/day.
- **Genetics** — no single gene; polygenic, with heritability of individual metabolic traits exceeding **50%**.
- **Diabetes / impaired glucose tolerance** — ~75% of patients with type 2 DM or IGT have metabolic syndrome.
- **Lipodystrophy** — both genetic (*Berardinelli-Seip congenital*, *Dunnigan familial partial*) and acquired (HIV / antiretroviral-related) forms cause severe insulin resistance and the syndrome.

Etiology and pathophysiology

- **Insulin resistance** is the central, unifying hypothesis. It is heralded by postprandial then fasting **hyperinsulinaemia**, culminating in hyperglycaemia once β-cell compensation fails.
- **Free fatty acid (FFA) excess** — an expanded adipose mass releases abundant albumin-bound FFAs (lipolysis is the most insulin-sensitive pathway, so resistance amplifies lipolysis). FFAs

flood the liver → ↑gluconeogenesis, ↑triglyceride and **VLDL (apoB)** production; in muscle they impair insulin-mediated glucose uptake and cause intramyocellular triglyceride accumulation.

- **Atherogenic dyslipidaemia** — ↑triglyceride-rich VLDL with elevated **apoC-III** (inhibits lipoprotein lipase, impairs remnant clearance); ↓HDL-cholesterol (cholesteryl-ester depletion via CETP making HDL small, dense, rapidly cleared); predominance of **small dense LDL** (when fasting TG >~180 mg/dL).
- **Hypertension** — in insulin resistance the vasodilator (nitric-oxide) action of insulin is lost while renal **sodium reabsorption** and **sympathetic** activation are preserved; ↑adipose **angiotensinogen → angiotensin II**; perivascular adipose ROS (NADPH oxidase) and **hyperuricaemia** (impaired NO synthase, RAAS stimulation) contribute.
- **Adipokines and inflammation** — adipose-tissue macrophages oversecrete **TNF-α, IL-6, IL-1, IL-18, resistin**, raising **CRP, fibrinogen and PAI-1** (a *pro-thrombotic state*); **adiponectin** (anti-inflammatory, insulin-sensitising; activates AMP-kinase) is **reduced**. Leptin resistance, mitochondrial/oxidative-stress dysfunction and an altered **gut microbiome** (↑Firmicutes/Bacteroidetes ratio) are additional contributors.

Clinical features and associated conditions

- Usually **asymptomatic**; examination shows **increased waist circumference and raised blood pressure**; less often **acanthosis nigricans** or lipoatrophy (markers of severe insulin resistance).
- **Cardiovascular disease** — patients are *twice as likely to die of CVD* and have a *threefold* higher risk of acute MI or stroke; relative risk for new-onset CVD ≈ 1.5–3×. Metabolic syndrome is present in up to **60%** of CHD patients >75 y and ~35% with premature CAD (≤45 y). In **INTERHEART** (26,903 subjects, 52 countries) diabetes (OR 2.72) and hypertension (OR 2.60) were the strongest components.
- **Type 2 diabetes** — risk increased **three- to fivefold**; in the Framingham Offspring Study the population-attributable risk was **62% (men)** and **47% (women)**, largely explained by rising fasting glucose.
- **Other associations** — **metabolic-(dysfunction)-associated fatty liver disease (MAFLD/MASLD)** and its progressive form **MASH/NASH** (affects ~10% of non-obese but up to **65%** of metabolic-syndrome patients; a route to cirrhosis and hepatocellular carcinoma); **polycystic ovary syndrome** (insulin resistance in 50–80%); **obstructive sleep apnoea**; hyperuricaemia/gout; microalbuminuria; raised homocysteine, apoB and viscosity.

Diagnosis and investigations

- Apply **Table criteria** at bedside + laboratory: measure **waist circumference and blood pressure**; **fasting lipid profile and fasting plasma glucose** are essential.
- Individualise additional tests: **apoB, hsCRP, fibrinogen, uric acid, urine albumin/creatinine ratio, liver function**; a **sleep study** if OSA is suspected; **testosterone, LH, FSH** if PCOS is suspected; assess MAFLD by the **FIB-4 fibrosis score or elastography**.
- Family history guides cardiovascular and diabetes risk; a **coronary artery calcium score** and the **10-year ASCVD risk estimator** refine primary-prevention decisions.

Management (target each component; weight loss is primary)

- **Lifestyle is first-line.** Weight reduction of **at least 5% (ideally ≥10%)** improves insulin sensitivity and most components. Caloric restriction is the key element (~3500 kcal ≈ 1 lb fat; a ~500-kcal/day deficit ≈ 1 lb/week); diet adherence matters more than macronutrient type, favouring fruit, vegetables, whole grains, lean poultry and fish. **Physical activity** 30 min/day minimum (60–90 min for weight loss) plus behaviour modification for maintenance.

Component	Preferred therapy (after lifestyle)
Obesity	Anti-obesity drugs — **semaglutide 2.4 mg** (~14.9% loss/68 wk), **tirzepatide** (GIP/GLP-1; ~15–20.9%), **liraglutide 3.0 mg** (~6%), **phentermine/topiramate** (~8% in half), **naltrexone/bupropion** (≥10% in ~20%), **orlistat** (blocks ~30% fat absorption). **Bariatric/metabolic surgery** if BMI >40 (or >35 with comorbidity; ≥30 with T2DM)
LDL-cholesterol	**Statins** first-line (lower LDL 15–60%); add **ezetimibe** (15–20%), **bempedoic acid** (combo up to 35%); **PCSK9 inhibitors** (45–60%) if FH or insufficient response
Triglycerides	**Fibrates** (fenofibrate/gemfibrozil, ↓30–45%); high-dose **EPA omega-3** (REDUCE-IT, JELIS); treat TG **>500 mg/dL** to prevent pancreatitis
Blood pressure	**ACE inhibitor or ARB** first choice; add diuretic / CCB / β-blocker / **finerenone**
Impaired fasting glucose	**Lifestyle ± metformin** to prevent progression to T2DM
Insulin resistance	**Metformin** and **pioglitazone (TZD)** — a meta-analysis (9 trials, 12,026 participants) showed pioglitazone reduced ASCVD events; GLP-1 RAs also improve insulin sensitivity

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow diagram (central diagram):** Centre box = *Expanded visceral adipose tissue / Insulin resistance*. Arrows to: **Liver** (↑FFA → ↑glucose, ↑VLDL-TG, ↑apoB, ↑CRP, ↑fibrinogen); **Muscle** (↓insulin-mediated glucose uptake, ↑intramuscular triglyceride); **Pancreas** (hyperinsulinaemia → β-cell failure → hyperglycaemia); **Blood vessel** (↑Na reabsorption, ↑SNS, ↑angiotensin II → hypertension); **Adipokines** (↑TNF-α, ↑IL-6, ↑PAI-1, ↓adiponectin). Output boxes: *small dense LDL, low HDL, pro-thrombotic state, ASCVD, type 2 diabetes*. Labels to include: **FFA, VLDL, apoC-III, PAI-1, adiponectin, IL-6, TNF-α, CRP, SNS**.
- **The "five-pointed star" of diagnostic criteria:** a central pentagon labelled *Metabolic syndrome (need ≥3)* with the five arms labelled **Central obesity (waist), ↑Triglycerides ≥150, ↓HDL (<40 M/<50 F), BP ≥130/85, Fasting glucose ≥100**.

Clinical / Diagnostic significance

- Identifies, beyond LDL-cholesterol, a **high cardiometabolic-risk phenotype** warranting aggressive global risk-factor modification.
- Fasting glucose within the cluster is the **best predictor of incident type 2 diabetes**; the syndrome flags the need for diabetes screening and prevention.

- Mandates screening for **MAFLD/MASH, OSA and PCOS**, each of which both reflects and aggravates insulin resistance.
- Treatment is **component-directed**: weight loss is the highest-yield single intervention because it improves all five components simultaneously.

High-yield exam pointers

- Synonyms: **syndrome X / insulin-resistance syndrome**; core defect = **insulin resistance + visceral adiposity**.
- **Diagnosis = any 3 of 5** (NCEP:ATP III / Harmonized); **IDF makes central obesity mandatory**; waist cut-points are **ethnicity-specific** (lower for South Asians: ≥90 cm men / ≥80 cm women).
- Five components: **waist, TG ≥150, HDL <40(M)/<50(F), BP ≥130/85, FPG ≥100 mg/dL**.
- Confers **~2× CVD mortality, ~3× MI/stroke, 3–5× type 2 diabetes**.
- Key biochemical signature: **high TG, low HDL, small dense LDL, ↑apoB/apoC-III, ↑CRP/PAI-1/fibrinogen, ↓adiponectin**.
- **Acanthosis nigricans** = clinical clue to severe insulin resistance.
- First-line management = **≥5–10% weight loss**; antihypertensive of choice = **ACEi/ARB**; insulin sensitisers = **metformin, pioglitazone**.
- Strongly associated with **MAFLD/MASH, PCOS, OSA, hyperuricaemia**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "The Metabolic Syndrome" (primary source: definitions, epidemiology, etiology/pathophysiology, associated conditions, component-directed treatment); cross-referenced chapters on Disorders of Lipoprotein Metabolism, Diabetes Mellitus, and Obesity.
- **Williams Textbook of Endocrinology, 15e** — "Disorders of Lipoprotein Metabolism" (AHA/NHLBI 2005 diagnostic criteria table, Asian waist cut-points, atherogenic dyslipidaemia) and "Pathophysiology of Type 2 Diabetes Mellitus" (insulin-resistance/adipokine and gut-microbiome mechanisms).
- **CMDT 2026** — current-management context for the component disorders (lipids, diabetes/obesity, hypertension).

Coverage note: Harrison Ch 420 provides full, dedicated coverage of this topic. The detailed WHO 1998 and IDF-2005 obligatory criteria (e.g., microalbuminuria) are summarised from universally accepted standard internal medicine, as Harrison and Williams give only the NCEP:ATP III, Harmonized and AHA/NHLBI cut-point tables verbatim.

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Newer hypoglycaemic agents for type 2 diabetes

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — "Newer" glucose-lowering agents are the classes that have entered type 2 diabetes (T2DM) management after the traditional triad of **metformin, sulfonylureas and thiazolidinediones (TZDs)**, and which target previously untapped pathophysiologic pathways — the **incretin axis** and **renal glucose handling**. The four key groups are the **DPP-4 inhibitors**, the **GLP-1 receptor agonists (GLP-1RAs)**, the **dual GIP/GLP-1 receptor agonist (tirzepatide)** and the **SGLT-2 inhibitors**. Their importance lies less in raw glucose lowering (modest HbA1c reduction of ~0.5–1%) than in their proven **cardiovascular, heart-failure and renal protection**, weight loss, and freedom from hypoglycaemia — which have moved them from "add-on" to **organ-protective first-line** agents in T2DM with comorbidity.

Classification of glucose-lowering agents (mechanistic)

Class	Site/Mechanism	Examples
Biguanide (context)	↓ Hepatic glucose output, ↑ insulin sensitivity	Metformin
Insulin secretagogues (older)	Close ATP-sensitive K^+ channel on β-cell	Sulfonylureas; glinides (repaglinide, nateglinide)
TZD (older)	PPAR-γ agonist → ↓ insulin resistance	Pioglitazone
DPP-4 inhibitors *(newer)*	Block GLP-1/GIP degradation (incretin *enhancers*)	Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin
GLP-1RAs *(newer)*	Incretin-mimetic; ↑ glucose-dependent insulin, ↓ glucagon, slows gastric emptying, satiety	Liraglutide, dulaglutide, semaglutide, lixisenatide, exenatide
GIP/GLP-1 dual agonist *(newest)*	Co-agonism at GIP + GLP-1 receptors	**Tirzepatide**
SGLT-2 inhibitors *(newer)*	Block proximal-tubule glucose reabsorption → glycosuria (insulin-independent)	Empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, bexagliflozin
Amylin analogue	Slows gastric emptying, ↓ glucagon	Pramlintide (injectable, with insulin)

Incretin-based therapies: DPP-4 inhibitors, GLP-1RAs and tirzepatide

- **The incretin effect**: oral glucose evokes a larger insulin response than IV glucose because intestinal L-cell **GLP-1** (and K-cell **GIP**) amplify *glucose-dependent* insulin secretion, suppress glucagon, slow gastric emptying and increase satiety. Native GLP-1 is degraded within **1–2 minutes** by **dipeptidyl peptidase-4 (DPP-4)**.
- **DPP-4 inhibitors** (incretin *enhancers*) block this enzyme, roughly doubling endogenous GLP-1/GIP. They lower **HbA1c by 0.5–0.8%**, act mainly on fasting glucose, are **weight-neutral**, oral, and do **not** cause hypoglycaemia alone or with metformin. They are very well tolerated; rare adverse effects include **pancreatitis, severe arthralgia, angioedema and Stevens-Johnson syndrome**. They must **not** be combined with a GLP-1RA (redundant mechanism).

- **GLP-1RAs** are DPP-4-resistant peptide agonists giving *pharmacologic* GLP-1 levels — far greater incretin action than DPP-4 inhibitors. They produce **HbA1c ↓ 0.5–1.5%**, substantial **weight loss**, and **cardiovascular + renoprotective** benefit. Long-acting once-weekly agents (dulaglutide, extended-release exenatide, semaglutide) are preferred over short-acting twice-daily exenatide/lixisenatide. **Oral semaglutide** (co-formulated with the absorption enhancer **SNAC**) is the first oral GLP-1RA. Liraglutide 3 mg and semaglutide 2.4 mg are separately licensed for **obesity**.
- **Tirzepatide** — a once-weekly **dual GIP/GLP-1 receptor agonist** — is the most potent agent yet: in head-to-head trial vs semaglutide 1 mg, HbA1c fell **2.3%** (from 8.3% baseline) with **>10% weight loss in 57%** of patients. CMDT quotes HbA1c reductions of **1.9–2.6%** and weight loss of 6–13 kg.

Agent	Route / frequency	Typical dose (titrated)	HbA1c ↓
Sitagliptin	Oral OD	100 mg (50 if eGFR 30–50; 25 if <30)	0.5–0.8%
Linagliptin	Oral OD	5 mg — *no renal adjustment* (biliary excretion)	0.5–0.8%
Alogliptin	Oral OD	25 mg (12.5 if eGFR 30–60; 6.25 if <30)	0.5–0.8%
Liraglutide	SC once daily	0.6 → 1.2 → 1.8 mg	0.6–1.5%
Dulaglutide	SC once weekly	0.75 → 1.5 → 4.5 mg	~1.5–1.8%
Semaglutide	SC once weekly	0.25 → 0.5 → 1 → 2 mg	1.5–2.1%
Oral semaglutide	Oral OD, fasting	3 → 7 → 14 mg	—
Tirzepatide	SC once weekly	2.5 → 5 → up to 15 mg	1.9–2.6%

SGLT-2 inhibitors

- **Mechanism**: SGLT-2 in the proximal convoluted tubule mediates ~90% of filtered glucose reabsorption. Inhibition **lowers the renal threshold for glucose**, producing glycosuria and an **insulin-independent** fall in plasma glucose (so efficacy is *eGFR-dependent* — weaker as CKD advances). Associated **natriuresis** gives a mild diuretic effect and a **3–6 mmHg fall in systolic BP**; caloric loss yields **2–5 kg weight loss**.
- **Efficacy**: HbA1c ↓ 0.5–1.0%; no intrinsic hypoglycaemia.
- **Cardiorenal benefit** is the defining feature: reduced **heart-failure hospitalisation** (most consistent effect), reduced MACE/CV mortality in established ASCVD, and **slowed progression of diabetic kidney disease**. Per KDIGO, may be initiated for renoprotection down to **eGFR ~20 mL/min/1.73 m²** and continued until dialysis, even though the *glucose-lowering* effect is lost below eGFR 45.
- **Adverse effects**: **genital mycotic infections and UTIs** (~8–9%); **euglycemic DKA** (insulin-deficient states, fasting, surgery, acute illness); volume depletion / transient creatinine rise; **necrotizing fasciitis of the perineum (Fournier gangrene)**; canagliflozin specifically — ↑

amputations (CANVAS, HR ~1.97), ↓ bone mineral density and ↑ fractures; small (3–8%) rise in LDL. **Withhold 3 days before major surgery** and during acute illness.

Agent	Glycaemic dose	eGFR caution (glycaemic)
Empagliflozin	10 mg OD (max 25)	Avoid <30
Dapagliflozin	10 mg OD (5 mg if liver failure)	Avoid <45 (renoprotection to eGFR 25)
Canagliflozin	100 mg OD (up to 300)	100 mg if eGFR 30–60; avoid <30
Ertugliflozin	5 → 15 mg OD	Avoid <45

Cardiorenal outcome trials (high-yield)

Trial	Drug	Key result
EMPA-REG OUTCOME	Empagliflozin	↓ all-cause mortality 32%, CV death 38%, HF hospitalisation 35%
CANVAS	Canagliflozin	↓ MACE & HF; ↑ **amputation (HR 1.97)**, ↑ fracture
DECLARE-TIMI 58	Dapagliflozin	↓ CV death / HF hospitalisation (incl. primary-prevention cohort)
CREDENCE	Canagliflozin	Renal-outcomes trial — ↓ progression of diabetic nephropathy
LEADER	Liraglutide	↓ MACE 13%, CV death 22%, all-cause mortality 15%, albuminuria 26%
SUSTAIN-6	Semaglutide	↓ MACE 26%; ↓ renal events; **retinopathy signal**; no mortality benefit
REWIND	Dulaglutide	↓ MACE and composite microvascular (retinopathy + nephropathy)
SAVOR-TIMI 53 / EXAMINE	Saxagliptin / Alogliptin	↑ **heart-failure hospitalisation** (DPP-4 class caution)
TECOS / CAROLINA	Sitagliptin / Linagliptin	CV-neutral (CAROLINA: neutral vs glimepiride)

Choice of agent — ADA/EASD-style algorithm (Harrison Fig 416-3)

- **Metformin + lifestyle** remains the foundation when there is no cardiorenal disease (efficacious, cheap, weight-favourable).
- **Comorbidity now drives selection, independent of HbA1c**:
  - **ASCVD or high CV risk → GLP-1RA or SGLT-2 inhibitor** with proven benefit.
  - **Heart failure (HFrEF or HFpEF) → SGLT-2 inhibitor.**
  - **Chronic kidney disease / albuminuria → SGLT-2 inhibitor** (GLP-1RA if SGLT-2i not tolerated).
  - **Weight loss a priority → GLP-1RA or tirzepatide** (greatest effect).

- These agents may be **combined with metformin or each other** (e.g. metformin + SGLT-2i + GLP-1RA) for additive effect — but **GLP-1RA + DPP-4 inhibitor is irrational**. Reassess HbA1c every 3 months; add basal insulin if targets unmet.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Sites of action of glucose-lowering agents** (label: *intestine/L-cell → GLP-1*, *DPP-4 inhibitor*, *GLP-1RA*, *pancreatic β-cell (insulin) & α-cell (glucagon)*, *liver — hepatic glucose output / metformin*, *muscle & fat — insulin sensitivity / TZD*, *kidney proximal tubule — SGLT-2 inhibitor → glycosuria*).
- **Diagram 2 — Comorbidity-driven treatment algorithm** (boxes: *T2DM + metformin/lifestyle* → branch to *ASCVD/high risk → GLP-1RA or SGLT-2i*, *Heart failure → SGLT-2i*, *CKD → SGLT-2i*, *Weight loss → GLP-1RA / tirzepatide*).

Clinical / Diagnostic significance

- **Cardiorenal first**: in T2DM with ASCVD, HF or CKD, start an **SGLT-2 inhibitor and/or GLP-1RA early** regardless of baseline HbA1c — they reduce hard outcomes (CV death, HF hospitalisation, ESKD).
- **Hypoglycaemia avoidance**: incretin agents and SGLT-2i do not cause hypoglycaemia alone; reduce the dose of a co-prescribed **sulfonylurea or insulin** to prevent it.
- **Euglycemic DKA**: a "normal glucose" does **not** exclude DKA in a patient on an SGLT-2 inhibitor — check ketones in any unwell SGLT-2i user; hold the drug during fasting, acute illness and perioperatively.
- **GLP-1RA / tirzepatide safety**: contraindicated with **personal/family history of medullary thyroid carcinoma or MEN-2** (rodent C-cell tumours); avoid in prior **pancreatitis**; warn re nausea/vomiting and stop if persistent abdominal pain; SUSTAIN-6 flagged worsening **retinopathy** with rapid glucose lowering.
- **Renal dosing**: linagliptin needs no adjustment (biliary); liraglutide/semaglutide/dulaglutide are safe in renal failure; exenatide is contraindicated below eGFR 30.

High-yield exam pointers

- "Newer" = **DPP-4 inhibitors, GLP-1RAs, GIP/GLP-1 dual agonist (tirzepatide), SGLT-2 inhibitors**.
- **DPP-4i = incretin enhancer (weak, weight-neutral, oral); GLP-1RA = incretin mimetic (strong, weight loss, CV/renal benefit).**
- **EMPA-REG** = first CVOT to show CV/HF benefit of an SGLT-2 inhibitor; **LEADER** = first for a GLP-1RA.
- SGLT-2i triad of harm: **genital mycotic infection, euglycemic DKA, Fournier gangrene**; canagliflozin → **amputation + fracture**.
- **Tirzepatide** (dual GIP/GLP-1) gives the greatest HbA1c (≈2–2.6%) and weight reduction.
- **Linagliptin** = the DPP-4 inhibitor needing **no renal dose adjustment**.
- Never combine **GLP-1RA with a DPP-4 inhibitor**.

- Metformin: max ~2000 mg/day; reduce at eGFR 30–45; **stop if eGFR <30** (lactic-acidosis risk).
- Comorbidity, not HbA1c alone, now selects the second agent.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Management and Therapies" (glucose-lowering agent classes, mechanisms, Table of agents, glycaemic-management algorithm Fig 416-3).
- **Williams Textbook of Endocrinology, 15e** — "Therapeutics of Type 2 Diabetes Mellitus" (incretin physiology, DPP-4 inhibitors, GLP-1RAs, tirzepatide, SGLT-2 inhibitors, and the cardiovascular/renal outcome trials EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, LEADER, SUSTAIN-6, REWIND, CAROLINA).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycemia" (current drug doses, eGFR thresholds, KDIGO renoprotection cut-off, Fournier gangrene, euglycemic DKA, peri-operative discontinuation).

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Newer insulins

Asked in: Paper IV 17 Apr 2026 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — "Newer insulins" denotes the **insulin analogues** — insulin molecules whose amino-acid sequence is deliberately altered by recombinant DNA technology to modify absorption kinetics (onset, peak, duration) while preserving full biologic activity. They comprise **rapid-acting** and **ultra-rapid** prandial analogues, **long-acting / ultra-long-acting** basal analogues (including the **once-weekly** insulin), their **concentrated**, **biosimilar**, **premixed** and **fixed-ratio GLP-1RA combination** forms, and **inhaled** insulin. They were developed to mimic physiologic basal–bolus secretion more closely than the older human (regular, NPH) insulins.

Rationale — limitations of conventional human insulins

- **Regular (soluble) insulin** self-aggregates into hexamers in solution, giving a slow onset (~30–60 min, so it must be injected 20–30 min pre-meal), a delayed peak (2–3 h) and a long tail (6–8 h) that causes **late post-prandial hypoglycaemia**.
- **NPH (isophane)** has a pronounced peak (4–10 h) and a duration (10–20 h) too short for true 24-h basal cover, mandating twice-daily dosing and producing **nocturnal hypoglycaemia**; its action is variable within and between patients.
- Goal of analogue design: rapid analogues that match the post-prandial glucose excursion and decay with it, plus **peakless, reproducible, ~24-h (or longer) basal** insulin — together permitting flexible basal–bolus therapy with less hypoglycaemia.

Classification and pharmacokinetics

Category	Members (analogue)	Onset	Peak	Effective duration
Rapid-acting	Lispro, Aspart, Glulisine	<15 min	0.5–1.5 h	3–5 h

Category	Members (analogue)	Onset	Peak	Effective duration
Ultra-rapid	Faster aspart (Fiasp), Lispro-aabc (Lyumjev)	~10–11 min faster than parent	—	shorter tail
Inhaled	Technosphere human insulin (Afrezza)	<15 min	~1 h	~3 h
Long-acting	Glargine U-100, Detemir	2–4 h	flat / minimal	20–24 h (detemir 12 –24 h)
Ultra-long-acting	Degludec, Glargine U-300	1–9 h	flat	>42 h (degludec); >24 h (U-300)
Once-weekly	Insulin icodec	basal	flat	~1 week

(Standard human insulins for comparison: regular onset 0.5–1 h, peak 2–3 h, duration 6–8 h; NPH onset 2–4 h, peak 6–10 h, duration 12–20 h.)

Rapid-acting and ultra-rapid (prandial) analogues

- **Mechanism** — single/dual amino-acid changes abolish self-aggregation, so the insulin is absorbed as monomers → **faster onset, lower/earlier peak, shorter duration** than regular insulin. This entrains insulin action to the post-meal glucose rise and, because action decays as glucose falls, **reduces hypoglycaemia**.
- **Lispro** — proline and lysine at positions **B28/B29 are reversed** (Lys-B28, Pro-B29).
- **Aspart** — proline at **B28 replaced by aspartic acid**.
- **Glulisine** — asparagine-B3 → lysine and lysine-B29 → glutamic acid.
- Injected **just before (<10 min)** a meal; may be given **after** a meal in gastroparesis or unpredictable intake. Preferred over regular insulin for prandial coverage and are the insulins used in **CSII pumps**.
- **Ultra-rapid formulations** — *Fiasp* = aspart + **niacinamide (vitamin B3)** (onset ~10 min faster); *Lyumjev* (lispro-aabc) = lispro + **treprostinil + citrate** (local vasodilation + increased vascular permeability; onset ~11 min faster, lower 1–2 h post-prandial excursions). A **biosimilar lispro (Admelog)** is available.

Long-acting, ultra-long-acting and once-weekly (basal) analogues

- **Glargine** — asparagine at **A21 replaced by glycine** and **two arginines added to the C-terminus of the B chain**; this raises the isoelectric point so it is soluble at acidic pH but forms **microprecipitates at neutral subcutaneous pH**, releasing slowly → **peakless ~24-h** action with **less nocturnal hypoglycaemia than NPH**. Must **not be mixed** with other insulins (acidic pH). Biosimilars: **Basaglar, Semglee, Rezvoglar**.
- **Detemir** — fatty-acid (myristic acid) acylation at Lys-B29 promotes **reversible albumin binding**, prolonging action (12–24 h); being **phased out** of the market.
- **Degludec** — extension/modification of the B-chain carboxy-terminus causes formation of **soluble multihexamer chains in subcutaneous tissue** plus **albumin binding** → half-life ~25 h, duration **>42 h**. Gives glycaemic control similar to glargine but with **less nocturnal and severe**

hypoglycaemia, and its long, flat profile allows **flexible (varying) injection timing**. Available U-100 and U-200.

- **Insulin icodec (once-weekly)** — Lys-B29 conjugated to a **C20 fatty diacid (1,20-icosanedioic acid)** with three substitutions (**A14E, B16H, B25H**); the diacid gives **strong reversible albumin binding** while the substitutions **attenuate receptor affinity and resist degradation**, yielding a ~1-week duration. Approved in Europe, Canada, Australia, China and Japan.

Concentrated, premixed, biosimilar and combination forms

- **Concentrated insulins** (smaller injection volume for high requirements / insulin resistance):
  - **U-300 glargine (Toujeo)** — one-third the volume, flatter and longer action, **less hypoglycaemia than U-100 glargine**.
  - **U-200 degludec**, **U-200 lispro**, and **U-500 regular** (for severe insulin resistance / total daily dose >200 U; *not bioequivalent* to U-100 — switch with care).
- **Analogue premixes** — Humalog Mix **75/25** and **50/50** (NPL + lispro), NovoLog Mix **70/30** (aspart protamine/aspart); **Ryzodeg 70/30** = degludec/aspart (can be given once or twice daily). Convenient (2 injections) but **not suitable for type 1 DM** as basal and prandial components cannot be titrated independently.
- **Fixed-ratio basal-insulin + GLP-1RA combinations** — **degludec + liraglutide (IDegLira, Xultophy)** and **glargine + lixisenatide (iGlarLixi, Soliqua)** — effective with **less weight gain**.
- **Biosimilars** lower cost (lispro and glargine biosimilars available).

Inhaled insulin

- **Technosphere insulin (Afrezza)** — dry-powder **regular human** insulin inhaled pre-meal; rapidly absorbed (peak insulin 12–15 min, baseline by ~3 h), effect comparable to rapid analogues when combined with basal insulin.
- Supplied as colour-coded **4-, 8-, 12-unit** single-use cartridges.
- **Adverse effects / cautions** — **cough (~27%)**, small early fall in **FEV1**; **contraindicated in smokers and in asthma/COPD**; perform **spirometry (FEV1) before and periodically during** therapy. A lung-cancer signal was noted (all in ever-smokers); the earlier inhaled insulin **Exubera** was withdrawn.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pharmacokinetic (action-profile) graph** — x-axis *Time (h) 0–42*, y-axis *Plasma insulin / glucose-lowering effect*; overlay labelled curves: **Rapid (aspart/lispro/glulisine)** sharp early peak; **Regular** broader peak; **NPH** intermediate dome; **Glargine U-100 / Detemir** flat ~24 h; **Degludec / Glargine U-300** flat >24–42 h; **Inhaled** narrow early spike. Label *onset, peak, duration* on the rapid and NPH curves.
- **Insulin molecule schematic** — A-chain and B-chain with labelled modification sites: **B28/B29 reversal (lispro)**, **B28 Asp (aspart)**, **A21 Gly + B-chain di-arginine (glargine)**, **B29 fatty-acid acylation (detemir/degludec/icodec)**.

Clinical / Diagnostic significance

- **Basal–bolus (MDI) regimen** — basal glargine/degludec once daily + rapid analogue (lispro/aspart/glulisine) at each meal; total **0.4–1.0 U/kg/day**, ~30–50% as basal. Prandial dose set by an **insulin-to-carbohydrate ratio** (commonly 1 U / 10–15 g) plus a **correction factor** (≈ 1500 ÷ total daily dose for mg/dL drop per unit).
- **Hypoglycaemia reduction** — flat, reproducible basal analogues markedly lower **nocturnal/severe hypoglycaemia** versus NPH; rapid analogues lower late post-prandial hypoglycaemia.
- **Flexibility** — degludec and U-300 glargine allow varied daily injection times; note degludec's long washout (~42 h) when a patient fasts for procedures or is switched to another basal insulin.
- **Special situations** — concentrated insulins for severe insulin resistance; ultra-rapid/inhaled insulin for unpredictable intake or needle-averse patients; fixed-ratio GLP-1RA combos when weight gain is a concern; biosimilars to reduce cost.
- Delivered by **pens (including Bluetooth "smart" pens)**, **vial/syringe**, or **CSII pumps / automated insulin-delivery (hybrid closed-loop)** systems using rapid analogues.

High-yield exam pointers

- Rapid analogues (lispro/aspart/glulisine): inject **<10–15 min pre-meal**; onset <15 min, duration 3–5 h; **do not self-aggregate**.
- **Glargine** = A21 Asn→Gly + 2 Arg on B-chain → microprecipitates; **peakless ~24 h**; never mix.
- **Degludec** = multihexamer + albumin binding; half-life ~25 h, duration **>42 h**; flexible timing.
- **Icodec** = once-weekly basal (C20 diacid → albumin binding; A14E/B16H/B25H substitutions).
- **Fiasp** = aspart + niacinamide; **Lyumjev** = lispro + treprostinil + citrate (ultra-rapid).
- **U-300 glargine / U-200 degludec / U-200 lispro / U-500 regular** = concentrated; U-500 for resistance >200 U/day.
- **Fixed-ratio combos**: IDegLira (Xultophy), iGlarLixi (Soliqua).
- **Inhaled (Afrezza)**: 4/8/12-U cartridges; cough ~27%, falls FEV1; **contraindicated in smokers/asthma/COPD**; spirometry first.
- Only **regular and aspart** insulin may be given **IV**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Management and Therapies" (insulin preparations, mechanisms of lispro/glargine/degludec, Table 416-5, basal–bolus regimens).
- **Williams Textbook of Endocrinology, 15e** — "Type 1 Diabetes Mellitus" (insulin types and action profiles, Table 35.6; ultra-rapid analogues; concentrated insulins; MDI/CSII dosing).
- **CMDT 2026** — "Diabetes Mellitus & Hypoglycemia" (analogue characteristics, ultra-rapid Fiasp/Lyumjev, glargine/degludec/**icodec** details, concentrated and premixed insulins, inhaled Technosphere insulin and its cautions).

Coverage note: The corpus richly covers all analogue classes including once-weekly icodec; insulin **detemir's** specific fatty-acid (myristoyl) acylation mechanism is stated here as universally accepted standard pharmacology (the corpus notes detemir is being phased out but does not detail its structure).

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Osteoporosis

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

Definition / Introduction — Osteoporosis is a condition characterised by a **reduction in the strength of bone leading to skeletal fragility and an increased risk of fractures**. Although bone mineral density (BMD) is used to define it, bone strength also depends on **bone quality** — microarchitecture, remodelling rate, mineralisation and the accumulation of microdamage. It is operationally defined by the **WHO** as a BMD that is **≥2.5 standard deviations below the young-adult mean (T-score ≤ –2.5)**. It is the commonest metabolic bone disease, affecting >10 million individuals in the United States, predominantly **postmenopausal women**, though **30% of fragility fractures occur in men**. The clinically important fractures are **vertebral, hip and wrist (Colles')** fractures.

Densitometric classification (WHO) and key definitions

- T-score compares an individual's BMD with the mean of a **young-adult (age 30), sex- and race-matched** population (1 T-score unit = 1 SD); the **Z-score** compares with an **age- and sex-matched** reference population.

Category	T-score (lumbar spine / femoral neck / total hip)
Normal	> –1.0
Low bone density / osteopenia	–1.0 to –2.5
Osteoporosis	≤ –2.5
Severe (established) osteoporosis	≤ –2.5 **with** a fragility fracture

- **Fragility (low-trauma) fracture** = fracture following a fall from standing height or less; in adults aged >50, any fracture **except those of fingers, toes, face and skull** is regarded as fragility. Any fracture in a **woman >50 or a man >60** should trigger investigation for osteoporosis.
- Because **>50% of fractures occur in individuals with osteopenia** (T-score −1.0 to −2.5), emphasis has shifted to **absolute fracture risk** (e.g., FRAX) rather than BMD threshold alone.

Pathophysiology — bone remodelling

- In adults the principal skeletal process is **remodelling** (not modelling), performed by the **basic multicellular unit (BMU)**: osteoclasts (monocyte–macrophage lineage) resorb a cavity, then osteoblasts (mesenchymal lineage) lay down osteoid that mineralises; **osteocytes** are terminally differentiated osteoblasts that orchestrate the process.
- **Peak bone mass** is achieved by early adulthood and is largely **genetically determined (heritability 50–80%)**; after age **30–45 years resorption exceeds formation**, producing slow bone loss, exaggerated in women by oestrogen deficiency.
- **RANK–RANKL–OPG axis:** RANKL (a TNF-family cytokine from osteoblasts, osteocytes, T cells) binds **RANK** on osteoclast precursors → osteoclast formation, activation and survival. **Osteoprotegerin (OPG)** is a decoy receptor that neutralises RANKL. The balance of these three determines bone resorption.
- **Wnt–sclerostin pathway:** Wnt signalling (stimulated by mechanical loading and PTH) promotes osteoblastic bone formation and lowers RANKL; **sclerostin**, an osteocyte protein, inhibits Wnt and bone formation. Both RANKL and Wnt pathways are major drug targets.
- **Oestrogen deficiency** (chiefly menopause, mean age 51 y) drives loss by **increasing RANKL and decreasing OPG**, increasing remodelling activation frequency and prolonging osteoclast (while shortening osteoblast) lifespan. **Trabecular bone** (80% of surface area) is affected first — hence **vertebral fractures are the earliest consequence**.
- **Calcium/vitamin D:** inadequate intake → **secondary hyperparathyroidism** → increased remodelling and bone loss. **LRP5** activating mutations cause high bone mass; inactivating mutations cause osteoporosis-pseudoglioma syndrome.

Aetiology — primary and secondary causes

- **Primary:** postmenopausal (type I, oestrogen-related, trabecular/vertebral) and age-related/senile (type II); idiopathic (including in men and pre-menopausal women).
- **Secondary** — suggested by very low Z-scores, fractures in younger patients, or atypical features.

Group	Risk factors / causes
Non-modifiable	Personal history of adult fracture, family history of hip fracture, advanced age, female sex, white race, dementia
Modifiable	Current smoking, oestrogen deficiency, **early menopause (<45 y) / oophorectomy**, prolonged amenorrhoea (>1 y), low calcium/vitamin D intake, alcoholism, impaired vision, recurrent falls, inadequate physical activity, low BMI
Endocrine	Cushing's syndrome, **hyperparathyroidism**, thyrotoxicosis, **diabetes mellitus (type 1 and 2)**, acromegaly, adrenal insufficiency, hypogonadism (Turner's, Klinefelter's, anorexia nervosa, hyperprolactinaemia)

Group	Risk factors / causes
GI / nutritional	Malabsorption, **coeliac disease**, gastrectomy, primary biliary cirrhosis, malnutrition
Marrow / malignancy	**Multiple myeloma**, lymphoma/leukaemia, mastocytosis, thalassaemia
Inherited / other	Osteogenesis imperfecta, Marfan's, Ehlers–Danlos, homocystinuria, hypophosphatasia; rheumatoid arthritis, ankylosing spondylitis, immobilisation, COPD, multiple sclerosis
Drugs (Table 423-3)	**Glucocorticoids** (commonest medication-induced; risk if ≥5 mg prednisone/day for >3 months), aromatase inhibitors, **androgen-deprivation therapy**, GnRH agonists, excess thyroxine, anticonvulsants, SSRIs, proton-pump inhibitors, thiazolidinediones, heparin, lithium, cyclosporine, cytotoxics

Clinical features

- Osteoporosis itself is **asymptomatic until fracture** ("silent disease").
- **Vertebral fractures:** ~70% are clinically silent; present with acute back pain (only ~30% are symptomatic), progressive **height loss (>4 cm)**, **dorsal kyphosis**, restrictive lung disease (thoracic) or abdominal distension/early satiety (lumbar). Chronic pain is largely myoligamentous, not bony.
- **Hip fracture:** almost always needs surgery; carries **20–25% mortality in the first year** and ~30% of survivors require long-term care.
- **Wrist (Colles')** fractures rise after menopause; a first fracture markedly increases further-fracture risk, especially in the next **12–24 months ("imminent fracture risk")**.

Diagnosis and investigations

- **DXA (dual-energy x-ray absorptiometry)** of lumbar spine and hip is the **standard** for BMD; the **total hip** best predicts hip-fracture risk. Serial scans should use the same machine. (QCT, HR-pQCT, peripheral QCT and ultrasound are alternatives; **trabecular bone score [TBS]** adds microarchitectural information to spinal DXA.)
- **Indications for BMD testing:** all **women ≥65 and men ≥70**; younger post-menopausal women / men 50–69 with risk factors; any adult with a fracture at/after age 50; adults on a high-risk drug (e.g., glucocorticoids) or disease.
- **FRAX®:** integrates age, sex, BMI, prior fracture, parental hip fracture, smoking, alcohol, glucocorticoids, rheumatoid arthritis and secondary causes (± femoral-neck BMD) to give the **10-year probability of major osteoporotic (hip, clinical spine, wrist, humerus) and of hip fracture**. US intervention threshold: **10-year major osteoporotic risk ≥20% and/or hip risk ≥3%**.
- **Vertebral fracture assessment (VFA)/lateral spine imaging** detects silent vertebral fractures.
- **Laboratory screen for secondary causes:** CBC, serum & 24-h urine calcium, renal and liver function, **serum 25(OH)D**, **TSH**, PTH (if hypercalcaemic), **serum/urine electrophoresis and free light chains** (myeloma), **testosterone in men**, 24-h urinary free cortisol/overnight dexamethasone (Cushing's), tissue transglutaminase IgA (coeliac), tryptase/urinary histamine (mastocytosis).

- **Biochemical bone-turnover markers** — formation: bone-specific alkaline phosphatase, osteocalcin, **P1NP** (preferred); resorption: urine/serum NTX, **serum CTX** (preferred, fasting 9 a.m.). Chiefly used to **monitor treatment response** (change earlier than BMD); a meaningful change is **≥30–40%**.

Management

Non-pharmacological / universal measures

- Adequate **calcium** (RDA **1000–1200 mg/day**; dietary preferred; supplement doses ≤600 mg) and **vitamin D** (target 25(OH)D >30 ng/mL; **800–2000 IU/day**, up to 4000 IU/day safe). Calcium + vitamin D reduces fractures mainly in the **deficient, institutionalised elderly**.
- **Weight-bearing and progressive resistance exercise** (small 3–4% BMD gains); **balance training/tai chi reduces falls by ~25%**.
- **Risk-factor reduction:** smoking cessation, limit alcohol, treat impaired vision, minimise sedating drugs, **home/fall-proofing**, hip protectors in nursing-home residents.

Pharmacological agents — antiresorptive (slow resorption) versus anabolic (build bone). Anabolics are first-line in **very-high-risk/imminent-risk** patients; the ideal sequence is **anabolic followed by an antiresorptive**.

Agent	Class / mechanism	Dose & route	Fracture reduction
Alendronate	N-bisphosphonate (inhibits farnesyl-PP synthase → osteoclast apoptosis)	70 mg PO weekly	Vertebral ~50%, hip up to 50%
Risedronate	N-bisphosphonate	35 mg PO weekly	Vertebral 40–50%, hip 40%
Ibandronate	N-bisphosphonate	150 mg PO monthly / 3 mg IV q3-monthly	Vertebral ~40%, no overall non-vertebral benefit
Zoledronic acid	N-bisphosphonate	5 mg IV annually (30-min infusion)	**Vertebral 70%, hip 40%, non-vertebral 25%**
Denosumab	Human anti-RANKL monoclonal antibody	60 mg SC every 6 months	Vertebral 68%, hip 40%, non-vertebral 20%
Raloxifene	SERM (oestrogen agonist on bone)	60 mg PO daily	Vertebral 30–50%; also ↓ER+ breast cancer
Teriparatide	PTH(1–34), anabolic (Wnt/osteoblast)	20 µg SC daily	Vertebral 65%, non-vertebral 53%
Abaloparatide	PTHrP analogue, anabolic	SC daily	Vertebral 86%, non-vertebral 43% (ACTIVE)
Romosozumab	Anti-sclerostin antibody (↑formation, ↓resorption)	210 mg SC monthly ×12	Vertebral 73% (FRAME)
Calcitonin	Hormone (osteoclast inhibition)	200 IU/day intranasal	Weak; analgesic in acute vertebral fracture

- **Oestrogen/hormone therapy** reduces hip & spine fracture (WHI: –34%) but raises MI, stroke, VTE and breast cancer; **not recommended for disease prevention** — reserved for menopausal symptoms.
- **Key adverse effects/precautions:** oral bisphosphonates cause **oesophagitis** (take fasting with a full glass of water, remain upright ≥30 min) and are **contraindicated if eGFR <30–35 mL/min**; class effects include **medication-related osteonecrosis of the jaw (MRONJ)** and **atypical femoral (subtrochanteric) fractures** (lateral thigh/groin pain warning), hypocalcaemia, and an **acute-phase reaction** with IV zoledronate. **Denosumab** has a **rebound increase in bone turnover with multiple vertebral fractures on discontinuation** — never give a drug holiday; bridge with a bisphosphonate. **Teriparatide** carried a (rodent) osteosarcoma signal. **Romosozumab** carries a **cardiovascular warning — avoid after recent MI/stroke** (ARCH trial).
- **Glucocorticoid-induced osteoporosis (GCIOP):** commonest cause of drug-induced osteoporosis; use lowest steroid dose, ensure calcium/vitamin D, and treat with bisphosphonates (alendronate, risedronate, zoledronate), denosumab or teriparatide.
- **Monitoring:** repeat DXA ~every 2 years; a significant change must exceed **~3% at spine, ~6% at hip**; turnover markers detect response earlier (~3 months). **"Drug holidays"** apply to bisphosphonates only (long skeletal half-life) — avoided with denosumab and anabolic agents.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **RANK–RANKL–OPG and Wnt–sclerostin remodelling unit:** label *osteoblast/osteocyte*, *RANKL*, *RANK (on preosteoclast)*, *osteoprotegerin (OPG, decoy)*, *multinucleated osteoclast resorbing bone*, *Wnt signal → bone formation*, *sclerostin (inhibits Wnt)*; mark drug targets — *denosumab → RANKL*, *romosozumab → sclerostin*, *bisphosphonates → osteoclast*.
- **T-score normal distribution curve:** label *young-adult mean (T = 0)*, *normal (> –1.0)*, *osteopenia (–1.0 to –2.5)*, *osteoporosis (≤ –2.5)*, with a marker at **T = –2.5**.

Clinical / Diagnostic significance

- Osteoporosis is a **silent disease diagnosed only after fracture or screening** — hence proactive **DXA + FRAX** in at-risk groups.
- A **first fragility fracture predicts imminent further fractures**; **fracture liaison services** improve secondary-fracture prevention (~20% fall in hip-fracture rate in the Kaiser system).
- Distinguish from **osteomalacia** (defective mineralisation, low/normal calcium and phosphate, raised ALP, looser zones) and **multiple myeloma** (punched-out lytic lesions, paraproteinaemia).
- Always exclude **secondary causes** before labelling primary osteoporosis, especially in men, premenopausal women and unexpectedly low Z-scores.

High-yield exam pointers

- **WHO T-score ≤ –2.5 = osteoporosis; –1.0 to –2.5 = osteopenia**; T = young-adult reference, Z = age-matched.
- **>50% of fractures occur in osteopenic patients** → use **absolute risk (FRAX)**; US thresholds **≥20% major / ≥3% hip**.

- **RANKL–RANK–OPG** and **Wnt–sclerostin** are the central pathways and the basis for **denosumab** and **romosozumab**.
- **Zoledronic acid** (annual IV) gives the largest bisphosphonate fracture reduction (vertebral 70%, hip 40%).
- **Denosumab** — never stop abruptly (rebound vertebral fractures); bridge with bisphosphonate.
- **Romosozumab** — anabolic + antiresorptive but **cardiovascular boxed warning**.
- **Anabolic-first then antiresorptive** in very-high/imminent-risk patients.
- **Glucocorticoids** = commonest drug cause (risk ≥5 mg prednisone/day >3 months).
- Oral bisphosphonate rules: **fasting, full glass of water, upright ≥30 min; avoid if eGFR <30**; watch for **MRONJ** and **atypical femoral fracture**.
- Hip fracture carries **20–25% one-year mortality**.

SOURCE & COVERAGE

Harrison 22e — Ch 423 "Osteoporosis" (P.R. Ebeling). Standard definitions (normal/osteopenia/osteoporosis T-score bands, "severe/established osteoporosis", type I/II classification) and the osteomalacia/myeloma differential are universally accepted internal-medicine teaching used to round out the answer; all drug doses, fracture-reduction figures, trial names and thresholds are taken verbatim from the chapter. No coverage gap.

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Pituitary hormones

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

Definition / Introduction — The pituitary gland (~600 mg, lying within the sella turcica ventral to the diaphragma sella) is the "master gland" that, with the hypothalamus, orchestrates most endocrine function. It has two embryologically and functionally distinct lobes: the **anterior pituitary (adenohypophysis)**, derived from *Rathke's pouch*, which secretes **six major hormones** — prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH); and the **posterior pituitary (neurohypophysis)**, a neural extension storing **arginine vasopressin (AVP/ADH)** and **oxytocin**. All are secreted in a pulsatile manner under hypothalamic and feedback control.

Anatomy, development and regulatory principles

- **Vascular supply:** superior and inferior hypophyseal arteries. The **hypothalamic-pituitary portal plexus** carries hypothalamic releasing/inhibiting peptides to the anterior lobe in high concentration *without systemic dilution*, so anterior cells receive discrete hypothalamic pulses.
- The **posterior lobe** is supplied by the inferior hypophyseal arteries and is *directly innervated* by hypothalamic neurons via the supraopticohypophyseal and tuberohypophyseal tracts — hence AVP/oxytocin output is sensitive to stalk or hypothalamic damage.
- **Development from Rathke's pouch** is governed by lineage-specific transcription factors: *Prop-1* and *Pit-1* (GH, PRL, TSH lineages), *SF-1* and *DAX-1* (gonadotropes), and *T-Pit*

(corticotropes/POMC). Their mutations cause selective or combined pituitary hormone deficiency.

- **Three regulatory layers:** (1) hypothalamic releasing/inhibiting factors via the portal system; (2) **negative feedback** by peripheral target-gland hormones (e.g., cortisol on ACTH, T3/T4 on TSH); (3) **hormonal rhythms** — most pituitary hormones are entrained to sleep/circadian cycle (e.g., ACTH–cortisol peak ~6 a.m., nadir ~midnight; GH and PRL peak in non-REM/early sleep).

Anterior pituitary hormones — summary

Hormone	Cell (% of anterior cells)	Chemical nature	Hypothalamic stimulator	Inhibitor	Target	Principal action
PRL	Lactotrope (~20%)	Polypeptide, 198 aa	TRH, VIP, estrogen	**Dopamine** (tonic, D2 receptor)	Breast	Lactation; suppresses GnRH/gonadotropins
GH	Somatotrope (up to 50%)	Polypeptide, 191 aa (22 kDa)	GHRH, ghrelin	Somatostatin (SRIF), IGF-1	Liver, bone, tissues	IGF-1 generation, linear growth, insulin antagonism, lipolysis
ACTH	Corticotrope (~20%)	Polypeptide, 39 aa (from POMC, 266 aa)	CRH, AVP, cytokines (IL-6)	Glucocorticoids	Adrenal cortex	Cortisol/adrenal steroidogenesis
LH	Gonadotrope (~10%)	Glycoprotein (α + β)	GnRH	Sex steroids (feedback)	Ovary/ testis	Ovulation, corpus luteum; Leydig cell testosterone
FSH	Gonadotrope (~10%)	Glycoprotein (α + β)	GnRH, activin	Inhibin	Ovary/ testis	Folliculogenesis, ovarian estrogen; spermatogenesis
TSH	Thyrotrope (~5%)	Glycoprotein (α + β)	TRH	T3/T4, dopamine, somatostatin, glucocorticoids	Thyroid	T4 synthesis and secretion

The glycoprotein hormones (LH, FSH, TSH; also hCG) share a common α subunit; biologic specificity resides in the hormone-specific β subunit.

Individual anterior hormones — key mechanisms

- **Prolactin:** 198 aa, weakly homologous to GH and human placental lactogen; half-life ~50 min. Uniquely, its predominant hypothalamic control is **inhibitory** (tonic dopamine via **D2 receptors**) — so stalk section (trauma, compressive lesions) *raises* PRL. The PRL receptor is a **type I cytokine receptor** signalling through **JAK/STAT**. PRL induces and maintains lactation and **suppresses reproductive function** by inhibiting hypothalamic GnRH and pituitary gonadotropins → hypogonadism (this underlies amenorrhoea-galactorrhoea and male hypogonadism in hyperprolactinaemia). PRL rises ~10-fold in pregnancy.

- **Growth hormone / IGF-1:** Most abundant anterior hormone. Stimulated by **GHRH** (44-aa peptide) and **ghrelin**; inhibited by **somatostatin (SRIF)** and by IGF-1 feedback. Of the five somatostatin receptor subtypes (SST1–SST5), **SST2 and SST5** suppress GH (and TSH). GH receptor belongs to the cytokine/haematopoietic family (JAK/STAT). GH causes protein synthesis/nitrogen retention, **insulin antagonism** (impaired glucose tolerance), lipolysis, and Na+/K+/water retention; much of its growth action is mediated by **IGF-1** (chiefly hepatic, carried by IGFBP3). *Pegvisomant*, a GH-receptor antagonist, treats acromegaly.
- **ACTH:** A 39-aa peptide cleaved from the **proopiomelanocortin (POMC, 266 aa)** precursor, which also yields β-lipotropin, β-endorphin, met-enkephalin, **α-MSH** and CLIP. POMC is stimulated by **CRH** (41-aa, paraventricular nucleus), AVP and cytokines, and suppressed by glucocorticoids. ACTH acts via the **melanocortin-2 receptor** (GPCR) to drive adrenal cortisol synthesis; it shows a marked circadian rhythm and mediates the neuroendocrine stress response.
- **Gonadotropins (LH, FSH):** Controlled by **GnRH** (10-aa peptide) released in **pulses every 60–120 min**, itself regulated by **kisspeptin** (KISS1 gene). *Pulsatile* GnRH is essential; *continuous* exposure desensitises gonadotropes — the basis for long-acting **GnRH agonists** in precocious puberty and prostate cancer. **Inhibin** selectively suppresses FSH while **activin** stimulates it. Estrogen is normally inhibitory, but the rising preovulatory estrogen exerts **positive feedback** to trigger the mid-cycle LH surge.
- **TSH:** Stimulated by **TRH** (a hypothalamic tripeptide, pyroglutamyl-histidyl-prolinamide) and suppressed by thyroid hormone (the predominant negative regulator), dopamine, somatostatin and glucocorticoids. Long half-life and low pulse amplitude mean a single TSH level reliably reflects status. It acts on a thyroid follicular-cell GPCR.

Posterior pituitary (neurohypophysis) hormones

- The neurohypophysis is the distal axons of **magnocellular neurons** whose cell bodies lie in the **paraventricular and supraoptic nuclei**.
- **Arginine vasopressin (AVP/ADH):** a **nonapeptide** (six-member disulfide ring + tripeptide tail) synthesised as a precursor yielding AVP, **neurophysin II** and **copeptin** (single gene, chromosome 20). Secretion is governed mainly by **osmoreceptors** in the anteromedial hypothalamus; the osmotic set point is ~**275 mosmol/L** (plasma Na+ ~135 meq/L), with a 2–4% rise giving maximal antidiuresis. AVP is also released by a fall in BP or volume loss **>10–20%** (baroregulated), and potently by nausea/emesis. **Action:** via renal **V2 receptors** → cAMP → insertion of **aquaporin-2 (AQP2)** channels into principal-cell apical membrane → water reabsorption (urine osmolarity up to **1200 mOsmol/L** at AVP 1–3 pg/mL). **V1a/V1b** receptors mediate vasoconstriction, hepatic glycogenolysis and ACTH potentiation. Half-life 10–30 min; *desmopressin (DDAVP)* resists vasopressinase and acts longer.
- **Oxytocin:** also a nonapeptide, differing from AVP at **positions 3 and 8**; little antidiuretic effect. It stimulates **milk letdown** (suckling reflex) and uterine smooth-muscle contraction in labour, and centrally regulates socioemotional behaviour (bonding, empathy).
- **Thirst** is regulated by a hypothalamic osmostat set ~**3% higher** than the AVP osmostat, ensuring fluid intake before plasma tonicity exceeds the antidiuretic defence.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hypothalamic-pituitary axes (Fig. 390-1):** Hypothalamus (label releasing factors: *CRH, GnRH, TRH, GHRH, somatostatin/SRIF, dopamine*) → portal vessels → anterior pituitary (label cells: *corticotrope-ACTH, gonadotrope-LH/FSH, thyrotrope-TSH, somatotrope-GH, lactotrope-PRL*) → target glands (*adrenal-cortisol, gonads-sex steroids/inhibin, thyroid-T4/T3, liver-IGF-1, breast*); draw **negative-feedback arrows** from target hormones back to hypothalamus/pituitary.
- **Posterior pituitary / AVP pathway (Fig. 393-1/2):** Label *supraoptic + paraventricular nuclei → magnocellular axons → posterior pituitary → AVP release*; and renal collecting-duct cell with labels *V2 receptor, Gs–cAMP, AQP2 (apical), AQP3/AQP4 (basolateral), water reabsorption*.

Clinical / Diagnostic significance

- **Hormone-excess syndromes from adenomas:** prolactinoma (amenorrhoea-galactorrhoea, hypogonadism), GH excess (gigantism/acromegaly; treat with somatostatin analogues, pegvisomant), ACTH excess (Cushing disease), TSH-secreting adenoma (central hyperthyroidism with inappropriately normal/high TSH).
- **Hypopituitarism** may be inherited (Pit-1/Prop-1 mutations) or acquired (tumour, surgery, irradiation, apoplexy, Sheehan syndrome); mass effect adds headache and **bitemporal hemianopia** (optic chiasm).
- **Stalk compression** raises PRL (loss of dopamine inhibition) — a useful localising clue.
- **Pulsatility matters:** pulsatile GnRH stimulates but continuous GnRH suppresses gonadotropins (therapeutic GnRH agonists).
- **Posterior pituitary disorders:** AVP **deficiency** (central DI) vs AVP **resistance** (nephrogenic DI) cause hypotonic polyuria (>40–50 mL/kg/24 h); differentiate with serum Na+, the desmopressin test and **copeptin** (baseline >21.4 pmol/L = AVP resistance; stimulated >4.9 pmol/L at Na+ ≥150 mmol/L diagnoses AVP deficiency, ~96.5% accuracy). The **pituitary "bright spot"** on T1 MRI marks AVP-containing vesicles and may be lost in AVP deficiency. Excess/inappropriate AVP causes **SIAD/hyponatraemia**.

High-yield exam pointers

- Six anterior hormones: **PRL, GH, ACTH, LH, FSH, TSH**; posterior stores **AVP and oxytocin** (made in hypothalamus, not the posterior lobe).
- Cell proportions: **GH ~50%**, PRL ~20%, ACTH ~20%, LH/FSH ~10%, **TSH ~5%**.
- **Prolactin is the only anterior hormone under tonic inhibitory (dopaminergic D2) control** → stalk section causes hyperprolactinaemia.
- Glycoprotein hormones (LH, FSH, TSH, hCG) share a **common α subunit**; β subunit confers specificity.
- ACTH derives from **POMC** (also yields α-MSH, β-endorphin, β-lipotropin); receptor = **melanocortin-2**.
- GH actions are largely mediated by **IGF-1**; GH itself is **diabetogenic** (insulin antagonist).

- GnRH pulses every **60–120 min**; kisspeptin is the upstream gatekeeper; continuous GnRH desensitises.
- AVP is a **nonapeptide** acting via **V2 receptors–AQP2**; osmotic set point ~**275 mosmol/L**; copeptin is its stable surrogate.
- **Inhibin ↓FSH, activin ↑FSH**; rising estrogen gives positive feedback → LH surge.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 390 "Physiology of Anterior Pituitary Hormones" (anterior lobe, synthesis/secretion/action of PRL, GH, ACTH, LH/FSH, TSH; anatomy, development, regulation) and Ch 393 "Disorders of the Neurohypophysis" (AVP and oxytocin physiology, osmoregulation, DI/copeptin). Coverage note: the topic is fully supported by the two provided chapters; specific adenoma-syndrome management details (e.g., bromocriptine/cabergoline doses) are clinical add-ons drawn from standard internal medicine and are summarised, not source-detailed.

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Regulation of energy balance

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

Definition / Introduction — *Energy balance* is the state in which **energy intake** (calories from food) equals **total energy expenditure (TEE)**, so that body energy stores (chiefly adipose triglyceride) and body weight remain stable over long periods. It is not a matter of conscious choice alone but a tightly **homeostatically regulated** process: the amount of stored energy is defended by fundamental physiologic mechanisms essential to survival. The **hypothalamus** is the master integrator, receiving adiposity signals (leptin, insulin) and gut signals (ghrelin, GLP-1, PYY, CCK, etc.) and translating them, via the **leptin–melanocortin pathway**, into adjustments of hunger, satiety and energy expenditure. Chronic imbalance (intake > expenditure) of as little as **~7 kcal/day** sustained over years produces obesity.

The energy balance equation and components of energy expenditure

- **Fundamental equation:** Change in energy stores = Energy intake − Total energy expenditure. Positive balance → fat storage (as triacylglycerol, which yields >2× the energy/gram of carbohydrate and needs no accompanying water); negative balance → mobilisation of free fatty acids and glycerol.
- **Macronutrient fuel value:** carbohydrate **4 kcal/g**, protein **4 kcal/g**, fat **9 kcal/g**, alcohol **7 kcal/g** (alcohol is a fuel but not a nutrient).
- **Total energy expenditure** (TEE) has three quantitatively important parts plus a minor one:

Component	Approx. share of TEE	Nature / regulation
Resting energy expenditure (REE / BMR)	**~70%**	Energy for basal cellular and organ function; chiefly regulated by **thyroid hormone** (thyrotoxicosis ↑ REE → weight loss)

Component	Approx. share of TEE	Nature / regulation
Physical activity (exercise + NEAT)	**~20%**	Voluntary exercise + **non-exercise activity thermogenesis** (posture, fidgeting); most variable component
Thermic effect of food (TEF / specific dynamic action)	**~10%**	Energy of chewing, digestion, absorption and post-prandial sympathetic activation
Cold-induced (shivering) thermogenesis	minor	Thermoregulatory

- **Estimating requirements (Harrison/DRI):** the **Estimated Energy Requirement (EER)** = REE × **physical activity level (PAL)**. In weight-stable adults, **REE = 900 + 10m** (males) and **REE = 700 + 7m** (females), where *m* = mass in kg. PAL multipliers: **1.4 (inactive)**, **1.6 (low active)**, **1.75 (active)**, **2.05 (very active)**. Average intake ≈ 2600 kcal/d (US men), 1800 kcal/d (US women).

The hypothalamus — the integrating centre

- The hypothalamus is **partially outside the blood–brain barrier**, allowing it to sample circulating hormones and combine them with neural, sensory and cognitive inputs.
- **First-order (primary) neurons** lie in the **arcuate nucleus** and fall into two antagonistic, leptin-responsive populations:

Neuronal population (arcuate n.)	Peptides released	Effect on appetite	Response to leptin
POMC neurons (anorexigenic)	Pro-opiomelanocortin → **α-/β-MSH**	↓ Food intake, ↑ energy expenditure	**Stimulated** by leptin
NPY/AGRP neurons (orexigenic)	**NPY**, **AGRP**, inhibitory **GABA**	↑ Food intake	**Inhibited** by leptin

- **α-/β-MSH act on the melanocortin-4 receptor (MC4R)** on **second-order neurons** in the **paraventricular nucleus (PVN)** → reduced intake and ↑ sympathetically-driven energy expenditure. **AGRP** is an endogenous antagonist that actively *switches off* melanocortin receptors. **γ-MSH (MC3 receptor)** influences linear growth and nutrient partitioning (lean vs fat).
- **Downstream effectors: BDNF** (ventromedial nucleus) and its receptor **TrkB**, and **SIM1** (acts downstream of MC4R) — disruption causes hyperphagia and severe obesity.
- **Lateral hypothalamus** harbours orexigenic peptides **melanin-concentrating hormone (MCH)** and **orexin** (orexin loss → narcolepsy). The **endocannabinoid system** (CB1 receptors; ligands **anandamide** and **2-arachidonoylglycerol**) also promotes feeding.

Peripheral signals: adiposity (long-term) and gut (short-term)

- **Adiposity (long-term tonic) signals** report the *size of energy stores*: **leptin** (from adipocytes) and **insulin** (β-cells) rise with fat mass and act centrally to suppress intake.

- **Gut (short-term episodic) signals** report *the meal*: ghrelin drives hunger before meals; the post-prandial incretin/satiety peptides terminate the meal, often acting via **vagal afferents → brainstem → hypothalamus**.

Hormone	Source	Action on energy balance
Leptin	Adipocytes	**Anorexigenic**; rises with fat stores; stimulates POMC, inhibits NPY/AGRP; falls *faster than fat* during caloric restriction
Insulin	Pancreatic β-cells	Central anorexigenic adiposity signal
Ghrelin	Stomach	**Orexigenic**; rises in the unfed state/pre-meal, falls after eating — the only known circulating appetite *stimulant*
CCK	Duodenal I cells	Satiety via vagal CCK-A receptors → brainstem
GLP-1	L cells, small intestine	Satiety + incretin (glucose-dependent insulin release)
GIP	K cells, duodenum/proximal jejunum	Incretin; modulates adipocyte metabolism
PYY (PYY3-36)	L cells, large intestine	Satiety via **Y2 receptor (NPY2R)**
Oxyntomodulin	L cells, large intestine	Satiety
Amylin	Pancreatic β-cells (co-secreted with insulin)	Slows gastric emptying, hindbrain-mediated satiety, restores leptin sensitivity
GDF15	Many tissues under stress	Anorexia via brainstem **GFRAL** receptor

- Diets richer in **protein and fat** induce earlier satiation, partly because the appetite-suppressing gut hormones rise more in response to protein than to carbohydrate.

Set-point, adaptive thermogenesis and leptin resistance

- **Set-point / homeostatic defence:** classic 1940s rodent experiments showed animals *defend* a fixed body-fat level — after forced over- or under-feeding they return to baseline. In humans, body weight is similarly defended: weight loss triggers a *fall* in energy expenditure and a powerful *rise* in hunger that drive regain.
- **Adaptive (metabolic) thermogenesis:** hypocaloric feeding reduces energy expenditure by ~**8 kcal/kg lean body mass** in obese and ~**6 kcal/kg** in normal-weight individuals (a **15–20%** daily fall) — beyond what the loss of body mass alone explains. This makes the dieter transiently more "energy-efficient" and promotes weight regain. (REE rebounds once weight stabilises.)
- **Asymmetry of leptin action explains "why leptin doesn't prevent obesity":** a *fall* in leptin below the habitual level is a **strong** stimulus to eat, whereas *rises* above normal have a **weak** suppressive effect — and at high levels extra leptin has little effect (**leptin resistance**). Evolution wired the system to defend against starvation, not against surfeit. Even "leptin-resistant" obese people retain *some* leptin action — otherwise they would be as hyperphagic as a congenitally leptin-deficient child.

- **Genes vs environment:** twin/adoption studies confirm a strong genetic basis for adiposity; the predisposition is exerted **mainly through the brain's control of food intake** (predisposed individuals eat more and are less readily satiated), not through a measurably lower metabolic rate (severe hypothyroidism is the main "low-REE" exception). The recent epidemic, however, reflects an **obesogenic environment** (cheap, energy-dense, ubiquitous palatable food + mechanisation + thermoneutral living) acting on susceptible genotypes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Hypothalamic leptin–melanocortin circuit (sagittal/box scheme).** Labels: *Adipose tissue* → *Leptin*; *Arcuate nucleus*; *POMC neuron (LEPR)*; *NPY/AGRP/GABA neuron (LEPR)*; *α/β-MSH*; *AGRP (antagonist)*; *MC4R neuron in Paraventricular nucleus*; *BDNF (ventromedial nucleus)*; *SIM1*; arrows to "**↓ Food intake, ↑ Energy expenditure.**" Show leptin **stimulating POMC** and **inhibiting NPY/AGRP**.
- **Diagram 2 — Energy-balance / peripheral signals scheme.** Central box "**Hypothalamus**" with **Brainstem** relay; arrows in from **Adipose (leptin)**, **Pancreas (insulin, amylin)**, **Stomach (ghrelin — orexigenic)**, **Small intestine (GLP-1, GIP, CCK)**, **Large intestine (PYY, oxyntomodulin)**, and **vagus nerve**. Adjacent pie chart of **TEE: REE 70% / Physical activity 20% / TEF 10%**.

Clinical / Diagnostic significance

- **Monogenic obesity (treatable forms):** *Congenital leptin deficiency* → severe early-onset obesity + hyperphagia, hypogonadotrophic hypogonadism — **treatable with recombinant leptin**; *leptin-receptor deficiency* is leptin-unresponsive. **MC4R mutations** are the **commonest monogenic obesity** (5–6% of severe early-onset obesity; ~1 in 300 of the population). **POMC deficiency** → obesity + ACTH deficiency (adrenal crisis, cholestatic jaundice) + **red hair/pale skin**. **PCSK1** deficiency → obesity + neonatal enteropathy + post-prandial hypoglycaemia.
- **Pharmacological exploitation of the pathway: setmelanotide** (MC4R agonist) is licensed for **leptin-receptor, POMC and PCSK1 deficiency** and trialled in hypothalamic (e.g. craniopharyngioma) obesity. The modern incretin-based anti-obesity drugs (**GLP-1 RA e.g. semaglutide; dual GIP/GLP-1 e.g. tirzepatide**; amylin analogues) act on these same satiety pathways; bariatric surgery works largely by **altering the gut-hormone milieu**, not merely by restriction/malabsorption.
- **Secondary causes to screen: hypothyroidism** (check TSH ± free T4 — ↓ REE), **Cushing's syndrome** (centripetal fat, striae, myopathy), insulinoma, and **hypothalamic damage** (craniopharyngioma, head injury) causing acquired hyperphagic obesity.
- **Bedside assessment:** BMI (WHO: overweight 25–29.9, obese ≥30 kg/m^2; lower Asian cut-offs), **waist-to-hip ratio** (>0.9 women, >1.0 men) and waist circumference as surrogates of visceral fat and metabolic risk.

High-yield exam pointers

- **TEE = REE (70%) + physical activity/NEAT (20%) + thermic effect of food (10%)**; REE is governed mainly by **thyroid hormone**.

- **EER = REE × PAL**; REE = 900 + 10m (M) / 700 + 7m (F); PAL 1.4 → 2.05. Macronutrient kcal/g: **CHO 4, protein 4, fat 9, alcohol 7**.
- **Arcuate nucleus** = first-order integrator: **POMC/CART (anorexigenic)** vs **NPY/AGRP/GABA (orexigenic)**; leptin **stimulates POMC, inhibits NPY/AGRP**.
- The effector arm is the **leptin → POMC → α-MSH → MC4R (PVN)** axis; **AGRP antagonises MC4R**; **BDNF/TrkB** and **SIM1** act downstream.
- **Ghrelin** = the only orexigenic gut hormone (rises pre-meal); **GLP-1, PYY, CCK, GIP, oxyntomodulin, amylin** = satiety/incretin signals.
- **Leptin** is a "fat-store" (adiposity) signal that defends *against starvation* more than against obesity → **leptin resistance** explains why high leptin fails to curb obesity.
- **Adaptive thermogenesis**: dieting lowers energy expenditure (~15–20%), driving weight regain — the metabolic basis of the **set-point**.
- A sustained surplus of just **~7 kcal/day** can cause obesity over years; predisposition is mediated chiefly through **appetite (food intake)**, not low metabolic rate.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pathobiology of Obesity" (physiologic regulation of energy balance; leptin–melanocortin/hypothalamic circuitry; adiposity and gut signals; leptin resistance; monogenic syndromes; setmelanotide) and "Nutrient Requirements and Dietary Assessment" (EER, REE formulae, PAL, TEE components, macronutrient fuel values).
- **Williams Textbook of Endocrinology, 15e** — "Obesity and Neuroendocrine Control of Energy Stores" (energy homeostasis; homeostatic vs hedonic intake; arcuate POMC/NPY-AGRP and MC4R; MCH/orexin/endocannabinoid systems; gut peptides incl. GDF15/GFRAL and amylin; **energy expenditure components 70/20/10**; set-point and adaptive thermogenesis; NEAT).
- *Coverage note:* The corpus covers this topic richly. CMDT was not required (spec cmdt=false). Standard physiological attributions (CCK from duodenal **I cells**; ghrelin from gastric X/A-like cells) are stated per universally-accepted textbook physiology where Harrison's prose is loosely phrased ("CCK from the stomach").

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GLP-1 in pathogenesis and management of type 2 diabetes

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

Definition / Introduction — *Glucagon-like peptide 1 (GLP-1)* is an **incretin hormone**: an intestinally derived peptide that, together with *glucose-dependent insulinotropic peptide (GIP)*, binds specific beta-cell receptors to **amplify glucose-stimulated insulin secretion and suppress inappropriate glucagon secretion**. Its action is *glucose-dependent* (operative only when blood glucose is above the fasting level), so it does not, by itself, cause hypoglycaemia. A relative deficiency of incretin action contributes to the impaired insulin secretion of type 2 DM, and harnessing the GLP-1 pathway — with **GLP-1 receptor agonists (GLP-1RAs)**, the **dual GIP/GLP-1 agonist tirzepatide**, and **DPP-4 inhibitors** — is now central to its management, with proven cardiorenal benefit.

Physiology of GLP-1 and the incretin axis

- **Source:** GLP-1 is classically released from **neuroendocrine L-cells of the gastrointestinal tract** after food ingestion; GIP is released from intestinal K-cells. Recent preclinical data suggest **intra-islet production of GLP-1 from pancreatic alpha cells** may also regulate insulin secretion.
- **Beta-cell action:** GLP-1 and GIP bind specific receptors on the beta cell and stimulate insulin secretion **through cyclic AMP production** — but *only when blood glucose is above the fasting level* (glucose-dependent insulinotropic effect).
- **Alpha-cell action:** incretin hormones also **suppress glucagon production and secretion**.
- **Incretin effect:** this enteroinsular amplification (the augmented insulin response to enterally absorbed glucose) accounts for a large share of meal-stimulated insulin output. "Incretins" thereby *amplify glucose-stimulated insulin secretion and suppress inappropriate glucagon secretion.*
- **Inactivation:** native GLP-1 and GIP are rapidly degraded by the enzyme **dipeptidyl peptidase IV (DPP-4)**, which is widely expressed on the surface of endothelial cells and some lymphocytes and degrades a wide range of peptides (i.e., it is *not incretin-specific*). This short half-life is the rationale for both DPP-4-resistant analogues and DPP-4 inhibitors.
- **Extrapancreatic actions:** the **GLP-1 receptor is expressed in several tissues, including the brain**; pharmacologically GLP-1RAs **slow gastric emptying** and promote **satiety and weight loss**.

Role of GLP-1 / incretins in the pathogenesis of type 2 DM

- Type 2 DM arises from the interaction of **insulin resistance, impaired (and progressively failing) insulin secretion, and increased hepatic glucose production**. Incretin biology intersects each of these.
- **Beta-cell secretory defect:** in early type 2 DM the secretory defect selectively involves **glucose-stimulated insulin secretion, with a greatly reduced first secretory phase**; overall beta-cell function is reduced by *as much as 50%* at onset and the defect is **progressive**. Because GLP-1/GIP normally augment glucose-stimulated insulin release, blunting of the **incretin axis** removes an important amplifier of meal-time insulin secretion.
- **Glucagon dysregulation:** a *decline in insulin secretion and/or increased glucagon secretion* drives hyperglycaemia. Loss of the incretin-mediated **suppression of glucagon** contributes to inappropriate post-prandial and fasting glucagon excess.

- **Hepatic glucose overproduction:** failure of hyperinsulinaemia to suppress gluconeogenesis produces fasting hyperglycaemia; glucagon excess aggravates this — both are partly counter-regulated by intact incretin signalling.
- **Islet milieu:** chronic hyperglycaemia ("glucose toxicity"), free-fatty-acid "lipotoxicity", islet inflammation and **islet amyloid (amylin) deposition** further impair beta-cell function, compounding the deficient incretin response.
- *Coverage note:* Harrison establishes that incretins amplify glucose-stimulated insulin secretion and suppress glucagon, and that type 2 DM has a progressive secretory defect; that the **incretin effect is quantitatively diminished in established type 2 DM** is universally accepted physiology but is not separately quantified in these chapters (see Source).

GLP-1-based therapeutic agents (classification & key data)

GLP-1RAs are modified to **resist enzymatic inactivation by DPP-4**, giving sustained receptor activation. They are approved for type 2 DM **and obesity**; *higher doses of liraglutide and semaglutide than those used for glucose lowering are effective for weight loss in obesity.*

Class	Examples (per Harrison)	HbA1c reduction	Salient features
GLP-1 receptor agonists	Dulaglutide, exenatide (sustained-release), liraglutide, lixisenatide, semaglutide (**oral formulation available**)	**0.5–1.0%**	↑ glucose-stimulated insulin, ↓ glucagon, slow gastric emptying, satiety; weight loss; ↓ **CV events**, modest renoprotection; *no hypoglycaemia unless combined with a secretagogue/insulin*
Dual GIP + GLP-1 receptor agonist	**Tirzepatide**	**1.8–2.4%**	Once-weekly SC; dual agonism at **GIPR and GLP-1R**; *greater weight loss than a GLP-1RA alone*
DPP-4 inhibitors (enhance endogenous incretins)	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	**0.5–0.8%**	Inhibit degradation of native GLP-1/GIP → **enhance the incretin effect**; oral; *no hypoglycaemia or weight gain*; preferential post-prandial effect; reduce dose in renal impairment

- **Long-acting GLP-1RAs** (per Harrison: sustained-release exenatide, dulaglutide, lixisenatide, semaglutide) are **administered weekly** and are the most commonly used; **daily oral semaglutide** uses a formulation enabling gastric absorption that avoids proteolytic degradation in the small intestine.
- **GLP-1 action achieved is greater with GLP-1RAs than with DPP-4 inhibitors** — explaining the superior glucose lowering, weight loss and cardiovascular outcomes of the injectable/oral agonists.
- It is **not known** whether GLP-1RAs enhance beta-cell survival or proliferation, and it is unclear whether they alter the natural history of type 2 DM.

Place in management of type 2 DM

- **Glucose-dependent, low-hypoglycaemia control:** GLP-1RAs lower fasting and post-prandial glucose without intrinsic hypoglycaemia risk, an advantage over sulfonylureas/insulin.
- **Cardiorenal indication:** because GLP-1RAs (and SGLT-2 inhibitors) **reduce cardiovascular events and slow progression of renal disease**, a **GLP-1RA or an SGLT-2 inhibitor should be used in most individuals with type 2 DM**, with choice dictated by whether **ASCVD, heart failure or CKD** is present or whether **weight loss is a major goal**. Liraglutide, semaglutide and dulaglutide each reduced CVD events in trials; dulaglutide also reduced composite microvascular (retinopathy/nephropathy) outcomes; semaglutide was associated with an *increased rate of retinopathy-related complications*.
- **Combination therapy:** useful regimens include **metformin + GLP-1RA** and **long-acting insulin + GLP-1RA**; fixed-dose long-acting-insulin/GLP-1RA combinations (**degludec + liraglutide**, **glargine + lixisenatide**) are effective and cause *less weight gain*. Adding a GLP-1RA to insulin **limits weight gain and reduces the insulin dose needed**. (The NIH-funded **GRADE** comparative-effectiveness study evaluated add-on agents to metformin, including **liraglutide** and basal insulin.)
- **Obesity / prediabetes:** GLP-1RAs and tirzepatide are weight-lowering and, given their greater weight loss, are transforming pharmacologic prevention of type 2 DM in prediabetes; intensive lifestyle measures remain foundational.
- **Practical use:** start at a **low dose and up-titrate** to minimise initial side effects (nausea being limiting); GLP-1RAs may **alter absorption of other oral drugs** because they slow gastric emptying.

Adverse effects, cautions and contraindications

- **Common:** nausea, vomiting and GI intolerance (dose-limiting; mitigated by slow titration).
- **Pancreatitis:** evidence of a **possibly increased risk of acute pancreatitis** with GLP-1RAs (less so DPP-4 inhibitors); avoid in pancreatic disease or risk factors — **heavy alcohol use, severely elevated triglycerides, hypercalcaemia**.
- **Thyroid:** FDA **black-box warning** for increased **thyroid C-cell tumours in rodents**; *contraindicated in medullary carcinoma of the thyroid or multiple endocrine neoplasia (MEN)*.
- **Other cautions:** renal disease; co-administration with agents that also slow GI motility; previous ileus; possible worsening of retinopathy. DPP-4 inhibitors: allergy/rash, hypersensitivity (anaphylaxis, angioedema, **Stevens-Johnson syndrome**), severe joint pain — reduce dose in renal insufficiency.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — The incretin axis and drug targets (flow diagram).** Labels: *Ingested nutrients* → *Intestinal L-cell* → *GLP-1* and *K-cell* → *GIP* → arrow to **Pancreatic beta cell (↑ glucose-dependent insulin, via cAMP)**; arrow to **Pancreatic alpha cell (↓ glucagon)**; arrow to **Stomach (delayed gastric emptying)**; arrow to **Brain/hypothalamus (↑ satiety, ↓ appetite)** → net ↓ **post-prandial glucose + weight loss**. Mark **DPP-4 (rapid inactivation of GLP-1/GIP)**, and the two drug actions: **GLP-1RA (DPP-4-resistant agonist)** and **DPP-4 inhibitor (blocks inactivation)**.
- **Diagram 2 — Pathogenic triad of type 2 DM.** Central box *Hyperglycaemia* fed by three labelled arrows: **(1) Insulin resistance (muscle, liver, adipose)**, **(2) Progressive beta-cell secretory defect — loss of first-phase insulin**, **(3) Increased hepatic glucose production / glucagon excess**, with a fourth contributing arrow **Reduced incretin (GLP-1/GIP) action**.

Clinical / Diagnostic significance

- **Outcome-driven prescribing:** GLP-1RAs are a preferred add-on (or partner to SGLT-2 inhibitors) when **established ASCVD, high CV risk, CKD, or obesity** coexist with type 2 DM.
- **Weight and metabolic dysfunction:** in type 2 DM with metabolic-dysfunction-associated steatotic liver disease/steatohepatitis, a **GLP-1RA or GIP/GLP-1 RA (± pioglitazone)** should be considered.
- **Safety screening:** take a personal/family history of **medullary thyroid carcinoma/MEN** and pancreatitis risk before initiation; counsel on GI side effects and slow titration; review timing of orally absorbed drugs given delayed gastric emptying.
- **Hypoglycaemia logic:** glucose-dependence means hypoglycaemia occurs essentially only when **combined with a sulfonylurea or insulin** — pre-emptively reduce those agents.

High-yield exam pointers

- GLP-1 = **incretin from intestinal L-cells**; acts via **cAMP**, is **glucose-dependent**, and **suppresses glucagon** — hence low intrinsic hypoglycaemia risk.
- **DPP-4** rapidly inactivates GLP-1/GIP → GLP-1RAs are *engineered to resist DPP-4*; DPP-4 inhibitors *block* this degradation.
- Four cardinal GLP-1RA actions: ↑ **insulin,** ↓ **glucagon,** ↓ **gastric emptying,** ↑ **satiety/weight loss**.
- HbA1c lowering: **GLP-1RA 0.5–1.0%, DPP-4i 0.5–0.8%, tirzepatide 1.8–2.4%**.
- **Tirzepatide** = once-weekly **dual GIP/GLP-1 agonist** → greater weight loss than a GLP-1RA alone.
- Weekly long-acting GLP-1RAs + **oral semaglutide**; GLP-1 action is **greater with GLP-1RAs than DPP-4 inhibitors**.
- **Cardiorenal benefit** (liraglutide, semaglutide, dulaglutide) → a **GLP-1RA or SGLT-2 inhibitor in most type 2 DM**.
- Key safety flags: **acute pancreatitis caution**, **medullary thyroid carcinoma/MEN contraindication (rodent C-cell tumours, black-box)**, nausea/vomiting, semaglutide–retinopathy signal.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 416 "Diabetes Mellitus: Management and Therapies"** (GLP-1RAs, tirzepatide, DPP-4 inhibitors, Table 416-6, combination/cardiorenal strategy) and **Ch 415 "Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology"** (incretin physiology — GLP-1/GIP, cAMP, glucose-dependence, glucagon suppression, L-cell/alpha-cell source; type 2 DM secretory defect). *Coverage note:* the chapters describe incretin amplification of insulin secretion and the progressive beta-cell defect of type 2 DM but do not separately quantify the magnitude of the *incretin effect* or explicitly state that it is *reduced* in type 2 DM — that statement and the broad "ominous octet" framing are standard textbook physiology included here for completeness, not verbatim from these two chapters.

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Sick euthyroid syndrome

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

Definition / Introduction — *Sick euthyroid syndrome (SES)*, also termed *nonthyroidal illness syndrome (NTIS)* or *euthyroid sick syndrome*, refers to the constellation of abnormal circulating thyroid-function tests that arise in acutely or severely ill patients **in the absence of intrinsic hypothalamic–pituitary–thyroid (HPT) axis disease**. The hallmark is a fall in serum triiodothyronine (T3) with a reciprocal rise in reverse T3 (rT3), and in the most severely ill, a fall in thyroxine (T4) and thyrotropin (TSH). It is largely an **adaptive** response to systemic illness, fasting and inflammation rather than a true thyroid disorder, and it normalises with recovery. Its great clinical importance lies in the diagnostic confusion it creates and in the temptation to inappropriately treat it.

Pathophysiology

- **Triggers:** any acute, severe systemic illness — sepsis, trauma, burns, myocardial infarction, surgery, starvation/caloric deprivation, bone-marrow transplantation, critical illness in the ICU. The principal mediators are **pro-inflammatory cytokines, especially interleukin-6 (IL-6)** (also IL-12 and IL-18, implicated in the TSH changes).
- **Altered peripheral deiodination (the central mechanism):**
  - **Type 1 deiodinase (D1)** activity is *reduced* → impaired outer-ring (5′) deiodination of T4 to active **T3**.
  - **Type 3 deiodinase (D3)** activity is *increased* (activated in muscle and liver, especially with hypoperfusion) → increased inner-ring (5) conversion of T4 to the inactive **reverse T3 (rT3)**; D3 is the most important source of rT3 in SES.
  - Net effect: **low T3, raised rT3, and a fall in the T3:rT3 ratio.**
- **Reverse-T3 kinetics:** rT3 is normally cleared by D1 (5′-deiodination). Because D1 is impaired, *decreased clearance* of rT3 — rather than increased production — is the major basis for the elevated rT3. T4 is also alternately metabolised to the inactive **T3 sulfate**.

- **Adaptive teleology:** the same low-T3 pattern can be induced in normal individuals by **fasting**; the fall in T3 is thought to limit catabolism and conserve energy/protein in the starved or ill patient.
- **Central (hypothalamic–pituitary) suppression — prolonged illness:** with sustained critical illness, **hypothalamic TRH gene expression falls**, pulsatile TSH secretion is lost, and TSH and T4 decline. Endogenous dopamine and hypercortisolaemia contribute; an altered feedback set-point via local type 2 deiodinase may also be involved.
- **Iatrogenic contributors** that further suppress the axis: dopamine, high-dose glucocorticoids, somatostatin, amiodarone, and iodine-containing contrast/wound dressings.

Biphasic model (acute vs prolonged critical illness)

Feature	Acute phase (hours–days)	Prolonged phase (weeks)
Dominant mechanism	Altered **peripheral** metabolism (↓D1, ↑D3)	Added **central** suppression (↓TRH, ↓pulsatile TSH)
T3	↓	↓↓ (further fall)
rT3	↑	Normalising / high-normal
T4	Brief rise → normal	↓
TSH	Brief rise → normal	Low / inappropriately normal
Interpretation	**Adaptive** (energy conservation)	Possibly **maladaptive** in part

Spectrum of biochemical patterns

- **Low T3 syndrome (most common):** ↓ total and unbound **T3**, with **normal T4 and TSH**; rT3 increased. Reflects impaired peripheral T4→T3 conversion.
- **Low T4 syndrome (very sick patients):** dramatic fall in both **total T4 and T3** — carries a **poor prognosis** (mortality rises as T4 falls). Driven by accelerated metabolism (muscle/liver D3 with hypoperfusion) and reduced TBG binding. Note: routine **free-T4 immunoassays are subject to artefact** when binding proteins are low and tend to *underestimate* the true free T4.
- **TSH fluctuations:** subnormal TSH (0.01–0.1 mIU/L) is seen in ~10% (especially with dopamine or glucocorticoids); raised TSH (>20 mIU/L) is seen in ~5%, characteristically during the **recovery phase**. A truly *undetectable* TSH (<0.01 mIU/L) makes **intrinsic thyroid disease (thyrotoxicosis)** more likely and warrants endocrine evaluation.
- **Recovery phase:** a rise in TSH (sometimes transiently >20 mIU/L) **precedes** normalisation of T3 and can mimic primary hypothyroidism if tested in isolation.

Disease-specific patterns (distinctive variants)

- **Acute liver disease:** initial rise in *total* (not unbound) T3 and T4 from TBG release; levels become subnormal as liver failure progresses.
- **Acute psychiatric illness:** transient rise in total and unbound **T4** (usually with normal T3) in 5–30%; TSH may be low, normal or high.

- **HIV/AIDS:** T3 and T4 *rise* in early HIV (even with weight loss); T3 falls with progression to AIDS, but TSH usually stays normal.
- **Renal disease:** low T3 but with **normal rather than increased rT3** (an unusual feature) due to increased hepatic uptake of rT3.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — HPT axis in SES (acute vs prolonged):** Draw a vertical axis. Boxes top-to-bottom: *Hypothalamus (TRH)* → *Anterior pituitary (TSH)* → *Thyroid (mainly T4)* → *Peripheral tissues*. In peripheral tissues show two arrows from T4: one via **D1/D2 (5′-deiodination)** → **T3 (active)** and one via **D3 (5-deiodination)** → **rT3 (inactive)**. Label: *Acute phase* — D1↓, D3↑, **T3↓, rT3↑, T3:rT3↓**, TSH and T4 normal/brief rise. *Prolonged phase* — **TRH↓** → **TSH↓** → **T4↓, T3↓↓**. Mark trigger arrow: *Cytokines (IL-6), fasting, hypoperfusion*.
- **Diagram 2 — Deiodinase pathway:** Central T4 molecule; arrow labelled **D1/D2 (outer-ring 5′)** to **T3**; arrow labelled **D3 (inner-ring 5)** to **rT3**; both T3 and rT3 converging by further deiodination to **T2 (diiodothyronine)**. Annotate D1↓ and D3↑ in SES.

Clinical / Diagnostic significance

- **Avoid routine thyroid testing in acutely ill patients** unless a thyroid disorder is strongly suspected — abnormal values are common, transient and misleading.
- **Distinguishing SES from true central hypothyroidism** is the key diagnostic challenge (both show low T4/T3 with non-elevated TSH):
  - **rT3 is high (or normal) in SES** but **low in true hypothyroidism** — the most useful discriminator.
  - Supportive: absence of thyroid history/antibodies, the clinical context and time-course of the acute illness, and review of drugs (dopamine, glucocorticoids, amiodarone, phenytoin) affecting hormone levels or binding.
  - A low/normal TSH does **not** exclude pre-existing primary hypothyroidism in the critically ill; conversely, an **elevated T3 is highly unusual** in critical illness and should raise suspicion of thyrotoxicosis/thyroid storm.
- **Confirmation is often presumptive** — only resolution of the abnormal tests with clinical recovery clearly establishes the diagnosis; **repeat thyroid function after recovery**.
- **Management — treat the underlying illness, not the labs:**
  - **Thyroid hormone replacement (T4 and/or T3) is generally NOT recommended.** Interventional trials of hormone supplementation in the acute phase have shown **no outcome benefit**; experimentally, lowering T4 appears deleterious while a low T3:rT3 ratio seems beneficial/adaptive. CMDT explicitly states levothyroxine is **not indicated** for euthyroid sick syndrome.
  - Monitor thyroid function through recovery; give thyroid hormone only where there is genuine historic/clinical evidence of hypothyroidism.

- In patients with **pre-existing hypothyroidism**, continue usual levothyroxine; if switching to IV, reduce the dose by ~25% (oral bioavailability ~75%).

- **Prognostic marker:** the magnitude of T3/T4 fall (the **low T4 syndrome**) correlates with illness severity and mortality; a persistently low T3:rT3 ratio after recovery has been linked to poorer functional recovery (weaker handgrip, shorter 6-minute walk).

High-yield exam pointers

- Most common pattern = **low T3 syndrome** (↓T3, normal T4/TSH, ↑rT3).
- Mechanism = ↓ **type 1 deiodinase** + ↑ **type 3 deiodinase**, driven by **IL-6**; rT3 rises mainly from **reduced clearance**, not overproduction.
- **rT3 = high in SES, low in true hypothyroidism** — the single best differentiator.
- **Low T4 syndrome = poor prognosis** (marker of severity / mortality).
- **TSH >20 mIU/L during recovery** can mimic primary hypothyroidism; **TSH <0.01 mIU/L** suggests true thyrotoxicosis.
- The low-T3 state is **adaptive** — also reproduced by **fasting**.
- **Do NOT give thyroid hormone**; treat the underlying illness and recheck TFTs after recovery (no proven benefit of replacement; CMDT — levothyroxine not indicated).
- Aggravating drugs: **dopamine, glucocorticoids, somatostatin, amiodarone, iodinated contrast**.
- Renal failure variant = low T3 with **normal rT3**; acute liver disease = early rise then fall in total T3/T4.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hyperthyroidism and Other Causes of Thyrotoxicosis" (Sick Euthyroid Syndrome / Nonthyroidal Illness section) and "Thyroid Gland Physiology and Testing" (deiodinases, rT3, laboratory interpretation).
- **Williams Textbook of Endocrinology, 15e** — "Endocrine Disorders of Critical Illness" (acute vs prolonged thyroid-axis alterations, TRH suppression, treatment evidence and recovery).
- **CMDT 2026** — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (euthyroid sick syndrome — diagnosis and that levothyroxine is not indicated).

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Thyroid function tests

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

Definition / Introduction — Thyroid function tests (TFTs) are the biochemical, immunological and radioisotopic investigations used to assess the **hypothalamic–pituitary–thyroid (HPT) axis**, to confirm and grade thyroid dysfunction, and to establish its aetiology. Because thyroid hormone secretion is governed by a classic **negative-feedback loop**, serum **TSH** is the single most useful physiologic marker of thyroid hormone action and the first-line screening test; it is interpreted alongside free hormone levels, autoantibodies, thyroglobulin and radioiodine studies. Rational testing follows a **"TSH-first" strategy**, since with rare exceptions a normal TSH excludes a primary thyroid abnormality.

Physiologic basis & the testing strategy

- The thyroid secretes **T4** and **T3**; T4 is secreted in ~**15-fold excess** over T3 and acts as a prohormone, being converted peripherally to the more potent T3 by **deiodinases** (Type I — liver/kidney/thyroid; Type II — pituitary/brain/brown fat; Type III — inactivates T4/T3 and is the chief source of **reverse T3**).
- **TRH** from the hypothalamus stimulates pituitary **TSH**; T4/T3 feed back (mainly via *TRβ2*) to suppress TRH and TSH. Reduced hormone raises TSH; high hormone rapidly suppresses TSH.
- TSH has a long plasma **half-life (~50 min)** and only modest pulsatility/diurnal variation (peak at night), so a **single random measurement** is adequate.
- Because TSH changes dynamically and *logarithmically* in response to small T4/T3 shifts, the logical approach is to **first determine whether TSH is suppressed, normal or elevated**, then confirm with circulating (preferably free) hormone levels.

Serum TSH — the primary screening test

- Measured by highly sensitive, specific **immunometric (immunoradiometric) assays** that easily separate normal from suppressed values. Modern "third-generation" assays detect TSH down to **≤0.004 mIU/L**; assays sensitive to **≤0.01 mIU/L** suffice for practice.
- **Low TSH** → primary hyperthyroidism/thyrotoxicosis; **High TSH** → primary hypothyroidism. A suppressed TSH **<0.01 mIU/L** usually indicates thyrotoxicosis.
- The sensitive TSH assay has rendered the **TRH stimulation test obsolete** — failure of TSH to rise after an IV bolus of **200–400 µg TRH** carries the same meaning as a suppressed basal TSH.
- **Caveat — central (secondary) disease:** in hypothalamic–pituitary disease, TSH is *inappropriately* low-to-high-normal for a low T4; TSH must therefore **not** be used as an isolated test when pituitary/hypothalamic disease is suspected. Rare causes of an *inappropriately normal/high TSH with high hormones* are **TSH-secreting pituitary adenoma**, **resistance to thyroid hormone (RTH)** and **assay artefact**.

Pattern	TSH	Free T4	Free T3	Interpretation
Primary hyperthyroidism	Low (<0.01)	High	High/normal	Graves', toxic nodule/MNG
T3 toxicosis	Low	Normal	High	2–5% of thyrotoxicosis

Pattern	TSH	Free T4	Free T3	Interpretation
Subclinical hyperthyroidism	Low	Normal	Normal	Risk of AF, bone loss
Primary hypothyroidism	High	Low	Low/normal	Hashimoto's, post-ablation
Subclinical hypothyroidism	High	Normal	Normal	Antibody-positive at risk
Central hypothyroidism	Low/normal (inappropriate)	Low	Low	Pituitary/hypothalamic
Inappropriate TSH secretion	Normal/High	High	High	TSH-oma or RTH

Measurement of thyroid hormones — total vs free

- Automated immunoassays measure serum **total T4 and total T3**, but ~**99.98% of T4 and 99.7% of T3 are protein-bound**, so total levels track binding-protein changes. The biologically active fraction is the **free (unbound) hormone**, which is preferred.
- **Direct free-hormone methods:** (1) competition of unbound hormone with radiolabelled T4/analogue for a solid-phase antibody, and (2) physical separation by **equilibrium dialysis** or **ultracentrifugation** (reference standard, but technically demanding/expensive).
- **Indirect method (now less used):** the **Free T4/T3 index** = total hormone × **thyroid hormone binding ratio (THBR)**, where THBR is derived from the **T3-resin uptake** test (resin uptake rises when binding sites are reduced, e.g. TBG deficiency, and falls in the opposite situation). The index "corrects" anomalous total values caused by binding variation.
- **Free T4** usually suffices to confirm thyrotoxicosis, but because **2–5% have isolated T3 toxicosis**, measure **free T3** when TSH is suppressed but free T4 is normal.

Binding proteins, drugs & analytic interferences

- Carrier proteins: **TBG** (low concentration 1–2 mg/dL but high affinity, carries ~80% of bound hormone), **albumin** (~3.5 g/dL, binds up to 10% of T4, 30% of T3) and **transthyretin/TTR** (formerly TBPA, ~10% of T4).
- These confound *total* (not free) hormone, so free-hormone assays are preferable when binding is altered.

Factor	Effect on binding	Total T4/T3	Free T4/T3	Thyroid status
Estrogen (pregnancy, OCP, HRT, tamoxifen/SERM), inflammatory liver disease	↑ TBG	↑	Normal	Euthyroid
Androgens, nephrotic syndrome	↓ TBG	↓	Normal	Euthyroid
X-linked **TBG deficiency**	↓↓ TBG	Very low	Normal	Euthyroid (do not treat)

Factor	Effect on binding	Total T4/T3	Free T4/T3	Thyroid status
FDH (albumin R218H), familial TTR excess	↑ affinity	↑	Normal	Euthyroid (normal TSH)

- **Drugs** displacing hormone or perturbing binding/conversion: salicylates, salsalate, NSAIDs, phenytoin, carbamazepine; **propranolol, amiodarone, ipodate, glucocorticoids, PTU** also impair T4→T3 conversion.
- **Biotin interference (high-yield):** biotin supplements/multivitamins containing **≥1000 µg** taken <18 h before sampling interfere with biotinylated antibodies and streptavidin capture, giving **falsely low TSH and falsely high T4/T3** (mimicking Graves'). Advise stopping biotin **≥2 days** before testing.

Tests to determine the aetiology — antibodies & thyroglobulin

- **Anti-TPO antibodies** are the key marker of autoimmune thyroid disease: present in *almost all* autoimmune (Hashimoto's) hypothyroidism and up to **80% of Graves' disease**, usually at high titre. Since anti-Tg antibodies alone are less common, measuring **TPO antibodies alone is reasonable**. About **5–15% of euthyroid women and up to 2% of euthyroid men** are antibody-positive and are at increased risk of future dysfunction.
- **TSH-receptor antibodies (TRAb / TSI):** stimulating antibodies of **Graves' disease**, usually measured by tracer-displacement **TRAb** assays. Uses: confirm Graves' aetiology, predict **remission** after antithyroid-drug withdrawal (higher if TRAb disappears), and predict **fetal/neonatal thyrotoxicosis** when maternal TRAb/TSI is **>3× the upper limit of normal** in the last trimester.
- **Serum thyroglobulin (Tg):** raised in all thyrotoxicoses *except* **thyrotoxicosis factitia** (helps distinguish factitious from endogenous disease) and markedly raised in **thyroiditis**. Its principal role is **follow-up of differentiated thyroid cancer** — after total thyroidectomy + radioablation, Tg should be **<0.2 ng/mL** (in absence of anti-Tg antibodies); measurable Tg signals residual/recurrent disease. Always interpret with **anti-Tg antibodies**, which interfere with the assay.

Radioiodine uptake & thyroid scintigraphy

- The gland selectively traps/organifies iodine isotopes (^{123}**I,** ^{125}**I,** ^{131}**I**) and traps ^{99m}**Tc-pertechnetate** (imaged but not organified; fractional **uptake quantitation only for iodine isotopes**).
- **24-h RAIU** is **10–25%** in iodine-replete normals, rising to **70–90% in Graves'**.

Disorder	RAIU	Scan appearance
Graves' disease	High (70–90%)	Diffuse, homogeneous ↑ uptake, enlarged
Toxic adenoma	Focal high	"Hot" nodule; rest of gland suppressed
Toxic multinodular goiter	Patchy	Multiple hot + suppressed/cold areas
Subacute/viral/postpartum thyroiditis	**Very low**	Patchy/absent (follicular damage)

Disorder	RAIU	Scan appearance
Thyrotoxicosis factitia	**Very low**	Exogenous hormone suppresses TSH
Iodine contamination (contrast)	Reduced	Low uptake despite ↑ hormone

- Scintigraphy is **not routine** for thyroid nodules but is indicated when **TSH is subnormal** to identify autonomously functioning ("hot") nodules — these are almost never malignant, so **FNA is not required**.

Thyroid testing in special situations

- **Pregnancy:** use **trimester-specific reference ranges**. hCG weakly stimulates the TSH-R → first-trimester TSH falls; estrogen raises TBG so **total T4/T3 are ~1.5× higher** throughout pregnancy, while free T4 falls toward/below the non-pregnant range by the third trimester.
- **Non-thyroidal illness (sick-euthyroid syndrome):** any severe illness can derange TSH and lower T3 (↑Type III deiodinase, ↑reverse T3); avoid testing in acute illness unless thyroid disease is strongly suspected.
- **End-organ tests** (basal metabolic rate, ankle-reflex relaxation time, serum cholesterol) are insensitive and not used clinically.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
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> - **HPT feedback axis:** boxes for *Hypothalamus (TRH)* → *Anterior pituitary (TSH)* → *Thyroid (T4, T3)* → *Peripheral tissues*; draw **negative-feedback arrows** from T4/T3 back to pituitary and hypothalamus. Label *TSH-R*, *negative feedback*, and the deiodinase step *T4 → T3*.
> - **TSH-first testing algorithm:** top box *Measure serum TSH* branching to **Low TSH → free T4 (±free T3) → thyrotoxicosis / T3 toxicosis**, **Normal TSH → euthyroid**, **High TSH → free T4 → primary hypothyroidism**; side-branch *discordant pattern → suspect central disease / RTH / assay (biotin) artefact*. Label *anti-TPO*, *TRAb*, *RAIU/scan*.

Clinical / Diagnostic significance

- **TSH** is the screening and monitoring test for primary thyroid disease and for titrating levothyroxine and antithyroid therapy.
- **Free T4 + TSH** together classify overt vs **subclinical** dysfunction and identify central disease (discordant TSH–T4).
- **Anti-TPO** confirms autoimmune aetiology and stratifies risk of progression; **TRAb** confirms Graves', predicts relapse and neonatal thyrotoxicosis.
- **RAIU/scan** differentiates high-uptake thyrotoxicosis (Graves', toxic nodule/MNG) from low-uptake states (thyroiditis, factitia, iodine load) — directing therapy.
- **Thyroglobulin** is the tumour marker for differentiated thyroid cancer surveillance.
- Recognising **binding-protein and biotin artefacts** prevents misdiagnosis and inappropriate treatment.

High-yield exam pointers

- **Test TSH first** — a normal TSH (with rare exceptions) excludes primary thyroid disease.

- Sensitive TSH assay detects **≤0.004 mIU/L**; it made the **TRH stimulation test obsolete**.
- Always measure **free** hormones; total T4/T3 are misleading because **~99.98% T4 / 99.7% T3 are protein-bound** (TBG carries ~80%).
- **T3 toxicosis (2–5%)** — measure **free T3** when TSH is low but free T4 normal.
- **Biotin ≥1000 µg** → falsely **low TSH, high T4/T3**; stop biotin **2 days** before testing.
- **Anti-TPO** in ~all autoimmune hypothyroidism and up to **80% of Graves'**; **TRAb** = Graves' marker and predicts **neonatal thyrotoxicosis (>3× ULN)**.
- Post-thyroidectomy/ablation **Tg <0.2 ng/mL**; rising Tg = recurrence (interpret with anti-Tg antibodies).
- **24-h RAIU**: normal 10–25%, Graves' 70–90%; **low uptake** = thyroiditis / factitia / iodine load.
- Central hypothyroidism = **low free T4 with inappropriately non-elevated TSH** — never rely on TSH alone in pituitary disease.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 394 "Thyroid Gland Physiology and Testing"** (Jameson, Weetman, Mandel), with cross-references to Ch 395 (hypothyroidism), Ch 396 (thyrotoxicosis) and Ch 397 (nodules) as cited in the chapter. Coverage note: the TSH/free-T4/free-T3 interpretation grid and the deiodinase/sick-euthyroid summary are standard textbook syntheses consistent with the chapter; quantitative limits (RAIU 10–25%/70–90%, Tg <0.2 ng/mL, biotin ≥1000 µg, TRAb >3× ULN, TRH 200–400 µg) are verbatim from Ch 394.

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Thyroid hormone physiology

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

Definition / Introduction — The thyroid gland produces two related iodothyronine hormones, **thyroxine (T4)** and **triiodothyronine (T3)**, derived by iodination and coupling of tyrosyl residues on the precursor protein **thyroglobulin (Tg)**. Acting via nuclear **thyroid hormone receptors (TR) α and β**, they are critical for cell differentiation and organogenesis during development and for maintaining **thermogenic and metabolic homeostasis** in the adult. T4 is essentially a *prohormone* that is converted in peripheral tissues to the more potent **T3**, the principal active hormone. Output is governed by a classic negative-feedback endocrine loop — the **hypothalamic–pituitary–thyroid (HPT) axis**.

Functional anatomy and the synthetic unit

- The gland (*Greek thyreos*, shield + *eidos*, form) has two lobes joined by an isthmus, lies anterior to the trachea between the cricoid cartilage and suprasternal notch, weighs **12–20 g**, and is highly vascular.
- It develops from the floor of the primitive pharynx in the **3rd week of gestation** and descends along the **thyroglossal duct** — explaining ectopic *lingual thyroid* and thyroglossal duct cysts. Hormone synthesis begins at ~**11 weeks**.

- Development is orchestrated by transcription factors **TTF1, TTF2, NKX2-1, FOXE1 and PAX8**, which induce thyroid-specific proteins: **Tg, thyroid peroxidase (TPO), the sodium–iodide symporter (NIS) and the TSH receptor (TSH-R)**.
- The functional unit is the **follicle** — follicular cells surrounding colloid (rich in Tg). Cells are *polarized*: the **basolateral** membrane faces blood (bears NIS, TSH-R), the **apical** membrane faces the lumen (bears TPO, pendrin).
- Neural-crest–derived **parafollicular C cells** (from the ultimobranchial body) secrete **calcitonin** (minimal role in human calcium homeostasis) and are the origin of medullary thyroid cancer.

Hypothalamic–Pituitary–Thyroid (HPT) axis and its regulation

- Hypothalamic **TRH** is the major positive regulator of **TSH** synthesis/secretion by anterior-pituitary thyrotropes; TSH then stimulates all steps of thyroid hormone production. Peak TSH occurs ~**15 min** after TRH.
- **TSH** is a 31-kDa glycoprotein with **α and β subunits**; the α subunit is shared with LH, FSH and hCG, whereas the **β subunit is unique** to TSH and confers specificity.
- T4 and T3 exert **negative feedback** predominantly through the **TRβ2** isoform in the hypothalamus and pituitary, inhibiting both TRH and TSH. High hormone levels rapidly suppress TSH gene expression; low levels increase basal TSH and enhance TRH responsiveness — establishing the axis **"set point."**
- **Dopamine, glucocorticoids and somatostatin** suppress TSH (significant only at pharmacologic doses).
- TSH is secreted in a **pulsatile** fashion with a **diurnal rhythm** (highest at night) but has a long plasma **half-life (~50 min)**, so a *single TSH measurement* reliably reflects circulating levels.
- TSH acts via the **TSH-R**, a seven-transmembrane **G-protein-coupled receptor** linked to **Gsα → adenylyl cyclase → cyclic AMP**; it also activates **phospholipase C** (phosphatidylinositol turnover).

Biosynthesis of thyroid hormones (sequential steps)

- **Iodide trapping** — NIS on the basolateral membrane actively concentrates iodide; in the iodine-replete state the gland takes up **10–25%** of a tracer dose over 24 h, rising to **70–90% in Graves' disease**. NIS is up-regulated by low iodine/TSH and suppressed by high iodine. (Pendrin on the apical membrane effluxes iodide into the lumen; its mutation causes **Pendred syndrome** — defective organification, goiter, sensorineural deafness.)
- **Organification** — at the apical surface, TPO with **H2O2** (generated by **DUOX/DUOXA**) oxidises iodide and adds it to tyrosyl residues of Tg, forming **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)**.
- **Coupling** — TPO catalyses ether-linkage coupling of iodotyrosines: **DIT + DIT → T4**; **MIT + DIT → T3**, stored within Tg in colloid.
- **Storage and release** — TSH triggers reuptake (endocytosis) of Tg into the follicular cell, lysosomal proteolysis, and secretion of **T4 and T3**. Uncoupled MIT/DIT are deiodinated by **iodotyrosine deiodinase**, recycling iodide.

- **Autoregulation** — excess iodide transiently inhibits its own organification, the **Wolff–Chaikoff effect**; a normal gland "escapes" this within days.
- *Iodine requirement:* RDA **220 µg/day** (pregnancy) and **290 µg/day** (lactation); the ATA advises prenatal supplements containing **150 µg/day**; urinary iodine **>100 µg/L** indicates sufficiency.

Transport, binding proteins and peripheral metabolism

- T4 is secreted in ~**15-fold excess** over T3. Both circulate almost entirely **protein-bound** — **~99.98% of T4** and **~99.7% of T3** — to **thyroxine-binding globulin (TBG), transthyretin (TTR / thyroxine-binding prealbumin) and albumin**. Only the small **unbound (free) fraction** is biologically active; homeostasis defends free-hormone levels.

Binding protein	Plasma level / affinity	Share of bound hormone
TBG	Low conc. (1–2 mg/dL), high affinity (T4 > T3)	carries ~**80%**
Albumin	High conc. (~3.5 g/dL), low affinity	binds up to 10% T4, 30% T3
Transthyretin (TTR)	Intermediate	~**10% of T4**, little T3

Property (Table 394-1)	T4	T3
Total serum concentration	8 µg/dL	0.14 µg/dL
Fraction unbound (free)	0.02%	0.3%
Production rate (incl. peripheral conversion)	90 µg/d	32 µg/d
Fraction arising directly from thyroid	100%	~20% (rest = peripheral conversion)
Serum half-life	~7 days	~1 day
Relative metabolic potency	0.3	1

- **Deiodinases** convert/inactivate hormone in the periphery and determine local T3 availability:

Enzyme	Reaction / site	Physiologic role
Type I (D1)	5'-deiodination; thyroid, **liver, kidney**; low T4 affinity	major source of circulating T3
Type II (D2)	5'-deiodination; **pituitary, brain, brown fat, thyroid**; high T4 affinity	local intracellular T3; induced in hypothyroidism; important during **levothyroxine (T4) replacement**
Type III (D3)	5-(inner-ring) deiodination; **placenta**, muscle/liver in illness	**inactivates** T4 & T3; chief source of **reverse T3 (rT3)**; up in **sick-euthyroid syndrome**; large hemangiomas → consumptive hypothyroidism

- **Drugs/states impairing T4 → T3 conversion** (raising rT3): **propylthiouracil, propranolol, amiodarone, glucocorticoids**, iodinated contrast (ipodate, iopanoic acid), fasting, acute illness/trauma — the basis of the **sick-euthyroid (low-T3) syndrome**.

Mechanism of action

- Thyroid hormones enter cells by passive diffusion and via specific transporters — **MCT8, MCT10 and OATP1C1**; *MCT8* mutations cause X-linked psychomotor retardation (low T4, high T3, high TSH).
- They act mainly through **nuclear receptors TRα and TRβ** (tissue distribution: **TRα** — brain, kidney, gonads, **muscle, heart**; **TRβ** — pituitary, liver; **TRβ2** — hypothalamus/pituitary feedback).
- **T3 binds TR with 10–15× greater affinity than T4**, explaining its greater potency; receptors are occupied mainly by T3.
- TR forms heterodimers with the **retinoid X receptor (RXR)** and binds **thyroid response elements (TREs)** in target-gene promoters. *Without hormone*, TR binds **co-repressors** that silence transcription; *T3 binding* dissociates co-repressors and recruits **co-activators**, altering transcription (stimulating e.g. myosin heavy chain α, or repressing e.g. TSH β-subunit).
- **Non-genomic actions** also occur via mitochondrial enzymes and **integrin receptors** on blood vessels and heart.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
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> - **HPT axis feedback loop:** Hypothalamus → **TRH** (+) → Anterior pituitary → **TSH** (+) → Thyroid → **T4 / T3** → negative feedback (–) arrows back to pituitary (via **TRβ2**) and hypothalamus. Label modulators: dopamine/glucocorticoids/somatostatin (–), peripheral **deiodinase (T4→T3)**.
> - **Follicular cell synthesis schematic:** Label **bloodstream**, **basolateral membrane (NIS, TSH-R)**, **apical membrane (TPO, pendrin)**, **colloid/lumen with Tg**, steps — **iodide trapping (NIS)** → **organification (TPO + H2O2)** → **MIT/DIT** → **coupling** → **T4/T3**; cAMP second messenger from TSH-R.

Clinical / Diagnostic significance

- **TSH is the single best first-line test** of thyroid status: high in primary hypothyroidism, low in thyrotoxicosis; modern assays detect ≤0.01 mIU/L. An abnormal TSH is confirmed with **free T4 (± free T3)**.
- **TSH is unreliable** in central (secondary) hypothyroidism, recent treatment of thyrotoxicosis, severe non-thyroidal illness and TSH-secreting adenoma — here measure **free T4** directly.
- Altered binding proteins (estrogen/pregnancy raise **TBG**; androgens/nephrotic syndrome lower it; **FDH**, RTH) change **total** but not **free** hormone — measure free fractions to avoid misdiagnosis.
- **Pregnancy physiology:** hCG weakly stimulates TSH-R (first-trimester TSH dip ± gestational thyrotoxicosis/hyperemesis); estrogen raises TBG (total T4/T3 ~1.5×); placental **D3** increases hormone turnover; levothyroxine needs rise by up to **45%**.
- Etiologic tests: **anti-TPO/anti-Tg antibodies** (autoimmune disease), **TRAb/TSI** (Graves'), serum **Tg** (thyroid-cancer follow-up), and **radioiodine uptake/scan** (high homogeneous in Graves', focal "hot" toxic adenoma, low in thyroiditis/factitia).

High-yield exam pointers

- **DIT + DIT → T4; MIT + DIT → T3**; coupling and organification are both **TPO-catalysed**.
- **NIS = basolateral** (iodide in); **pendrin = apical** (iodide to lumen) — Pendred syndrome = goiter + deafness.
- **T4 half-life ~7 days, T3 ~1 day; T4:T3 secretion ~15:1; >99% protein-bound; only free hormone is active.**
- **D1** (liver/kidney) → circulating T3; **D2** (pituitary/brain/brown fat) → local T3; **D3** → inactivation + **rT3**.
- **TRβ2** mediates pituitary feedback; **RTH** is usually a dominant-negative **TRβ** mutation (high T4/T3 with non-suppressed TSH).
- **Wolff–Chaikoff effect** = iodide excess transiently blocks organification; **TSH-R = Gsα/cAMP GPCR**.
- Drugs blocking **T4→T3**: PTU, propranolol, amiodarone, glucocorticoids, iodinated contrast — recall in **sick-euthyroid syndrome**.
- TSH α-subunit is shared (LH/FSH/hCG); **β-subunit is hormone-specific**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 394 "Thyroid Gland Physiology and Testing"** (Jameson, Weetman, Mandel). Fully covers the ask. *Coverage note:* T3 serum half-life is stated here as the standard textbook value (~1 day) as the source Table 394-1 OCR value is ambiguous; MCT8-mutation eponym (Allan–Herndon–Dudley syndrome) is standard medicine and not named verbatim in the provided text.

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Vitamin D in health and disease

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

Definition / Introduction — Vitamin D is a fat-soluble *secosteroid* that functions as a **hormone precursor** rather than a true vitamin, since in the proper biologic setting it can be synthesised endogenously in skin. Its active metabolite, **1,25-dihydroxyvitamin D [1,25(OH)$_2$D, calcitriol]**, is the major steroid hormone regulating mineral-ion homeostasis, acting through the nuclear **vitamin D receptor (VDR)** to maintain serum calcium and phosphate and to mineralise the skeleton. Deficiency produces **rickets** in children and **osteomalacia** in adults, while the wide tissue distribution of the VDR underlies proposed (largely unproven) non-skeletal roles.

SOURCE & COVERAGE

- **Two forms, equal activity:** Vitamin **D$_2$ (ergocalciferol)** from plant sources; vitamin **D$_3$ (cholecalciferol)** from animal sources and cutaneous synthesis. Both are activated equally by human vitamin D hydroxylases.
- **Cutaneous synthesis (major source):** UV-B radiation (290–320 nm) cleaves **7-dehydrocholesterol** in skin to vitamin D$_3$. Reduced by **melanin, high-SPF sunblock, ageing, and limited sun exposure**, increasing reliance on diet (fortified cereals/dairy, fish oils, egg yolks).
- **Transport:** Vitamin D circulates bound to **vitamin D–binding protein (DBP)**, an α-globulin made in the liver.
- **First hydroxylation (liver):** A hepatic cytochrome P450 oxidase performs **25-hydroxylation → 25-hydroxyvitamin D [25(OH)D]**, the major circulating and storage form. This step is *not tightly regulated*. Half-life ~2–3 weeks; ~88% bound to DBP, ~0.03% free.
- **Second hydroxylation (kidney) — the rate-limiting, regulated step:** The **25(OH)D-1α-hydroxylase (CYP27B1)** in proximal convoluted tubule cells produces active **1,25(OH)$_2$D**.
  - *Inducers:* **PTH and hypophosphatemia.** *Repressors:* **calcium, FGF23, and 1,25(OH)$_2$D itself.**
- **Extra-renal 1α-hydroxylase:** Present in keratinocytes, placental trophoblast, and **macrophages of granulomas and lymphomas** — induced by **IFN-γ and TNF-α**, unregulated by calcium → cause of **PTH-independent hypercalcemia** (e.g., sarcoidosis).
- **Inactivation: 24-hydroxylase (CYP24A1)** adds a hydroxyl group; induced by 1,25(OH)$_2$D (negative feedback) and FGF23. *CYP24A1 loss-of-function* causes infantile hypercalcemia, hypercalciuria, nephrocalcinosis and nephrolithiasis.

Mechanism of Action and Physiological Roles

- **VDR:** Member of the nuclear-receptor superfamily; binds DNA as a **heterodimer with the retinoid X receptor (RXR)** at vitamin D response elements, recruiting coactivators to regulate transcription. Affinity for 1,25(OH)$_2$D is ~**1000-fold** higher than for other metabolites.

- **Intestine (the dominant action):** Induces **calbindin-9K** and the calcium channels **TRPV5 and TRPV6**, increasing the efficiency of **active calcium absorption**. (Phosphate is absorbed efficiently even without vitamin D.)
- **Bone:** In osteoblasts upregulates **osteocalcin and osteopontin** and represses type I collagen; with PTH induces **RANK ligand**, driving osteoclast differentiation and **bone resorption**; induces **FGF23** in osteocytes (phosphate regulation).
- **Parathyroid:** Antiproliferative on parathyroid cells and **suppresses transcription of the PTH gene** — the rationale for vitamin D analogue therapy in renal hyperparathyroidism.
- **Non-classical:** Antiproliferative effects on keratinocytes, breast and prostate cancer cells; roles proposed in muscle, immune function and inflammation. Alopecia of VDR mutation is *ligand-independent*.

Vitamin D Deficiency: Causes and Pathophysiology

Mechanistically, deficiency arises from defective production, intake, loss, activation, or resistance (**Table 421-6**):

Mechanism	Representative causes
Impaired cutaneous production	Ageing, dark skin, sunblock, northern latitude, institutionalisation
Dietary absence / malabsorption	Poor intake; short-gut syndrome, **gastric bypass**, fat malabsorption
Accelerated loss / inactivation	**Barbiturates, phenytoin, rifampin** (P450 induction); impaired enterohepatic circulation (terminal ileal disease); nephrotic syndrome (urinary DBP loss); CYP3A4 gain-of-function
Impaired 25-hydroxylation	Severe liver disease, **isoniazid**, 25-hydroxylase mutation
Impaired 1α-hydroxylation	**Hypoparathyroidism**, ketoconazole, CYP27B1 mutation, **FGF23 excess / oncogenic osteomalacia**, X-linked hypophosphatemia, **chronic kidney disease**
Target-organ resistance	**VDR mutation**, phenytoin
Other	**Obesity**

- **Pathophysiologic cascade:** ↓ intestinal calcium absorption → ↓ serum (ionised) calcium → **secondary hyperparathyroidism** → ↑ bone turnover (raised **alkaline phosphatase**), ↓ urinary calcium and **phosphaturia** → **hypophosphatemia**, which worsens the mineralisation defect.
- **Rickets (children, before epiphyseal fusion):** Growth retardation with **expansion of the hypertrophic chondrocyte zone** of the growth plate (impaired apoptosis of late hypertrophic chondrocytes); clinically rachitic rosary, bowed legs, frontal bossing.
- **Osteomalacia (adults):** Defective mineralisation of bone matrix → biomechanically inferior bone, **bowing of weight-bearing limbs and fractures**.
- **Proximal myopathy:** Striking feature in severe deficiency; resolves rapidly with treatment.
- Severe acute hypocalcemia is uncommon unless precipitated by concurrent **hypomagnesemia** or potent bisphosphonates.

Inherited Rickets — VDDR Type I vs Type II

Feature	Pseudovitamin D–deficiency rickets (VDDR I)	Hereditary vitamin D–resistant rickets (VDDR II)
Defect	Mutation in renal **1α-hydroxylase (CYP27B1)**	**VDR** mutation (hormone resistance)
Inheritance	Autosomal recessive	Autosomal recessive
Serum $1,25(OH)_2D$	**Low** (despite normal 25(OH)D)	**Markedly elevated**
PTH	Elevated	Elevated
Alopecia	Absent	Often **present** (ligand-independent VDR role in hair follicle)
Treatment	**Calcitriol / $1,25(OH)_2D$** (bypasses block)	High-dose calcium ± phosphate, often IV infusions

Assessment, Treatment, Prevention and Toxicity

- **Best test:** Serum **25(OH)D** (reflects stores). Levels **<37 nmol/L (<15 ng/mL)** associate with rising PTH and lower bone density.
- **Sufficiency (National Academy of Medicine): >50 nmol/L (>20 ng/mL)**; some experts advocate **>30 ng/mL** for non-skeletal endpoints (to convert ng/mL → nmol/L, ×2.496).
- **RDA: 600 IU/d (15 µg/d)** for most adults; **800 IU/d (20 µg/d)** for those **>70 years**.
- **Treatment of deficiency: 50,000 IU vitamin D weekly for 6–8 weeks**, then maintenance **800 IU/d (20 µg/d)** from food and supplements once levels normalise. D_2 and D_3 have similar long-term effect.
- **Glucocorticoid-induced osteoporosis prevention: Calcium 1000–1200 mg/d + vitamin D 600–800 IU/d** with weight-bearing exercise.
- **Toxicity:** Tolerable **upper limit 4000 IU/d**; true intoxication is rare and usually from excessive supplements or faulty fortification → **hypercalcemia** (high $1,25(OH)_2D$ and very high 25(OH)D displacing $1,25(OH)_2D$ from DBP). Manage by stopping vitamin D/calcium and treating hypercalcemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vitamin D activation cascade (Fig 421-4/421-5):** Boxes/arrows — *Skin: 7-dehydrocholesterol → (UV-B) → Vitamin D_3; Diet: D_2/D_3; → Liver: 25-hydroxylase → 25(OH)D (major circulating form)*; → *Kidney: 1α-hydroxylase (CYP27B1) → 1,25(OH)$_2$D*. Label regulators on the renal step — **+ PTH, + low PO_4 / – Ca^{2+}, – FGF23, – 1,25(OH)$_2$D** — and the **24-hydroxylase (CYP24A1) → inactivation** branch. Show targets: **Intestine (↑Ca absorption), Bone, Parathyroid (– PTH).**
- **Deficiency feedback loop:** ↓Vitamin D → ↓intestinal Ca → ↓serum Ca → ↑PTH (secondary hyperPTH) → ↑bone resorption + phosphaturia → ↓PO_4 → impaired mineralisation (**rickets/osteomalacia**).

Clinical / Diagnostic significance

- **Diagnostic panel of deficiency:** ↓ or low-normal calcium, **low phosphate**, **high alkaline phosphatase**, **high PTH**, low 25(OH)D; radiographs show osteopenia/Looser zones/rachitic changes.
- **Vitamin D analogues** suppress PTH gene transcription — used in **secondary hyperparathyroidism of CKD**.
- **Granulomatous/lymphoma hypercalcemia** (extra-renal 1α-hydroxylase) responds to **glucocorticoids, ketoconazole or chloroquine**.
- Calcium + vitamin D supplementation reduces **hip fractures** in deficient elderly/nursing-home residents; deficiency is associated with increased overall and cardiovascular mortality.
- **Evidence caveat (high-yield):** Recent placebo-controlled trials show **no therapeutic benefit of vitamin D for prevention of cancer, cardiovascular disease, type 2 diabetes, depression, tuberculosis or respiratory infection** — supplementation is justified mainly for **bone health/correction of deficiency**, not as a population-wide disease-prevention strategy.

High-yield exam pointers

- Active hormone = **1,25(OH)$_2$D (calcitriol)**; storage/best-test form = **25(OH)D**.
- Rate-limiting, regulated step = renal **1α-hydroxylase (CYP27B1)**: ↑ by PTH/low phosphate, ↓ by Ca/FGF23/1,25(OH)$_2$D.
- VDR acts as **VDR–RXR heterodimer**; chief action is **intestinal calcium absorption** (calbindin, TRPV5/6).
- **Deficiency biochemistry:** ↓Ca, ↓PO_4, ↑ALP, ↑PTH, ↓25(OH)D.
- **Rickets** = growth-plate (hypertrophic-zone) expansion; **osteomalacia** = defective matrix mineralisation; **proximal myopathy** reversible.
- **VDDR I** = enzyme defect → low 1,25(OH)$_2$D, give calcitriol; **VDDR II** = receptor defect → high 1,25(OH)$_2$D + **alopecia**, resistant.
- Sufficiency **>20 ng/mL**; RDA **600 IU/d** (**800** if >70 y); treat with **50,000 IU/week ×6–8 wk**; upper limit **4000 IU/d**.
- **Sarcoidosis/lymphoma** → 1,25(OH)$_2$D-mediated hypercalcemia, steroid-responsive.

SOURCE & COVERAGE

Harrison 22e — Ch 421 "Bone and Mineral Metabolism in Health and Disease" (vitamin D synthesis, metabolism, VDR action, deficiency, rickets/osteomalacia, VDDR I/II, diagnosis) + Ch 344 "Vitamin and Trace Mineral Deficiency and Excess" (dietary sources, reference ranges, RDA/treatment dosing, toxicity, non-skeletal-disease evidence). *Coverage note:* All classifications, doses, enzyme/gene names and cut-offs above are drawn from these two chapters; standard deficiency-panel correlations (Looser zones, frontal bossing) are universally accepted textbook medicine added for completeness.

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Vitamin D physiology

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

Definition / Introduction — *Vitamin D* is best regarded as a **prohormone**, not a true vitamin: in the proper biologic setting it can be synthesised endogenously in skin, and its active metabolite **1,25-dihydroxyvitamin D [1,25(OH)$_2$D, calcitriol]** is the major **steroid hormone** regulating mineral-ion (calcium and phosphate) homeostasis. The native vitamin is biologically inert and must undergo **two sequential hydroxylations** — 25-hydroxylation in the liver and tightly regulated 1α-hydroxylation in the kidney — to become active. It acts through a nuclear **vitamin D receptor (VDR)** to optimise intestinal calcium and phosphate absorption, support skeletal mineralisation, and complete the parathyroid–calcium feedback loop.

SOURCE & COVERAGE

- **Cutaneous synthesis (major source):** ultraviolet (UV-B) radiation of skin causes photochemical cleavage of **7-dehydrocholesterol → vitamin D$_3$**. This is the dominant physiological source.
- Cutaneous production is **reduced** by melanin (dark skin), high-SPF sunblocks (which block UV-B skin penetration), reduced solar exposure, and ageing — driving increased reliance on dietary vitamin D.
- **Dietary sources:** fortified cereals and dairy products, fish oils, egg yolks.
  - **Vitamin D$_2$ (ergocalciferol)** — from plant sources.
  - **Vitamin D$_3$ (cholecalciferol)** — from animal sources.
  - Both forms have **equivalent biologic activity** and are activated equally well by human vitamin D hydroxylases.

Synthesis and two-step metabolic activation

Whether absorbed from the gut or synthesised in skin, vitamin D enters the circulation bound to **vitamin D–binding protein (DBP)**, an α-globulin made in the liver, then undergoes ordered activation:

Step	Site / enzyme	Product	Regulation
25-hydroxylation	Liver — cytochrome P450 oxidase (mitochondria + microsomes)	**25-hydroxyvitamin D [25(OH)D]**	**Not** tightly regulated; reflects substrate supply
1α-hydroxylation	Kidney — **CYP27B1** (25-OH-D-1α-hydroxylase) in proximal convoluted tubule	**$1,25(OH)_2D$ (calcitriol)** — the active hormone	**Tightly** regulated
24-hydroxylation (inactivation)	Most tissues — **CYP24A1** (24-hydroxylase)	$24,25(OH)_2D$ / $1,24,25(OH)_3D$ (inactive)	Induced by $1,25(OH)_2D$ and FGF23

- **25(OH)D** is the **major circulating and storage form**: ~**88%** bound to DBP, ~**0.03%** free, the remainder bound to albumin; half-life ~**2–3 weeks**. Hence it is the **best index of vitamin D status**.
- DBP affinity is lower for the D_2 metabolites, so **$25(OH)D_2$** has a shorter half-life than $25(OH)D_3$; half-life also shortens when DBP is lost (e.g., **nephrotic syndrome**).

Regulation of the active hormone (hormonal control loop)

- **CYP27B1 (1α-hydroxylase)** is the key control point:
  - **Induced (↑$1,25(OH)_2D$) by: PTH** and **hypophosphatemia**.
  - **Repressed (↓$1,25(OH)_2D$) by: calcium**, **FGF23**, and the product **$1,25(OH)_2D$** itself (negative feedback).
- **Integrated calcium loop:** a fall in serum calcium below ~**2.2 mmol/L (8.8 mg/dL)** stimulates **PTH** secretion → mobilises bone calcium and stimulates renal **$1,25(OH)_2D$** synthesis → $1,25(OH)_2D$ enhances **intestinal calcium absorption** and, with PTH, restores serum calcium; $1,25(OH)_2D$ in turn **suppresses PTH gene transcription** (closing the loop).
- **Auto-limitation:** $1,25(OH)_2D$ is the major inducer of its own catabolising enzyme **CYP24A1**, promoting its own inactivation and limiting biologic effect.
- **Extrarenal 1α-hydroxylase** is expressed in keratinocytes, the placental trophoblast, and **macrophages of granulomas and lymphomas**, where it is induced by **IFN-γ and TNF-α** and is **NOT** regulated by calcium or $1,25(OH)_2D$ — explaining the **hypercalcemia of sarcoidosis/granulomatous disease and lymphoma** (responsive to glucocorticoids, ketoconazole, chloroquine in sarcoid).

Mechanism of action — VDR and target-organ effects

$1,25(OH)_2D$ binds the **vitamin D receptor (VDR)**, a member of the nuclear-receptor superfamily (related to thyroid hormone, retinoid, and PPAR receptors). The VDR heterodimerises with the **retinoid X receptor (RXR)**, binds vitamin D response elements, and recruits coactivators to modulate target-gene transcription. The VDR's affinity for $1,25(OH)_2D$ is ~**1000-fold (three orders of magnitude)** higher than for other metabolites.

Target tissue	Action of $1,25(OH)_2D$
Intestine	Induces **calbindin-9K** and calcium channels **TRPV6** (gut) / TRPV5 (renal); increases efficiency of **active calcium absorption** and stimulates phosphate absorption (Na^+/PO_4 cotransporters, e.g., Npt2b)
Bone (osteoblast)	Upregulates **osteocalcin, osteopontin**; represses **type I collagen**; with PTH induces **RANK ligand** → osteoclast differentiation and **bone resorption**
Osteocyte	Induces **FGF23** → regulates phosphate homeostasis
Parathyroid	**Antiproliferative**; suppresses **PTH gene** transcription
Skin / other	Antiproliferative on keratinocytes, breast and prostate cancer cells; VDR mutation → **alopecia** (a ligand-independent effect, not seen in simple deficiency); regulates the bone–tendon attachment (**enthesis**)

- Active (transcellular, $1,25(OH)_2D$-dependent) calcium transport occurs mainly in **duodenum/proximal jejunum** and normally accounts for **20–70%** of dietary calcium absorption; passive paracellular absorption (~5%) is vitamin D–independent.

Vitamin D deficiency — causes and consequences

Biochemical cascade: deficiency → impaired intestinal calcium absorption → **hypocalcemia** → **secondary hyperparathyroidism** → increased bone turnover (↑**alkaline phosphatase**), **phosphaturia** → **hypophosphatemia** → impaired skeletal **mineralisation**.

- **Children (before epiphyseal fusion): rickets** — expansion of the growth-plate **hypertrophic chondrocyte zone** (of the reserve, proliferating, hypertrophic zones).
- **Adults: osteomalacia** — defective mineralisation of bone matrix; plus **proximal myopathy**, osteopenia/low BMD; associated with **increased overall (incl. cardiovascular) mortality**.

Mechanism	Examples (Table 421-6)
Vitamin D deficiency	Impaired cutaneous production; dietary absence; malabsorption (short-gut, gastric bypass)
Accelerated loss / catabolism	Hepatic P450 inducers — **barbiturates, phenytoin, rifampin**; impaired enterohepatic circulation (terminal ileal disease); **nephrotic syndrome**; CYP3A4 mutation
Impaired 25-hydroxylation	Liver disease, **isoniazid**; 25-hydroxylase mutation
Impaired 1α-hydroxylation	**Hypoparathyroidism**; ketoconazole; **CYP27B1 (1α-hydroxylase) mutation**; FGF23 excess; oncogenic osteomalacia; chronic kidney disease
Target-organ resistance	**VDR mutation**; obesity

- **Pseudovitamin D–deficiency rickets (vitamin D–dependent rickets type I):** autosomal-recessive **1α-hydroxylase (CYP27B1) mutation** — low $1,25(OH)_2D$, normal/high 25(OH)D, high PTH; responds to **calcitriol**.
- **Hereditary vitamin D–resistant rickets (type II): VDR mutation** with end-organ resistance — markedly **elevated $1,25(OH)_2D$**, often **alopecia**; needs calcium ± phosphate infusions to bypass the defect.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vitamin D synthesis and activation cascade (vertical flow):** *Skin: 7-dehydrocholesterol → (UV-B) → Vitamin D_3* and *Diet: D_2/D_3 → DBP-bound transport → Liver: 25-hydroxylase → 25(OH)D → Kidney (PCT): 1α-hydroxylase/CYP27B1 → 1,25$(OH)_2$D* → target organs. Side label: *24-hydroxylase/CYP24A1 → inactive 24,25$(OH)_2$D*.
- **Hormonal control loop (Harrison Fig. 421-5):** central box *Blood calcium*; arrows to **Parathyroid glands (PTH)**, **Kidney (1,25$(OH)_2$D)**, **Bone**, **Intestine**. Labels: *↓Ca^{2+} → ↑PTH*; *PTH + ↓PO_4 → ↑1α-hydroxylase*; *1,25$(OH)_2$D → ↑gut Ca^{2+}/PO_4 absorption*; *Ca^{2+}, FGF23, 1,25$(OH)_2$D ⊣ 1α-hydroxylase*; *1,25$(OH)_2$D ⊣ PTH gene (negative feedback)*.

Clinical / Diagnostic significance

- **Best screening test:** serum **25(OH)D** (reflects stores). **<37 nmol/L (<15 ng/mL)** associates with rising PTH and lower bone density; **National Academy of Medicine** defines **sufficiency as >50 nmol/L (>20 ng/mL)** (higher may be needed in the elderly/obese).
- Do **not** use serum 1,25$(OH)_2$D to assess deficiency — it may be normal or high (driven by secondary hyperparathyroidism) despite depleted stores.
- **Deficiency biochemistry:** ↓Ca, ↓PO_4, ↑PTH, ↑alkaline phosphatase, low 25(OH)D.
- **At-risk groups:** elderly/nursing-home residents (skin synthesis and gut absorption both decline with age), malabsorption/short-gut/bariatric surgery, terminal ileal disease, nephrotic syndrome, chronic liver/kidney disease, obesity, enzyme-inducing drugs.
- **Management principles (from chapter):** calcium + vitamin D supplementation reduces hip-fracture incidence in deficient elderly; in **CKD/hypoparathyroidism** use **calcitriol/active analogues** to bypass the 1α-hydroxylation block; type II resistant rickets needs calcium/phosphate infusions.
- **Hypercalcemia of granulomatous disease/lymphoma** is driven by unregulated extrarenal 1α-hydroxylase — treat with glucocorticoids (± ketoconazole/chloroquine).
- **CYP24A1 loss-of-function** mutation → impaired inactivation → **infantile hypercalcemia**, later hypercalciuria, nephrocalcinosis, nephrolithiasis.

High-yield exam pointers

- Vitamin D is a **prohormone**; **1,25$(OH)_2$D (calcitriol)** is the active steroid hormone.
- Activation = **liver 25-hydroxylase (not regulated)** then **renal CYP27B1/1α-hydroxylase (tightly regulated)**.
- **1α-hydroxylase:** ↑ by **PTH + hypophosphatemia**; ↓ by **calcium, FGF23, 1,25$(OH)_2$D**.
- **25(OH)D** = best status marker (half-life **2–3 weeks**, ~88% DBP-bound); sufficiency **>20 ng/mL**.
- Action via **VDR–RXR heterodimer**; affinity for 1,25$(OH)_2$D **1000× higher** than other metabolites.
- Gut: induces **calbindin-9K + TRPV6** → calcium absorption (duodenum/jejunum, 20–70%).
- Deficiency → ↓Ca, **secondary hyperPTH**, ↓PO_4, ↑ALP → **rickets (children)/osteomalacia (adults)** + proximal myopathy.

- **CYP24A1 (24-hydroxylase)** inactivates vitamin D; mutation → infantile hypercalcemia.
- **Type I rickets** = CYP27B1 mutation (treat calcitriol); **Type II** = VDR mutation + alopecia (very high $1,25(OH)_2D$).

SOURCE & COVERAGE

Harrison 22e — Ch 421 "Bone and Mineral Metabolism in Health and Disease" (Vitamin D: synthesis/metabolism, actions, deficiency; Figs 421-4 and 421-5; Tables 421-6). **Coverage note:** the chapter names the dietary forms as "vitamin D_2/D_3" but does not use the terms *ergocalciferol/cholecalciferol*; these (and *calcitriol* for $1,25(OH)_2D$) are added as universally accepted standard nomenclature. Harrison Ch 421 does not specify numeric vitamin D **RDA/IU** or repletion **dosing regimens**, so quantitative treatment doses are deliberately omitted; only the chapter's qualitative management points are stated.

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Hematology & oncology

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Apoptosis pathways and role in cancer

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

Definition / Introduction — *Apoptosis* is the genetically programmed, energy-dependent, **non-inflammatory** form of regulated cell death that culls aged, terminally differentiated, or irreparably damaged cells and so maintains tissue homeostasis. It is executed by a conserved family of cysteine-aspartate proteases (**caspases**) triggered through two principal routes — the **extrinsic (death-receptor)** pathway and the **intrinsic (mitochondrial)** pathway — that converge on common executioner caspases. Because the net cell number in a tissue reflects the balance between proliferation and death, *evasion of apoptosis* is a core enabling hallmark of malignancy: it lets cells carrying oncogenic mutations and genetic instability survive, expand clonally, and resist chemotherapy and radiation.

Regulated cell death — apoptosis and its alternatives

- The cell can respond to lethal stress by several distinct programmes: **apoptosis**, **autophagy** (lysosomal degradation of proteins/organelles), and irreversible growth arrest (**senescence**), plus newer caspase-variant deaths.
- Other regulated death modes (roles in cancer still being defined): **pyroptosis** — caspase-1-dependent, cleaves *gasdermins* to form plasma-membrane pores; **ferroptosis** — iron- and reactive-oxygen-species-dependent lipid peroxidation; **necroptosis** — caspase-*independent*, with cell rupture causing inflammation and tissue damage.
- Apoptosis is morphologically defined: cell shrinkage, chromatin condensation and nuclear fragmentation (pathologists' *karyorrhexis*, "nucleus bursting"), lamin and cytoskeletal cleavage, internucleosomal DNA degradation, and membrane blebbing into apoptotic bodies that are phagocytosed **without an inflammatory response** — contrasting with necrosis.

Feature	Apoptosis	Necrosis
Trigger	Physiologic or pathologic, programmed	Severe injury/ischaemia
Energy (ATP)	Required (active)	Not required (passive)
Cell volume	Shrinkage	Swelling
DNA	Internucleosomal cleavage ("ladder")	Random smear
Membrane	Intact; apoptotic bodies	Early rupture
Inflammation	Absent	Present

The extrinsic (death-receptor) pathway

- Activated by cross-linking of **TNF-receptor-superfamily** death receptors by their ligands: **CD95 (Fas)** by Fas ligand, and **DR4/DR5** by **TRAIL** (TNF-related apoptosis-inducing ligand).
- Ligation recruits the adaptor **FADD** (Fas-associated death domain) and **procaspase-8** to the receptor's cytoplasmic death domains, forming the death-inducing signalling complex (DISC).
- **Caspase-8** is autoactivated and directly cleaves the executioner **caspases-3 and -7**, producing the morphologic features of apoptosis.
- Physiologic brake: **FLIP**, which competes with caspase-8 for FADD; *decoy receptors* also blunt TRAIL signalling. Normal cells often express these inhibitors while tumour cells may not — the basis for therapeutic TRAIL/agonist-antibody selectivity.

The intrinsic (mitochondrial) pathway and the Bcl-2 family

- Initiated by **mitochondrial outer-membrane permeabilisation (MOMP)** in response to *DNA damage, oncogene-induced proliferation, loss of attachment to extracellular matrix, growth-factor deprivation, hypoxia, chemotherapy and radiation.*
- MOMP releases **cytochrome c** and **SMAC/DIABLO** from the mitochondrial intermembrane space. Cytochrome c associates with **dATP**, **procaspase-9** and the adaptor **APAF-1** to assemble the **apoptosome**, which activates **caspase-9** and then the effector caspases.
- **SMAC** binds and neutralises **inhibitor-of-apoptosis proteins (IAPs)** — e.g. **XIAP** — which otherwise restrain caspase activation.
- MOMP is governed by the **Bcl-2 family**, whose relative levels at the mitochondrial membrane set the apoptotic threshold:

Class	Members	Action
Anti-apoptotic (guardians)	**Bcl-2, Bcl-XL, Mcl-1**	Anchor to outer membrane; sequester pro-apoptotic proteins via a hydrophobic **BH (Bcl-2-homology) pocket**
Pro-apoptotic effectors	**Bax, Bak**	Oligomerise to form outer-membrane pores → cytochrome c release
BH3-only activators/sensitisers	**Bad, Bim, Bid, Puma, Noxa**	Neutralise anti-apoptotic members and/or activate Bax/Bak

- If BH3-only proteins are mopped up by Bcl-2/Bcl-XL/Mcl-1, pores do not form and apoptosis is averted; when they predominate, Bax/Bak oligomerise and the cell dies. The **mitochondrion is thus the central regulatory organelle of intrinsic apoptosis.**

Convergence, executioner caspases and survival signalling

- **Initiator caspases** (-8, -9, -10) sit atop each pathway; **executioner/effector caspases** (-3, -6, -7) are the common downstream blades that cleave structural and regulatory substrates (caspase-activated DNase, lamins, cytoskeletal proteins).
- **Cross-talk:** caspase-8 cleaves the BH3-only protein **Bid** to truncated tBid, amplifying the death signal through the mitochondrial pathway — linking extrinsic and intrinsic routes.
- **p53 — "guardian of the genome":** on DNA damage, ATM/ATR and Chk1/Chk2 phosphorylate p53 and MDM2, freeing p53 from MDM2-mediated degradation; oncogene stress induces **p14ARF**, which binds MDM2 and likewise stabilises p53. p53 then transactivates cell-cycle arrest (p21) or, if damage is severe, apoptosis via the pro-apoptotic BH3-only members **Puma and Noxa**.
- **Pro-survival pathways subverted in cancer:** the **PI3K/Akt** axis (Akt phosphorylates and inactivates BAD and FOXO/FKHR), **NF-κB** (held inactive by IκB; IKK phosphorylation → proteasomal IκB degradation → NF-κB-driven survival genes), and epigenetic silencing of **APAF-1** and **caspase-8**.

Apoptosis evasion as a hallmark of cancer

- **Bcl-2 overexpression** from the **t(14;18)** translocation underlies *follicular lymphoma*; Bcl-2 is also high in chronic lymphocytic leukaemia (CLL) and in prostate, breast, lung cancers and melanoma.
- **p53 inactivation** (the most frequent mutation in human cancer, chromosome 17p; germline loss = **Li-Fraumeni syndrome**; aflatoxin gives the codon-249 arginine→serine signature mutation in hepatocellular carcinoma) removes the damage-triggered death programme. **HPV E6** degrades p53 (and E7 inactivates Rb).
- Up-regulation of **IAPs/XIAP**, expression of **decoy death receptors** and **FLIP**, loss of **APAF-1/caspase-8**, and constitutive **PI3K-Akt / NF-κB** signalling all raise the apoptotic threshold.
- **Anoikis** — apoptosis normally triggered by loss of ECM contact — is suppressed in cells that invade and metastasise. **Cancer stem cells** further resist therapy through high anti-apoptotic Bcl-2 levels combined with **ABC/P-glycoprotein (MDR)** drug-efflux pumps.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Two-pathway apoptosis schematic.** Left **extrinsic limb**: FasL/TRAIL → *Fas / DR4 / DR5* → *FADD* → *procaspase-8* → *caspase-8*. Right **intrinsic limb**: death stimuli (DNA damage, growth-factor withdrawal, chemo/radiation) → *BH3-only proteins* → *Bax/Bak* pore in mitochondrial outer membrane → release of *cytochrome c* + *SMAC*; cytochrome c + *APAF-1* + *dATP* + *procaspase-9* → *apoptosome* → *caspase-9*; *Bcl-2/Bcl-XL/Mcl-1* shown blocking Bax/Bak; *SMAC* inhibiting *IAP/XIAP*. Both converge on *executioner caspases-3/-7* → substrate cleavage → DNA degradation, chromatin condensation, lamin cleavage (apoptosis). Show *caspase-8* → *tBid* arrow linking the two limbs. Label drug targets: **venetoclax/BH3-mimetic → Bcl-2**, **SMAC-mimetic → IAP**, **bortezomib → proteasome/NF-κB**.
- **Bcl-2 rheostat bar:** anti-apoptotic (Bcl-2, Bcl-XL, Mcl-1) on one side versus pro-apoptotic (Bax, Bak, BH3-only) on the other, balance point = apoptotic threshold.

Clinical / Diagnostic significance

- **BH3 mimetics: venetoclax (ABT-199)**, an oral BCL-2 inhibitor, is approved for relapsed/refractory **CLL with 17p deletion** and is active in **AML** (e.g. with azacitidine/hypomethylating agents); the tool compound **ABT-737** is synergistic with docetaxel preclinically — proof of "targeting the dependence."
- **Restoring the death signal:** recombinant TRAIL and agonist DR4/DR5 antibodies kill tumour (not normal) cells in preclinical work; **SMAC mimetics** lower the apoptotic threshold by neutralising IAPs; **HDAC inhibitors** up-regulate death receptors (DR4/5, FAS) and down-regulate XIAP.
- **Indirect pro-apoptotic agents: proteasome inhibitors** (bortezomib) prevent IκB destruction and block NF-κB survival signalling; **PI3K/Akt and BTK inhibitors** sensitise cells to apoptosis; **PARP inhibitors** exploit defective DNA-damage repair (BRCA-mutant tumours) to drive lethal DNA damage; **taxanes** stabilise microtubules and phosphorylate Bcl-2.
- **Diagnostic readouts:** apoptosis is detected by **annexin-V** (phosphatidylserine externalisation), **TUNEL** assay, caspase-3 activation, and the DNA "ladder" — used in tissue prognostication and as pharmacodynamic markers of drug response.
- **Therapeutic principle:** tumours "addicted" to anti-apoptotic proteins may be *more* vulnerable than normal cells to agents that re-engage apoptosis — the rationale for the whole BH3-mimetic class.

High-yield exam pointers

- Two pathways: **extrinsic** (Fas/DR4/DR5 → FADD → caspase-8) and **intrinsic** (mitochondrial: cytochrome c + APAF-1 + procaspase-9 → **apoptosome** → caspase-9); both converge on **executioner caspases-3/-7**.
- **Bcl-2 family rheostat:** anti-apoptotic **Bcl-2/Bcl-XL/Mcl-1** vs effectors **Bax/Bak** vs **BH3-only (Bad, Bim, Bid, Puma, Noxa)** sets MOMP.

- **SMAC/DIABLO** neutralises **IAP/XIAP**; **FLIP** blocks caspase-8 at the DISC; **caspase-8 → tBid** cross-links the pathways.
- **p53** ("guardian of the genome") drives apoptosis via **Puma/Noxa**; most-mutated cancer gene; germline loss = **Li-Fraumeni**.
- Apoptosis evasion = **hallmark of cancer**: Bcl-2 overexpression via **t(14;18)** in follicular lymphoma; loss of anoikis aids metastasis.
- **Venetoclax (BH3 mimetic, anti-BCL-2)** — CLL with 17p deletion, AML — is the flagship clinical translation.
- Apoptosis is **ATP-dependent, non-inflammatory**; necrosis is passive and inflammatory.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cancer Cell Biology" (apoptosis pathways, Bcl-2 family, extrinsic/intrinsic mechanisms, p53/MDM2/p14ARF checkpoint, evasion of apoptosis, cancer stem cells, *Figs. 77-1 and 77-5*) and "Cancer Genetics."
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — apoptosis-directed therapeutics: BH3 mimetics (**ABT-737, ABT-199/venetoclax**), taxane-induced Bcl-2 phosphorylation and caspase-8 scaffolding, venetoclax–azacitidine in AML.
- Coverage note: Harrison provides the full mechanistic and clinical content; DeVita's full text in this corpus is treatment-weighted, so it was used chiefly for the apoptosis-targeting drug detail. Apoptosis-versus-necrosis morphology, initiator/executioner caspase numbering, annexin-V/TUNEL detection, and the Bid→tBid cross-talk are standard, universally accepted internal-medicine content included for completeness.

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Aplastic anaemia

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

Definition / Introduction — Aplastic anemia is **pancytopenia accompanied by a hypocellular ("empty," fat-replaced) bone marrow**, with no abnormal infiltrate and no marrow fibrosis. It results from quantitative and qualitative failure of the pluripotent **haematopoietic stem cell (HSC)**, most often through immune-mediated (T-cell) destruction, less often from direct chemical/physical injury or an inherited stem-cell defect. It is distinguished from peripheral cytopenias (haemolysis, ITP, hypersplenism) by the *deficient production* of cells. Incidence is **2 per million/year in Europe and Israel and 5–7 per million in Thailand and China**, with a **biphasic age distribution** (major peak in the teens –twenties, second peak in older adults) and equal sex incidence.

Classification & Causes (Aetiology)

Aplastic anemia is broadly **acquired** (≈80%, usually immune/idiopathic) or **inherited/constitutional** (inherited bone marrow failure syndromes, IBMFS). The major recognised associations:

Category	Specific causes
Idiopathic (immune)	Most common; T-cell–mediated autoimmune HSC destruction

Category	Specific causes
Radiation	Marrow aplasia is a major acute sequela; accidental/occupational/therapeutic
Chemicals	**Benzene** (best-substantiated), toluene, insecticides
Drugs — regular (dose-dependent)	Cytotoxic chemotherapy: alkylators, antimetabolites, antimitotics
Drugs — idiosyncratic	**Chloramphenicol**, gold salts, sulfonamides, phenylbutazone/NSAIDs, anticonvulsants (phenytoin, carbamazepine, felbamate), antithyroid drugs (methimazole, PTU, carbimazole), penicillamine, allopurinol, quinacrine, tolbutamide
Viruses / infection	**Seronegative (non-A, non-B, non-C) hepatitis** (~5%, young men, very severe), EBV (infectious mononucleosis), parvovirus B19, CMV, HIV-1
Immune disorders	Eosinophilic fasciitis, SLE, thymoma/thymic carcinoma, hypoimmunoglobulinaemia, transfusion-associated GVHD, large granular lymphocytosis (LGL)
Clonal / other	Paroxysmal nocturnal haemoglobinuria (PNH); pregnancy (resolves with delivery)
Inherited (constitutional)	**Fanconi anemia** (AR; *FANCA* commonest; short stature, café-au-lait spots, thumb/radius & GU anomalies); **Dyskeratosis congenita / telomere biology disorders** (*DKC1* X-linked; *TERC/TERT* AD; *TINF2* shelterin); **Shwachman-Diamond** (*SBDS*; neutropenia + pancreatic insufficiency); **GATA2 deficiency**, **RUNX1** familial platelet disorder

- *Pearl:* "Association is not causation" — an incriminated drug may have merely been given to treat the *first* symptom of marrow failure (e.g., NSAIDs for petechiae, antibiotics for fever).

Pathophysiology

- **Immune destruction (the dominant mechanism in acquired disease):** activated, oligoclonal **cytotoxic CD8 T cells** and **Type-1 cytokines** (chiefly **interferon-γ** and TNF) suppress and kill $CD34^+$ progenitors. IFN-γ induces **Fas** on CD34 cells → **Fas/FasL-mediated apoptosis**. The stem-cell pool falls to **≤1% of normal** in severe disease; $CD34^+$ cells and committed progenitors are virtually absent. Response to anti-thymocyte globulin proves the immune basis.
- **Constitutional defect:** intrinsic stem-cell flaw — defective DNA inter-strand cross-link repair (Fanconi, FANCD2 mono-ubiquitination pathway), defective telomere maintenance/shelterin (telomere disorders), or impaired transcriptional regulation (GATA2, RUNX1) → limited proliferative capacity and genomic instability.
- **Chemical/drug injury:** generation of reactive **electrophilic intermediates** (e.g., benzene hydroquinones/quinolones) that bind cellular macromolecules; genetically determined detoxification differences explain idiosyncratic susceptibility.
- **Clonal escape:** PNH clones (PIG-A mutation) and somatic myeloid mutations may emerge, reflecting immune selection and explaining later clonal evolution.

Clinical features & Laboratory diagnosis

- **History/exam:** insidious or abrupt onset. **Bleeding is the commonest early symptom** (bruising, gum oozing, epistaxis, menorrhagia, petechiae); anaemic symptoms (fatigue, dyspnoea);

infection is an *unusual* presenting feature (unlike agranulocytosis). Patients often "look well." **Lymphadenopathy and splenomegaly are atypical** and should prompt another diagnosis. Look for IBMFS clues: short stature/café-au-lait (Fanconi), nail dystrophy/leukoplakia (dyskeratosis congenita), premature greying/pulmonary or hepatic fibrosis (telomere disorder), warts/unusual infections (GATA2).

- **Blood:** pancytopenia; normochromic, often **macrocytic (raised MCV)** RBCs; **reticulocytopenia**; no immature/abnormal forms (their presence suggests leukaemia/MDS).
- **Bone marrow:** aspirate dilute; **trephine biopsy (>1 cm) hypocellular with haematopoietic cells <25%**, mostly fat; megakaryocytes greatly reduced/absent; residual cells morphologically normal. MRI spine shows fatty marrow.
- **Ancillary / aetiological work-up: chromosome breakage test (diepoxybutane / mitomycin C)** in children & young adults for Fanconi; **leucocyte telomere length** for telomere disorders; **flow cytometry for a PNH clone** (CD55/CD59, FLAER); marrow **cytogenetics** (abnormal favours MDS); serology (EBV, HIV, hepatitis); **next-generation sequencing germline + myeloid panels** to separate inherited and clonal disease.

Severity grading (Camitta criteria) — guides treatment

Grade	Criteria
Severe aplastic anemia (SAA)	Marrow cellularity <25% **plus** any **two of three**: ANC **<500/µL**, platelets **<20,000/µL**, corrected reticulocyte count **<1%** (absolute reticulocytes <60,000/µL)
Very severe (VSAA)	As SAA but **ANC <200/µL**
Non-severe / moderate	Cytopenias not meeting SAA thresholds

- Better modern predictors of treatment response: **absolute reticulocytes >25,000/µL** and **lymphocytes >1000/µL**; presence of a PNH clone or small somatic mutations also informs prognosis.

Management

General principles: stop any suspected drug/chemical; glucocorticoids are **not effective as primary therapy**; spontaneous recovery is rare, so treat early in SAA. Choice between transplant and immunosuppression hinges on **age, donor availability and depth of neutropenia**. HLA-type early and **avoid family-member transfusions** in transplant candidates (sensitisation). Use **leucodepleted, irradiated** blood products.

1. Haematopoietic stem cell (bone marrow) transplantation — definitive/curative

- **First choice for the younger patient (<40 yr) with an HLA-matched sibling donor.** Long-term survival in children ≈90%; CMDT quotes **>80% under age 20 and ~65–70% in those 20–50**, dropping 10–15% with matched-unrelated donors.
- Matched-unrelated-donor transplant: initial option in children, salvage in adults failing immunosuppression. **Haploidentical** transplant with **post-transplant cyclophosphamide** (PT-Cy) is increasingly used as a donor is almost always available; cord blood for children.

- Radiation is generally omitted from conditioning (except some alternative-donor protocols) to reduce late malignancy.

2. Immunosuppressive "triple therapy" — for those without a donor or aged >40 yr

- **Standard of care (FDA-approved 2018): horse ATG + ciclosporin + eltrombopag**, achieving haematologic response in **70–80%** (CMDT cites up to ~90%; complete responses ~50%).
- **Equine (horse) ATG 40 mg/kg/day IV for 4 days** — *superior to rabbit ATG* (better response/survival); give with **methylprednisolone/prednisone 1–2 mg/kg/day for ~1 week then taper over 2 weeks** to prevent infusion reactions and **serum sickness** (occurs ~day 10).
- **Ciclosporin 6 mg/kg PO twice daily**, level-adjusted, generally continued **~2 years**; toxicities — **nephrotoxicity, hypertension, seizures** (tacrolimus is an alternative).
- **Eltrombopag (TPO-receptor mimetic) 150 mg PO once daily for 6 months** then stop in responders; stimulates the HSC; main toxicity **hepatotoxicity**. Romiplostim is an alternative.
- Response usually within **1–3 months** (assessed at ~4 months); responses are often partial. **Relapse** occurs in up to one-third (often on tapering ciclosporin/eltrombopag) and usually responds to re-treatment. Patients failing immunosuppression can be salvaged by later transplant.

3. Androgens — fluoxymesterone 10–20 mg/day or **danazol 200 mg PO twice daily**; modest, unproven benefit; useful in **moderate disease and telomere disorders** (up-regulate telomerase).

4. Supportive care (essential to survive to definitive therapy)

- **Infection:** neutropenic fever is an emergency — **prompt empirical broad-spectrum parenteral antibiotics**; suspect **fungal** disease (*Candida*, *Aspergillus*) with persistent fever and add antifungals; granulocyte transfusions for refractory infection.
- **Platelets:** prophylactic transfusion to keep count **>10,000/µL**; HLA-matched/single-donor units if alloimmunised; suppress menstruation; avoid aspirin/NSAIDs.
- **Red cells:** transfuse to **Hb ~70 g/L (90 g/L if cardiac/pulmonary disease)**; add iron chelation (**deferoxamine/deferasirox**) around the **50th transfusion** to prevent secondary haemochromatosis.
- **Not useful:** EPO and G-CSF are **ineffective** in aplastic anemia; reverse isolation and gut decontamination do not reduce mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology schematic of aplastic anemia (after Harrison Fig 107-1):** three aetiologic arrows — *Physical/chemical damage*, *Immune (T-cell) destruction*, *Constitutional genetic defect* — converging on **"empty bone marrow replaced by fat"**, with treatment boxes beneath each: *HGF/Support + BMT*; *IST + BMT + Eltrombopag*; *Sex hormones + BMT*. Labels: **HSC, CD34⁺ cell, cytotoxic T cell, IFN-γ, Fas/FasL, apoptosis, fatty marrow.**
- **Treatment algorithm:** Confirm SAA → assess **age & HLA-matched sibling** → *Young + matched sibling* → **Allogeneic HSCT**; *No donor / >40 yr* → **Horse ATG + Ciclosporin + Eltrombopag (triple therapy)** → response → taper; no response → **MUD/haploidentical transplant** or second IST. Side panel: **supportive care (antibiotics, platelets >10k, RBC to Hb 70, chelation).**

Clinical / Diagnostic significance

- **Differentiate from hypoplastic MDS** (favoured by dysplasia, increased blasts, clonal cytogenetics, spliceosome/cohesin mutations) and from **hypocellular hairy cell leukaemia** (splenomegaly, hairy cells) — both are pancytopenia mimics.
- A **PNH clone** at diagnosis supports an immune mechanism and predicts immunosuppression-responsiveness; it may later expand to clinical haemolytic PNH.
- **Clonal evolution to MDS/AML or PNH occurs in ~10–15% (up to one-quarter at 10 years)** after immunosuppression — long-term marrow surveillance is mandatory.
- Recognising **IBMFS** (Fanconi, telomere disorders, GATA2) changes management: avoid standard high-dose conditioning, screen relatives, and counsel on malignancy risk.

High-yield exam pointers

- Triad = **pancytopenia + reticulocytopenia + hypocellular (fatty) marrow** with **no organomegaly**.
- **Commonest acquired cause = idiopathic (immune, T-cell mediated)**; classic toxins = **benzene** and **chloramphenicol**; ~5% follow **seronegative hepatitis** in young men.
- **Camitta SAA:** marrow <25% + 2 of (ANC <500, platelets <20,000, retic <1%); **VSAA = ANC <200**.
- **Cure = HLA-matched sibling allogeneic transplant** (first choice in young patients).
- **No donor / older → triple therapy = horse ATG + ciclosporin + eltrombopag** (~70–90% response); **horse ATG > rabbit ATG**.
- **Eltrombopag** = TPO mimetic, 150 mg/day × 6 months, hepatotoxicity; **ciclosporin** continued ~2 years.
- **Glucocorticoids, EPO and G-CSF are NOT primary therapy.**
- Platelets transfused to keep **>10,000/μL**; RBC to **Hb 70 g/L**; iron chelation from ~50th unit.
- Always exclude **Fanconi anemia** (DEB/mitomycin C chromosome breakage) and **telomere disorders** in young patients.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia" (Neal S. Young & Emma M. Groarke) — primary source for definition, classification/aetiology, pathophysiology, Camitta severity, transplant and triple-therapy (ATG/ciclosporin/eltrombopag), androgens and supportive care.
- **CMDT 2026** — "Blood Disorders" (Aplastic Anemia) — current severity definition, drug regimens/doses (equine ATG 40 mg/kg × 4 days, ciclosporin 6 mg/kg BID, eltrombopag 150 mg/day, danazol/fluoxymesterone) and survival figures.
- **Coverage note:** The dedicated specialty text for this spec, *DeVita's Cancer (Principles & Practice of Oncology)*, is an oncology/haematologic-malignancy reference and addresses aplastic anemia only peripherally (as a differential of hypoplastic MDS and via the eltrombopag-immunosuppression trial); the substantive grounding here is therefore Harrison 22e (authored by the world authority on the disease) and CMDT 2026. The VSAA threshold (ANC <200) is universally accepted Camitta-criteria internal medicine and is included as standard.

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Cell cycle and regulation

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

Definition / Introduction — The **cell division cycle** is the ordered, tightly regulated sequence of events by which a cell duplicates its genome and divides into two daughter cells. It comprises four active phases — **G1** (growth/preparation for DNA synthesis), **S** (DNA synthesis), **G2** (preparation to divide) and **M** (mitosis) — together with a quiescent out-of-cycle state, **G0**. Orderly progression is driven by **cyclin–cyclin-dependent kinase (CDK) complexes** and policed at a series of **checkpoints** that verify genomic integrity before allowing the cell to advance. Loss of this control — through activation of positive regulators (oncogenes such as *Ras*, *Myc*, cyclin D) or inactivation of negative regulators (tumour-suppressors *Rb* and *p53*) — produces the deregulated proliferation that is the defining feature of cancer.

Phases of the cell cycle

- **G1 (gap 1):** the cell grows, senses growth-factor and nutrient signals, and takes "inventory" — Is the DNA-repair machinery in place? Are nucleotides, replicating enzymes and energy adequate? A late-G1 point of no return, the **restriction (R) point**, commits the cell irreversibly to division; beyond it the cell no longer needs external mitogens.
- **S (synthesis):** semiconservative replication; each segment of DNA must be copied **once and only once**.
- **G2 (gap 2):** the cell confirms faithful, complete duplication and synthesises the mitotic spindle and proteins needed to produce two daughter cells.
- **M (mitosis):** prophase → metaphase → anaphase → telophase + cytokinesis; chromosomes segregate to opposite poles.

- **G0 (quiescence):** a reversible resting state outside the cycle, maintained by signals including **Notch** and **STING** pathways; cells can be recalled into G1 by appropriate mitogenic/tissue-repair signals (e.g., hepatocytes after partial hepatectomy).

The molecular engine — cyclins, CDKs and CDK inhibitors

- **CDKs** are serine/threonine kinases that are catalytically inert until bound by their regulatory **cyclin** partner; the cyclin level oscillates ("cyclic") through the cycle while CDK protein is constant. Sequential cyclin–CDK activation phosphorylates downstream substrates to push the cell forward.
- Activity is opposed by two families of **CDK inhibitors (CKIs)**:
  - **INK4 family** — *p16^INK4a* and *p15^INK4b* — specifically inhibit CDK4/6.
  - **CIP/KIP family** — *p21^Cip1/Waf1*, *p27^Kip1*, *p57^Kip2* — broadly inhibit cyclin–CDK complexes; *p21* is the principal transcriptional effector of p53.

Phase / transition	Cyclin	CDK partner	Key action
Mid–late G1	Cyclin **D**	**CDK4 / CDK6**	Initial phosphorylation (inactivation) of Rb
G1 → S	Cyclin **E**	**CDK2**	Completes Rb inactivation; fires the R point
S	Cyclin **A**	**CDK2**	Drives/limits DNA replication
G2 → M	Cyclin **A / B**	**CDK1 (Cdc2)**	Triggers mitotic entry

Cell-cycle checkpoints — the quality-control machinery

Checkpoints are surveillance circuits that arrest the cycle until prerequisites are met; the critical proteins controlling them are frequently the **tumour-suppressor genes** mutated in cancer.

- **G1/S (restriction) checkpoint:** decides whether the cell is fit to replicate. When ready, cyclin D–CDK4/6 then cyclin E–CDK2 **phosphorylate Rb**, releasing the transcription factor **E2F/DP1**, which switches on S-phase genes. If not ready, CKIs (*p21*, *p16*, *p27*) block the CDKs. *Nearly every cancer has a defect in the G1 checkpoint.*
- **Intra-S checkpoint:** slows replication when DNA damage is sensed, allowing repair.
- **G2/M checkpoint:** verifies that DNA is fully and accurately replicated before mitosis. DNA damage activates the **ATM/ATR → Chk1/Chk2 → p53** axis (and WEE1 kinase, which restrains CDK1); damaged cells are held in G2.
- **M-phase spindle (spindle-assembly) checkpoint:** ensures every chromosome is correctly attached to the mitotic spindle before anaphase. Failure permits **aneuploidy** (abnormal chromosome number), a frequent feature of cancers.

The two master tumour-suppressors — Rb and p53

- **Retinoblastoma protein (Rb)** is the molecular "brake" at G1/S. In its hypophosphorylated state it sequesters **E2F/DP1**; CDK-mediated hyperphosphorylation releases E2F and licenses S-phase entry. Rb is inactivated in cancer by mutation/deletion (RB1 on **13q14**), by CDK4/6 hyperactivity, by loss of *p16^INK4a*, or by viral oncoproteins. Per **Knudson's two-hit hypothesis**

(derived from inherited vs sporadic retinoblastoma), **both alleles** of a tumour-suppressor must be inactivated; germline carriers inherit one "hit" and need only one somatic event, explaining earlier and multiple tumours.

- **p53 — "guardian of the genome"** — a transcription factor normally kept at very low levels by **MDM2** (an E3 ubiquitin ligase that both blocks p53 transactivation and targets it for proteasomal degradation). Two activating circuits:
  - **DNA-damage checkpoint:** ATM/ATR and Chk1/Chk2 **phosphorylate p53 and MDM2**, dissociating them; stabilised p53 then drives **cell-cycle arrest** (via *p21*), **DNA repair**, or, if damage is irreparable, **apoptosis** (via pro-apoptotic Bcl-2 members *Noxa* and *Puma*). Inducers include hypoxia, ionising/UV radiation, chemotherapy, ribonucleotide depletion and telomere shortening.
  - **Oncogene checkpoint:** hyperproliferative oncogenes (*Myc*, *E2F*) induce **p14^ARF**, which binds MDM2 and rescues p53 — eliminating "renegade" cells by senescence or apoptosis.
- **Clinical correlates of p53:** *TP53* on **17p** is among the most commonly mutated genes in human cancer; germline mutation causes **Li–Fraumeni syndrome**; aflatoxin produces a signature **codon 249 Arg→Ser** mutation in hepatocellular carcinoma; **HPV E6** degrades p53 and **HPV E7** inactivates Rb — together required for epithelial transformation.

Replicative senescence, telomeres and loss of apoptosis

- Normal somatic cells divide only **~25–50** population doublings, then enter **replicative senescence** (irreversible growth arrest, cells remaining viable) — a tumour-protective mechanism mediated by the **Rb, p16^INK4a and p53** pathways.
- Each S phase fails to copy chromosome tips, so **telomeres** (tandem **TTAGGG** repeats; ~15–20 kb at birth, forming a protective T-loop) shorten progressively; critically short telomeres trigger a p53-dependent damage response. **>90% of human cancers re-express telomerase** (catalytic subunit **hTERT** + RNA template) to maintain telomeres and achieve replicative immortality. *Germline telomerase defects cause dyskeratosis congenita.*
- Cancer cells also subvert **programmed cell death**: the **intrinsic (mitochondrial)** pathway — cytochrome c/SMAC release, APAF-1/caspase-9 activation, governed by the **Bcl-2 family** balance — and the **extrinsic (death-receptor)** pathway — Fas/DR4/DR5 → FADD → caspase-8. Overexpression of antiapoptotic **Bcl-2** or loss of p53 lets genetically damaged cells survive and accumulate further mutations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Circular cell-cycle map:** draw the ring G1 → S → G2 → M with **G0** branching off G1. Label the **restriction point** in late G1; mark the **G1/S**, **intra-S**, **G2/M** and **M (spindle)** checkpoints; annotate each segment with its cyclin–CDK pair (**Cyclin D–CDK4/6**, **Cyclin E–CDK2**, **Cyclin A–CDK2**, **Cyclin B–CDK1**) and the CKIs (**INK4**, **CIP/KIP**).
- **Rb/p53 control circuit:** boxes for **Cyclin D–CDK4/6 → P-Rb → release of E2F/DP1 → S-phase genes**, with *p16* inhibiting CDK4/6; and a parallel limb **DNA damage → ATM/ATR → Chk1/Chk2 → p53 ⊣ MDM2 → p21 (arrest) / Noxa-Puma (apoptosis)**, with *p14ARF* linking oncogenes to MDM2.

Clinical / Diagnostic significance

- **Therapeutic exploitation: CDK4/6 inhibitors** — *palbociclib, ribociclib, abemaciclib* — combined with endocrine therapy markedly improve progression-free survival in **ER-positive/HER2-negative metastatic breast cancer** (e.g., palbociclib + letrozole in PALOMA-2); intact **RB1** is required for response, and *RB1* loss confers resistance.
- **Disease associations: Cyclin D1 (CCND1)** overexpression from **t(11;14)** defines **mantle cell lymphoma**; *CDKN2A (p16)* deletion/methylation is common across many tumours; **CDK4 amplification** characterises well-/de-differentiated liposarcoma.
- **Checkpoint as a drug target: WEE1 inhibitors** (e.g., adavosertib) are synthetically lethal in *TP53*-deficient tumours (which rely on the G2/M checkpoint); **PARP inhibitors** exploit DNA-repair defects (BRCA1/2); proteasome inhibitors (bortezomib) raise p21/p27 and induce arrest/apoptosis in myeloma.
- **Proliferation markers: Ki-67** indexes the growth fraction; tumours grow by **Gompertzian kinetics** (growth fraction falls from 100% to <5% by presentation), explaining chemo-responsiveness and dose-limiting marrow/gut toxicity.

High-yield exam pointers

- Four active phases **G1–S–G2–M** + quiescent **G0**; commitment occurs at the **restriction point** in late G1.
- **Cyclins** (oscillating) activate **CDKs** (constant); pairs: D–CDK4/6, E–CDK2, A–CDK2, B–CDK1.
- CKIs: **INK4** (p16, p15) inhibit CDK4/6; **CIP/KIP** (p21, p27, p57) inhibit broadly; **p21** is the p53 effector.
- Checkpoints: **G1/S (Rb–E2F)**, **intra-S**, **G2/M (p53, ATM/ATR–Chk, WEE1)**, **M spindle-assembly** (prevents aneuploidy).
- **Rb** = G1/S brake; phosphorylation releases **E2F/DP1**. **Knudson two-hit** for tumour-suppressors (RB1 13q14).
- **p53 = "guardian of the genome"** (17p); MDM2-regulated; ATM/ATR–Chk activate it → *p21* arrest, repair, or *Noxa/Puma* apoptosis; **p14^ARF** = oncogene checkpoint.
- **HPV E6 → p53 degradation; HPV E7 → Rb inactivation**; **Li–Fraumeni** = germline *TP53*; aflatoxin **codon 249**.

- **Telomere shortening (TTAGGG)** limits division; **telomerase/hTERT** reactivated in **>90%** of cancers → immortality.
- Therapeutics: **CDK4/6 inhibitors (palbo/ribo/abemaciclib)** in ER+ breast cancer; **WEE1** and **PARP** inhibitors exploit checkpoint/repair defects.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cancer Cell Biology" (cell-cycle phases and checkpoints, Rb–E2F, p53/MDM2/p14ARF, ATM/ATR–Chk, spindle checkpoint, senescence/telomerase, apoptosis) and "Cancer Genetics" (Knudson two-hit hypothesis, tumour-suppressor biallelic inactivation).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — CDK4/6–cyclin D–RB1–E2F axis, *CDKN2A/CCND1/CCNE1*, Cyclin E–CDK2/Cyclin B–CDK1, CDK4/6 inhibitors (palbociclib/ribociclib/abemaciclib, PALOMA-2), WEE1 inhibition and synthetic lethality, mantle-cell t(11;14).
- **Coverage note:** The corpus is rich on checkpoint and Rb/p53 biology. The full per-phase cyclin–CDK pairing table (Cyclin A–CDK2, Cyclin B–CDK1) is standard, universally-accepted cell biology; the corpus explicitly names cyclins A, B, D, E and CDK1/2/4/6 and the Cyclin D–CDK4/6, Cyclin E–CDK2 pairings, but does not tabulate every pairing. *p57^Kip2* is included as a standard CIP/KIP member though the corpus names principally p21 and p27.

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Coagulation cascade

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

Definition / Introduction — The **coagulation cascade** is the sequence of reactions in which inactive plasma clotting factors (zymogens) are converted, in an amplifying, enzyme-driven chain, into active serine proteases that culminate in **thrombin** generation and the conversion of soluble **fibrinogen** to an insoluble **fibrin** clot. Originally described as a *waterfall* or *cascade* (Macfarlane; Davie & Ratnoff, 1964) with separate **extrinsic** and **intrinsic** limbs converging on a **common pathway**, it is now understood that *in vivo* coagulation is initiated by **tissue factor (TF)** exposure with critical amplification through intrinsic-pathway elements. It operates on activated, phospholipid (anionic) cell membranes, requires **calcium (factor IV)**, and is one arm of secondary hemostasis (fibrin formation), distinct from primary hemostasis (platelet plug).

Classification of clotting factors

- **Nomenclature:** Factors are numbered I–XIII (Roman numerals); the activated form carries the suffix *"a"* (e.g., factor Xa). There is no factor VI.
- **Functional groups:**

Group	Factors	Key feature
Fibrinogen / thrombin-sensitive group	I (fibrinogen), V (*proaccelerin*, labile), VIII (*antihaemophilic factor*), XIII (*fibrin-stabilising factor*)	Consumed in clotting; V & VIII are cofactors activated by thrombin
Prothrombin / vitamin K–dependent group	II (prothrombin), VII (*proconvertin*), IX (*Christmas factor*), X (*Stuart-Prower factor*)	Need vitamin K for γ-carboxylation; also anticoagulant proteins C, S, Z
Contact group	XII (*Hageman*), XI, prekallikrein (PK), high-molecular-weight kininogen (HMWK)	Initiate intrinsic limb *in vitro*
Cofactors	Tissue factor (III), Ca^{2+} (IV), V, VIII	Accelerate but are not enzymes

- **Vitamin K dependence:** Factors **II, VII, IX, X** and the natural anticoagulants **protein C, protein S, protein Z** require vitamin K–dependent **γ-glutamyl carboxylation** of glutamic acid residues (→ Gla residues), a step essential for **Ca^{2+}-mediated binding to phospholipid surfaces**. Warfarin inhibits **vitamin K epoxide reductase (VKORC1)**, depleting reduced vitamin K (Fig. 121-3).
- All coagulation factors are **synthesised in the liver** (TF and VWF are extrahepatic); hepatic failure → combined factor deficiencies.

The cascade: extrinsic, intrinsic & common pathways

- **Extrinsic (TF) pathway — physiologic initiator:** Vascular injury exposes blood to **tissue factor**, constitutively expressed on subendothelial smooth-muscle cells/fibroblasts (also on circulating microparticles). TF binds **factor VIIa**; the **TF/VIIa complex** activates **factor X → Xa** directly, and also activates **factor IX → IXa** (indirect route). Tested by the **PT**.
- **Intrinsic (contact) pathway:** *In vitro* begins with **factor XII, prekallikrein, HMWK** on a negatively charged surface → XIIa → activates XI → XIa → IXa (with VIIIa cofactor) → Xa. Tested by the **aPTT**. *In vivo* the contact factors are dispensable — **factor XII deficiency causes a long aPTT but NO bleeding**; physiologically **factor XI is activated chiefly by thrombin** (positive feedback), so XIa amplifies/propagates rather than initiates.
- **Common pathway: Factor Xa**, with cofactor **Va** on phospholipid (the *prothrombinase complex*), converts **prothrombin (II) → thrombin (IIa)**. Thrombin then cleaves **fibrinogen → fibrin monomer**, which polymerises; **factor XIIIa** (activated by thrombin) covalently **cross-links** fibrin to a stable clot. Tested by aPTT *and* PT; the fibrinogen→fibrin step by the **thrombin time (TT)**.
- **Thrombin — the pivotal protease (central amplifier):** Beyond cleaving fibrinogen, thrombin feeds back to activate **FV→Va, FVIII→VIIIa, FXI→XIa, and FXIII→XIIIa**, hugely amplifying its own generation; it also activates platelets and protein C.
- **Modern *in vivo* (cell-based) view** — three overlapping phases on cell surfaces:
- **Initiation:** TF/VIIa on TF-bearing cells generates small amounts of Xa and thrombin.
- **Amplification:** Trace thrombin activates platelets and cofactors V, VIII, XI on the platelet surface.
- **Propagation:** The **"tenase" (IXa/VIIIa)** and **"prothrombinase" (Xa/Va)** complexes assemble on activated platelet phospholipid → a **thrombin burst** → robust fibrin clot.

- **Key insight (Harrison):** Once TF/VIIa/Xa forms, **TFPI shuts off the TF/VIIa trigger**, making sustained coagulation dependent on the **amplification loop via factors XI, IX and VIII** — explaining why severe FVIII/FIX deficiency (haemophilia) bleeds despite an intact extrinsic start.

Natural anticoagulant (antithrombotic) mechanisms

Physiologic inhibitors localise clotting to the site of injury and preserve fluidity:

- **Antithrombin (AT):** Major plasma inhibitor of **thrombin and other serine proteases (Xa, IXa, XIa, XIIa)**; forms a 1:1 covalent complex. Its rate is accelerated **several-thousand-fold by heparin / endothelial heparan sulfate** — the basis of heparin action. Deficiency → lifelong VTE risk.
- **Protein C – protein S system:** Thrombin bound to endothelial **thrombomodulin** (with **endothelial protein C receptor, EPCR**) activates **protein C → activated protein C (APC)**; APC, with cofactor **protein S**, proteolytically **inactivates FVa and FVIIIa** (Fig. 69-3). A point mutation at the APC cleavage site in FVa (**factor V Leiden**) confers **APC resistance** and a hypercoagulable state.
- **Tissue factor pathway inhibitor (TFPI):** Inhibits the **TF/VIIa/Xa** complex, switching off extrinsic initiation; partly released from endothelium by heparin.
- **Endothelial antithrombotic products:** prostacyclin (PGI_2), nitric oxide, ecto-ADPase/**CD39** (inhibit platelets), plus heparan proteoglycans and thrombomodulin.

The fibrinolytic system

- **Plasmin** is the key fibrinolytic protease, generated from **plasminogen** by **tissue plasminogen activator (tPA)** and **urokinase (uPA)**, which cleave the **Arg560-Val561** bond.
- **Fibrin specificity:** Lysine-binding sites let plasminogen and tPA bind fibrin, forming a ternary (fibrin–plasminogen–tPA) complex that localises and accelerates plasmin generation on the clot.
- **Products:** Plasmin digests fibrin → **fibrin degradation products (FDPs)**; lysis of *cross-linked* fibrin releases **d-dimers** (specific marker of clot turnover; used to exclude DVT/PE; rises with age → age-adjusted cut-offs).
- **Regulation (three levels):** (1) **PAI-1 and PAI-2** inhibit tPA/uPA; (2) **TAFI** (thrombin-activatable fibrinolysis inhibitor) removes terminal lysines and limits lysis; (3) **α_2-antiplasmin** inactivates free plasmin.

Laboratory assessment of the cascade

Test	What it measures	Prolonged in
PT / INR	Extrinsic + common: I, II, V, VII, X	FVII deficiency, **warfarin**, early vitamin K deficiency, liver disease, direct Xa inhibitors (may be normal on apixaban)
aPTT	Intrinsic + common: XII, XI, IX, VIII, X, V, II, I, PK, HMWK	Haemophilia A/B, **heparin**, lupus anticoagulant, FXI/XII deficiency, vWD
Thrombin time (TT)	Fibrinogen → fibrin	Heparin, **direct thrombin inhibitors (dabigatran, argatroban, bivalirudin)**, dys-/afibrinogenaemia

Test	What it measures	Prolonged in
Reptilase time	Fibrinogen → fibrin (heparin-insensitive)	Dysfibrinogenaemia (normal with heparin)
Clot solubility	Fibrin cross-linking	**Factor XIII deficiency**

- **INR = (PT_patient / PT_mean-normal)^ISI**, where ISI = International Sensitivity Index; standardises warfarin monitoring across thromboplastins.
- **Mixing study:** Patient plasma + normal plasma 1:1. **Corrects** → factor deficiency; **fails to correct** → inhibitor (e.g., lupus anticoagulant, acquired FVIII inhibitor — the latter prolongs further on 37 °C incubation).
- Anti-Xa assay monitors LMWH/UFH and direct Xa inhibitors; **bleeding time is no longer recommended** for predicting bleeding risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — The coagulation cascade (Y-shaped scheme).** Left limb labelled *Intrinsic (contact) pathway*: **XII → XIIa** (with **PK, HMWK**) → **XI → XIa → IX → IXa**; right limb *Extrinsic pathway*: **Tissue factor + VIIa**. Both converge on **X → Xa** (*common pathway*); show **VIIIa** (tenase cofactor) and **Va** (prothrombinase cofactor) on a **phospholipid + Ca^{2+}** surface; then **Prothrombin (II) → Thrombin (IIa) → Fibrinogen (I) → Fibrin → (XIIIa) cross-linked fibrin clot**. Bracket the **aPTT** over the intrinsic+common limbs and the **PT** over the extrinsic+common limbs; mark **TT** at the fibrinogen→fibrin step.
- **Diagram 2 — Natural anticoagulant loops.** Label **TFPI** (on TF/VIIa/Xa), **antithrombin + heparin** (on thrombin & Xa), and the **thrombomodulin–EPCR → APC + protein S** loop inactivating **FVa/FVIIIa**.

Clinical / Diagnostic significance

- **Pattern recognition:** Isolated ↑**PT** → FVII deficiency/early warfarin; isolated ↑**aPTT** → haemophilia A/B or FXI deficiency (or heparin/lupus anticoagulant); **both** ↑ → deficiency of II, V, X or fibrinogen, late vitamin K deficiency, liver disease, **DIC**.
- **Haemophilia A (FVIII) & B (FIX):** X-linked; severity by factor level — **severe <1%, moderate 1–5%, mild 6–30%**; hallmark **haemarthrosis** and deep-muscle bleeds; treat with factor concentrates, **emicizumab** (bispecific FIXa/FX antibody mimicking FVIIIa), or gene therapy.
- **Acquired coagulopathies:** liver disease (combined deficiency + thrombocytopenia), **vitamin K deficiency/warfarin** (factors II, VII, IX, X), and **DIC** (consumption → ↑PT/aPTT, ↓fibrinogen, ↓platelets, ↑d-dimer).
- **Reversal/replacement: 4-factor PCC** (II, VII, IX, X + proteins C & S) for warfarin reversal; **FFP, cryoprecipitate** (fibrinogen, VIII, XIII, VWF); **FXIII concentrate** for FXIII deficiency.
- **Thrombophilia:** Factor V Leiden, prothrombin **G20210A**, and deficiencies of **antithrombin, protein C, protein S** predispose to VTE; test only when results change management, in steady state off anticoagulants.

High-yield exam pointers

- **Thrombin (IIa)** is the central enzyme — converts fibrinogen→fibrin, activates V, VIII, XI, XIII, platelets and protein C.
- *In vivo* the cascade is **TF-initiated**; the intrinsic limb chiefly **amplifies** — hence **FXII deficiency = long aPTT but no bleeding**.
- **Vitamin K–dependent factors: II, VII, IX, X + proteins C, S, Z** (mnemonic "1972 → 2,7,9,10").
- **FVII** has the **shortest half-life** → PT/INR is the earliest test to prolong with warfarin/vitamin K deficiency.
- **PT = extrinsic; aPTT = intrinsic; both = common pathway; TT = fibrinogen→fibrin.**
- **Factor XIII** is *not* detected by PT/aPTT — diagnose by **clot solubility (urea)**.
- **APC resistance = factor V Leiden** is the commonest inherited thrombophilia.
- **d-dimer** = lysis of cross-linked fibrin; sensitive for excluding VTE, not specific.
- **Mixing study corrects** = deficiency; **does not correct** = inhibitor.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Bleeding and Thrombosis"* (steps of haemostasis, the TF-initiated cascade with intrinsic amplification, antithrombotic mechanisms, fibrinolytic system, and laboratory evaluation incl. PT/aPTT/TT/INR and mixing studies) and *"Coagulation Disorders"* (Fig. 121-1 cascade with aPTT/PT/TT mapping, vitamin K cycle Fig. 121-3, factor groups, haemophilia, PCC composition).
- **CMDT 2026** — *Blood Disorders* (current laboratory/management framing).
- *Coverage note:* The Harrison corpus presents the cascade physiology, natural anticoagulants and fibrinolysis in full; classical factor **eponyms/synonyms** (Christmas, Stuart-Prower, Hageman, etc.) and the **three-phase cell-based model (initiation/amplification/propagation)** are universally accepted standard haematology nomenclature added for completeness, consistent with Harrison's TF-initiation-plus-amplification description. The spec's DeVita reference (heme malignancies) is peripheral to cascade physiology and was not required.

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Erythropoiesis — polycythaemia rubra vera

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

Definition / Introduction — **Erythropoiesis** is the regulated process of red cell production within the **erythron** — the dynamic "organ" comprising the rapidly proliferating pool of marrow erythroid precursors plus the large mass of circulating red cells. It begins with the pluripotent **haematopoietic stem cell (HSC)** and is driven principally by the hormone **erythropoietin (EPO)** so that tissue oxygen delivery is matched to demand. **Polycythaemia rubra vera (PV)** — polycythaemia *vera* — is a clonal HSC (myeloproliferative) neoplasm in which phenotypically normal red cells, granulocytes and platelets accumulate **in the absence of a recognisable physiologic stimulus**, almost always driven by a *JAK2* mutation.

Erythropoiesis — lineage, cell sequence and kinetics

- **Haematopoiesis** produces all formed elements from the HSC, which can generate red cells, all granulocytes, monocytes, platelets and immune cells. Erythroid cells arise from a **common erythroid/megakaryocytic progenitor** whose development requires the transcription factors **GATA-1** and **FOG-1** (friend of GATA-1).
- After lineage commitment, progenitors fall progressively under the control of growth factors/hormones; **EPO is the primary regulatory hormone**. EPO maintains committed erythroid progenitors, which **undergo apoptosis (programmed cell death) in its absence**.
- The first morphologically recognisable erythroid precursor is the **pronormoblast (proerythroblast)**; it undergoes **four to five cell divisions**, yielding **16–32 mature red cells** per pronormoblast.
- The mature red cell is **8 µm**, **anucleate**, **biconcave/discoid** and highly pliable; the biconcave disc maximises surface area for oxygen exchange and membrane integrity is sustained by **intracellular ATP**.
- **Kinetics:** normal production replaces **0.8–1% of circulating red cells daily**, since the average red cell survives **100–120 days**. Marrow cellularity is expressed as the **myeloid:erythroid (M:E) ratio, normally ~2.5:1 (range 2:1–5:1)**.
- The **reticulocyte** (residual ribosomal RNA, seen as *polychromasia* on Wright–Giemsa) is the youngest red cell released; the **reticulocyte count is the clinical marker of effective erythropoiesis** — high with haemolysis/blood loss, low/inappropriate with hypoproliferative marrow.

Erythropoietin and oxygen-sensing regulation (HIF axis)

- EPO is a **glycoprotein hormone** produced and released by **peritubular capillary lining (interstitial) cells of the kidney**, with a small contribution from **hepatocytes**.
- The **fundamental stimulus is oxygen availability** for tissue metabolism. The master regulator is **hypoxia-inducible factor-1α (HIF-1α)**:
  - In **normoxia**, HIF-1α is **hydroxylated at a key proline**, ubiquitinated and degraded by the **proteasome** → low EPO.
  - In **hypoxia**, hydroxylation fails → HIF-1α partners with other proteins, **translocates to the nucleus and upregulates the EPO gene**.

- Impaired renal O_2 delivery (and hence ↑EPO) results from **decreased red cell mass (anaemia)**, **impaired O_2 loading of haemoglobin/hypoxaemia**, a **high-O_2-affinity haemoglobin**, or **reduced renal blood flow** (e.g., renal artery stenosis).
- Normal plasma EPO is **10–25 U/L**; when haemoglobin falls below **100–120 g/L (10–12 g/dL)**, EPO rises logarithmically in proportion to anaemia severity. EPO **half-life is 6–9 h**.
- EPO binds receptors on marrow erythroid precursors → proliferation and maturation; with stimulation, **red cell output can increase 4–5 fold over 1–2 weeks**, but only if substrate is adequate.
- An effective erythron therefore requires **(1)** normal renal EPO production, **(2)** a functioning erythroid marrow, and **(3)** adequate substrate — **iron, vitamin B12 and folate**.

Polycythaemia — definition and classification

- **Polycythaemia** = haemoglobin above normal; *erythrocytosis* strictly implies a **documented increase in red cell mass**. A rise may be **real (absolute)** or **apparent (relative/spurious)** from plasma volume contraction.
- Thresholds prompting concern: **Hb >17 g/dL (men) / >15 g/dL (women)**; **Hct >50% (men)/>45% (women)** may be abnormal; **Hct >60% (men)/>55% (women)** almost invariably reflects a raised red cell mass. Red cell mass **<36 mL/kg (men) / <32 mL/kg (women)** indicates spurious polycythaemia.

Category	Mechanism	Examples
Relative / spurious	↓ plasma volume, normal red cell mass	Dehydration, diuretics, alcohol/tobacco; **Gaisböck's syndrome (stress erythrocytosis)**
Primary	Intrinsic clonal marrow defect; **EPO low/normal**	**Polycythaemia vera**; EPO-receptor mutation; familial polycythaemia
Secondary — appropriate EPO	Tissue hypoxia → physiologic ↑EPO	High altitude, chronic lung disease, sleep apnoea, cyanotic heart disease, **CO poisoning ("smoker's polycythaemia")**, high-O_2-affinity haemoglobinopathy
Secondary — inappropriate EPO	Autonomous/ectopic EPO; HIF-pathway defects	Renal cysts/artery stenosis, post-transplant; tumours — **hypernephroma, hepatoma, cerebellar haemangioblastoma, uterine myoma, phaeochromocytoma**; **Chuvash polycythaemia** (VHL), **PHD2/EGLN1**, **HIF-2α/EPAS1** mutations; exogenous androgens, recombinant EPO, **SGLT2 inhibitors**

Polycythaemia rubra vera — pathogenesis and clinical features

- **Pathogenesis:** PV is the **commonest myeloproliferative neoplasm**, incidence **~2.5/100,000** (rising with age to >10/100,000). The central lesion is a mutation (**V617F** — valine→phenylalanine) in the **autoinhibitory pseudokinase domain of *JAK2***, causing **constitutive kinase activation**.
- *JAK2* is the cognate non-receptor tyrosine kinase for the **EPO and thrombopoietin receptors**. Constitutive activation produces **EPO hypersensitivity, EPO-independent erythroid colony formation, ↑Bcl-XL and apoptosis resistance**.

- **>95% of PV patients carry JAK2 V617F**; most of the remainder carry **exon 12 mutations**. *JAK2* lies on chromosome **9p**; uniparental disomy causing **homozygosity for V617F** occurs in ~60% of PV. Non-random cytogenetic changes (del 20q, del 13q, trisomy 9) occur in up to 30%.
- **Clinical features** — PV is a *panmyelopathy*; presentation is often an **incidental high Hb/Hct/red cell count**:
  - **Hyperviscosity:** vertigo, tinnitus, headache, visual disturbance, **TIAs**; systolic hypertension; *ruddy* (plethoric) complexion.
  - **Thrombosis (arterial & venous)** — the dominant complication; cerebral, cardiac and mesenteric vessels; **Budd–Chiari (hepatic vein) thrombosis**, classically in young women (the only thrombosis specifically linked to JAK2 V617F); **portal vein thrombosis** commoner in men.
  - **Bleeding:** easy bruising, epistaxis, GI haemorrhage; extreme thrombocytosis (>900,000/μL) causes **acquired von Willebrand's disease**.
  - **Erythromelalgia** (erythema, burning, pain of digits ± infarction), **aquagenic pruritus**, splenomegaly, peptic ulcer disease, and **hyperuricaemia → secondary gout / uric acid stones**.

PV — diagnosis

- Diagnosis is straightforward when **erythrocytosis coexists with leukocytosis, thrombocytosis or splenomegaly**. With isolated red cell elevation it is harder, because in PV the **plasma volume expands and can mask a raised red cell mass** (especially in women) — true erythrocytosis cannot be reliably separated from plasma contraction unless **Hb ≥20 g/dL (Hct ≥60%)**.
- **Serum EPO** is the pivotal screening test: **low/unmeasurable EPO favours PV**, whereas an **elevated EPO points to a secondary cause**.
- **Quantitative *JAK2* V617F / exon 12 assay by next-generation sequencing** is now the confirmatory test and has superseded surrogate tests. Supportive findings: **leukocytosis, raised absolute basophil count, thrombocytosis**.
- Only **three causes** produce a **microcytic erythrocytosis**: **β-thalassaemia trait, hypoxic erythrocytosis and PV** (the latter two via associated iron deficiency, with raised RDW). Bone marrow aspirate/biopsy is **non-specific** (may resemble ET/PMF).
- *Standard add (WHO 2016 criteria, not detailed in the provided text):* Hb >16.5 g/dL (men)/>16.0 g/dL (women) or raised red cell mass + trilineage marrow panmyelosis + *JAK2* mutation, with **subnormal serum EPO** as a minor criterion.

PV — management

- PV is **indolent** (course measured in decades); **thrombosis from erythrocytosis is the most significant complication**, so red cell mass control is mandatory.

Modality	Role / target
Phlebotomy	First-line; maintain **Hct <45% (men)/<42% (women)** [Hb ≤14 / ≤12 g/dL]; induces iron deficiency limiting re-expansion — usually only **every ~3 months** once iron-deplete
Low-dose aspirin (salicylate)	Reduces thrombosis — **only if red cell mass is controlled**; risk of bleeding (esp. age >60) if uncontrolled

Modality	Role / target
Anticoagulation	After a thrombotic event; newer oral anticoagulants preferred (no monitoring)
Hydroxyurea	Cytoreduction; does **not** target the malignant HSC and is **mutagenic/leukemogenic** — short-course
Pegylated interferon-α	Targets involved HSC, non-mutagenic; ~20% complete haematologic/molecular remission
Ruxolitinib (JAK1/2 inhibitor)	Refractory pruritus, symptomatic splenomegaly (replaces splenectomy)
Anagrelide	Lowers platelets (PDE inhibitor); marrow-sparing but cardiotoxic/nephrotoxic in elderly
Allopurinol	Hyperuricaemia when cytoreduction is used; tranexamic/ε-aminocaproic acid for vWD-related bleeding

- **Avoid** alkylating agents and radioactive ^{32}**P** — strongly leukaemogenic.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Erythropoiesis pathway (vertical flow):** *HSC → common myeloid progenitor → BFU-E → CFU-E → Pronormoblast → basophilic normoblast → polychromatophilic normoblast → orthochromatic normoblast → Reticulocyte → Mature RBC*. **Side-label:** EPO **acting at CFU-E/pronormoblast;** GATA-1/FOG-1** at commitment; "16–32 RBC per pronormoblast"; "lifespan 100–120 days".
- **Diagram 2 — Renal O_2-sensing/EPO feedback loop:** labels *Tissue hypoxia → Kidney (peritubular cells) → HIF-1α stabilised → ↑EPO → Erythroid marrow → ↑Red cell mass → ↑O_2 delivery → (negative feedback) → HIF-1α hydroxylated/degraded*.

Clinical / Diagnostic significance

- **Serum EPO + JAK2 mutation** together separate PV (low EPO, JAK2+) from secondary polycythaemia (high EPO) — order both simultaneously.
- A **"normal" Hct in a PV patient with massive splenomegaly** should be assumed to mask a raised red cell mass until proven otherwise.
- **Suspect PV in any patient (esp. a young woman) with Budd–Chiari/splanchnic vein thrombosis**, aquagenic pruritus or erythromelalgia.
- The **reticulocyte count** triages anaemia (high = haemolysis/blood loss; low = hypoproliferative) and reflects EPO-driven erythropoiesis — the mirror image of the polycythaemia work-up.

High-yield exam pointers

- **EPO source = renal peritubular interstitial cells**; master switch = **HIF-1α** (degraded in normoxia via proline hydroxylation).
- **Pronormoblast → 4–5 divisions → 16–32 RBCs**; RBC lifespan **100–120 days**; daily turnover **0.8–1%**; normal **M:E ratio 2.5:1**.
- Normal EPO **10–25 U/L**; rises once Hb <10–12 g/dL; half-life **6–9 h**.

- **PV = JAK2 V617F (>95%)**, exon 12 in most others; **low/absent serum EPO** is the hallmark.
- **Hct targets: <45% men / <42% women**; phlebotomy + low-dose aspirin are first-line.
- **Budd–Chiari** is the thrombosis specifically tied to JAK2 V617F.
- Only **3 causes of microcytic erythrocytosis**: **β-thalassaemia trait, hypoxic erythrocytosis, PV**.
- **Avoid ^{32}P / alkylators** (leukaemogenic); hydroxyurea is short-course; **pegIFN-α and ruxolitinib** target the disease clone.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 66 "Anemia and Polycythemia"** (erythropoiesis, EPO/HIF regulation, definition and classification of polycythaemia) and **Ch 108 "Polycythemia Vera and Other Myeloproliferative Neoplasms"** (PV pathogenesis, clinical features, diagnosis, treatment). *Coverage note:* the intermediate erythroid maturation stages (BFU-E/CFU-E, basophilic→orthochromatic normoblast) and the explicit **WHO 2016 diagnostic criteria** are universally accepted standard haematology added for completeness — they are not spelled out verbatim in the provided chapters (which name only the *pronormoblast* and *reticulocyte*, and present a JAK2/EPO-based diagnostic algorithm).

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Vitamin B12 metabolism — neurological manifestations

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

Definition / Introduction — Vitamin **B12 (cobalamin)** is a water-soluble cobalt-containing vitamin synthesised solely by micro-organisms; humans obtain it only from animal foods. It is the obligatory cofactor for just two human enzymatic reactions, yet its deficiency produces both a **megaloblastic anaemia** (defective DNA synthesis) and a distinctive **neurological syndrome** (demyelination), the latter often dominating the picture in the non-anaemic patient. Understanding its metabolism — structure, dietary source, intrinsic-factor–dependent absorption, plasma transport and intracellular function — explains why deficiency develops slowly, why pernicious anaemia is the commonest cause, and how the neuropathy arises.

Structure and biochemical forms

- All cobalamins have a **cobalt atom at the centre of a corrin ring**. They differ only in the upper axial ligand.
- **Adenosylcobalamin (2-deoxyadenosyl / ado-cobalamin)** — the main natural form, located in **mitochondria**; cofactor for **L-methylmalonyl-CoA mutase**.
- **Methylcobalamin** — the predominant form in **human plasma and cell cytoplasm**; cofactor for **methionine synthase**.
- Minor amounts of **hydroxocobalamin** are present; methyl- and ado-cobalamin are converted to it rapidly on exposure to light (relevant to the therapeutic forms used).

Dietary sources, requirement and body stores

Parameter	Value (Harrison 22e)
Source	Synthesised only by micro-organisms; for humans, **animal origin only** — meat, fish, dairy. Plant foods free of B12 unless bacterially contaminated
Dietary content (Western diet)	**5–30 µg/day**
Daily loss / requirement	**1–3 µg/day** (~0.1% of body stores); body cannot degrade cobalamin
Body stores	**2–3 mg**, sufficient for **3–4 years** if intake stops

- Because stores are large and an enterohepatic circulation conserves cobalamin, dietary deficiency (strict vegans) develops only after years; in contrast, **malabsorption** depletes stores faster because biliary reabsorption is also lost.

Absorption (intrinsic-factor pathway)

- Two mechanisms exist: a **passive** route (through buccal, duodenal and ileal mucosa; rapid but very inefficient — <1% of an oral dose) and the physiological **active** route (ileal, **intrinsic-factor dependent**, efficient for small doses).
- Sequential steps of active absorption:

Step	Event
1	Dietary B12 released from protein in stomach/duodenum/jejunum by acid and enzymes
2	Binds salivary **haptocorrin (HC)** in the stomach
3	**Pancreatic trypsin** digests HC in the intestine; B12 transferred to **intrinsic factor (IF)**
4	**IF** (gene at **chromosome 11q13**) is secreted by gastric **parietal cells** (fundus/body); secretion parallels HCl
5	**IF–B12 complex** reaches the ileum and binds the receptor **cubilin** on enterocyte microvilli; cubilin traffics via **amnionless (AMN)**
6	Complex is endocytosed; IF is destroyed; after ~6 h B12 enters portal blood bound to **transcobalamin II**

- **0.5–5 µg** of B12 enters bile daily, binds IF and is largely **reabsorbed (enterohepatic circulation)** together with B12 from sloughed cells.

Plasma transport and cellular uptake

- Two plasma transport proteins each bind B12 one-to-one:
  - **Transcobalamin I (TC I / haptocorrin)** — gene *TCN1* (chr 11); derived mainly from **neutrophil granules**; normally ~two-thirds saturated; does **not** deliver B12 to tissues but carries analogues to the **liver for biliary excretion**.
  - **Transcobalamin II (TC II)** — gene on **chromosome 22q11–q13.1**; synthesised by liver, macrophages, ileum and vascular endothelium; carries only 20–60 ng/L but is the **functional delivery protein**, readily giving up B12 to marrow, placenta and other tissues.

- Cellular uptake of TC II–B12 is by **receptor-mediated endocytosis** via the **TC II receptor** and **megalin (LRP-2 gene)** through clathrin-coated pits; the complex is degraded and free B12 exported via an ABC transporter.

Intracellular biochemical functions (the two B12-dependent reactions)

- **Reaction 1 — Methylmalonyl-CoA → succinyl-CoA** (methylmalonyl-CoA mutase, needs **adocobalamin**). Block raises **methylmalonic acid (MMA)** — the basis of the MMA diagnostic test and a contributor to neuropathy.
- **Reaction 2 — Homocysteine → methionine** (methionine synthase, needs **methylcobalamin** + **5-methyl-THF**). This is the first step that regenerates intracellular **tetrahydrofolate (THF)** and produces **methionine → S-adenosylmethionine (SAM)**, the universal methyl donor for >100 methyltransferase reactions (including myelin lipids, myelin basic protein and DNA).
- **Methylfolate trap ("THF starvation"):** in B12 deficiency, 5-MTHF cannot be demethylated, so it accumulates in plasma while intracellular folate falls — explaining the **megaloblastic anaemia** and why it partially responds to large doses of folic acid (which must not be given alone, as it masks anaemia while neuropathy progresses).

Neurological manifestations of B12 deficiency (brief)

- Cobalamin is required for **myelination of the CNS**; deficiency causes demyelination.
- **Subacute combined degeneration (SCD) of the spinal cord** is the hallmark: **demyelination of the posterior (dorsal) columns and lateral (pyramidal) tracts** of the cervical and thoracic cord; MRI may show **"spongy" degeneration**.
- **Bilateral peripheral neuropathy** — symmetrical glove-and-stocking **paraesthesiae**, often the earliest symptom.
- **Posterior-column signs:** loss of **vibration and proprioception (position) sense**, **positive Romberg sign**, **Lhermitte sign**, sensory ataxia.
- **Pyramidal (lateral-column) signs:** spastic, ataxic gait with **hyperreflexia** and extensor plantars (a combination of upgoing toes with absent ankle jerks is classic).
- **Autonomic involvement:** postural hypotension, **impotence**, urinary/faecal incontinence.
- **Cerebral / cranial: dementia**, depression, psychotic symptoms, cognitive impairment ("megaloblastic madness"), **optic atrophy**, and **anosmia / loss of taste**; cranial-nerve involvement is less frequent.
- **Infancy:** poor brain and intellectual development, feeding difficulty, lethargy, coma, convulsions and myoclonus.
- Patients are **more often male** and may present with neurological disease **before or without anaemia** — the non-anaemic patient with neuropsychiatric features and a low/borderline serum B12 is an important clinical trap.
- **Proposed mechanism:** the neuropathy correlates with the **defect in homocysteine→methionine conversion**; accumulation of **S-adenosylhomocysteine** in brain inhibits transmethylation, and failure of **SAM**-dependent methylation of biogenic amines (e.g., dopamine), proteins and phospholipids is implicated (the exact biochemical basis "remains obscure"). Importantly, neuropathy can occur **without** methylmalonic aciduria (as in TC II deficiency).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — B12 absorption & transport pathway (flow diagram):** Label — *Dietary B12 (animal food) → Stomach: acid/enzymes + Haptocorrin (HC) → Duodenum: pancreatic trypsin → Intrinsic factor (IF) from gastric parietal cells → IF–B12 complex → Ileum: cubilin–amnionless receptor → enterocyte endocytosis → portal blood → Transcobalamin II (TC II) → tissues (marrow, CNS) via TC II receptor / megalin (LRP-2)*. Side branch: *Bile → enterohepatic recirculation*.
- **Diagram 2 — Spinal cord cross-section in SCD:** Label — *Posterior (dorsal) columns — fasciculus gracilis & cuneatus (demyelinated)*, *Lateral corticospinal (pyramidal) tracts (demyelinated)*, *Anterior columns spared*, *grey matter butterfly*; annotate "cervical & thoracic cord, bilateral, symmetrical."

Clinical / Diagnostic significance

- **Causes of deficiency: pernicious anaemia** (gastric atrophy, anti-IF / anti-parietal-cell antibodies) — commonest; total gastrectomy, ileal resection/Crohn's disease, **strict vegetarianism/veganism**, fish tapeworm (*Diphyllobothrium*), tropical sprue, stagnant-loop syndrome, and drugs — **metformin**, **proton-pump inhibitors / H2-blockers**.
- **Investigations: serum B12** by ELISA/CBLA (normal ≈160–1000 ng/L; deficiency usually <100 ng/L; **false-normal in up to 50% of PA** when anti-IF antibodies interfere). **Serum MMA and homocysteine** are raised and are sensitive early markers (homocysteine alone rises in folate deficiency too; **MMA is specific to B12**). Peripheral film: **oval macrocytes, MCV >100 fL, hypersegmented neutrophils (>5 lobes)**. PA work-up: **anti-IF and anti-parietal-cell antibodies**, raised serum gastrin, low pepsinogen I, endoscopy.
- **Treatment:** parenteral **hydroxocobalamin** (UK) or **cyanocobalamin** (US). Replenishment: **six 1000-µg IM hydroxocobalamin injections at 3–7 day intervals**; maintenance **1000 µg IM every 3 months** (hydroxocobalamin) or **1000 µg cyanocobalamin IM monthly**. High-dose **oral cyanocobalamin (1000–2000 µg/day)** exploits passive absorption. More frequent dosing is used if neuropathy is present.
- **Pearls:** never treat suspected B12 deficiency with **folate alone** (precipitates/worsens SCD). Neurological recovery depends on early treatment — long-standing cord signs may be irreversible. Watch for **hypokalaemia and thrombocytosis** during early response; give aspirin if platelets rise >800 × 10^9/L. Screen for coexisting **iron deficiency** in pernicious anaemia (occurs in 15–20% of those >60 y).

High-yield exam pointers

- B12 = **cobalt in a corrin ring**; only two human reactions need it — **methylmalonyl-CoA mutase (ado-B12)** and **methionine synthase (methyl-B12)**.
- **Body stores 2–3 mg last 3–4 years** → deficiency is slow; faster in malabsorption than in vegans (loss of enterohepatic recycling).
- Absorption chain to memorise: **HC → trypsin → IF (parietal cell) → cubilin/amnionless (ileum) → TC II**.

- **TC II** is the functional delivery protein; **TC I (haptocorrin)** carries analogues for biliary excretion.
- **Methylfolate trap** links B12 deficiency to megaloblastic anaemia and the folate response.
- **SCD = demyelination of dorsal columns + lateral pyramidal tracts** of cervical/thoracic cord.
- Classic sign-set: **absent ankle jerks + extensor plantars**, positive **Romberg** and **Lhermitte**, loss of vibration/position sense.
- **MMA specific for B12; homocysteine raised in both B12 and folate deficiency.**
- **Never give folate alone** — masks anaemia, worsens neuropathy.
- Neuropathy can precede anaemia and may occur with **normal serum B12** (use MMA/homocysteine).

SOURCE & COVERAGE

Harrison 22e — Ch 104 "Megaloblastic Anemias" (cobalamin structure, dietary source, IF-dependent absorption, TC I/TC II transport, the two B12-dependent reactions, methylfolate trap, neurologic manifestations, diagnosis and treatment) + Ch 344 "Vitamin and Trace Mineral Deficiency and Excess" (B12 deficiency clinical features — loss of vibratory/position sense, abnormal gait, dementia, impotence, bladder/bowel involvement, ↑homocysteine/↑MMA — and causes). *Coverage note:* The eponymous physical signs (Romberg, Lhermitte) and the "absent ankle jerks with extensor plantars" combination, plus the explicit term *subacute combined degeneration* and the standard PA causes/drug list, are universally accepted textbook internal medicine used here to satisfy the exam ask; Harrison Ch 104 describes the underlying tract demyelination, positive Romberg/Lhermitte signs and hyperreflexia, and Ch 344 lists the deficiency features verbatim.

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Chronic myeloid leukaemia

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

Definition / Introduction — Chronic myeloid leukemia (**CML**) is a clonal hematopoietic myeloproliferative *stem-cell* neoplasm driven by the **BCR::ABL1** chimeric gene, which encodes a constitutively active tyrosine kinase. It arises from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22, *t(9;22)(q34.1;q11.2)*, cytogenetically recognised as the **Philadelphia (Ph) chromosome**. Untreated, the course is biphasic/triphasic — an indolent **chronic phase**, followed by an **accelerated phase** and a terminal **blastic phase**. The introduction of BCR::ABL1 **tyrosine kinase inhibitors (TKIs)** in 2000 transformed CML from a fatal disease (pre-TKI median survival 3–7 years; 10-year survival ≤30%) to one with a 10-year survival >85%, approaching that of an age-matched population.

Epidemiology and pathophysiology

- CML accounts for **~15% of all leukemias**; male:female **1.6:1**; median age at diagnosis **55–65 years**; only ~3% are <20 years. Annual incidence ~**2 per 100,000**. No familial association; the only established risk factor is **ionizing radiation** exposure.

- The **t(9;22)** is present in >90% of classical CML and occurs in hematopoietic cells but not stromal cells. ABL1 (chr 9) is juxtaposed to the **major breakpoint cluster region (M-BCR)** of *BCR* (chr 22), generating the hybrid oncogene.
- Breakpoint determines transcript and oncoprotein: **M-BCR (e13/e14)** → e13a2 (b2a2)/e14a2 (b3a2) → **p210** (commonest in CML); **m-BCR (e1a2)** → **p190** (two-thirds of Ph-positive ALL; rare in CML; *worse* outcome); **μ-BCR (e19a2)** → **p230** (indolent course).
- p210 has **constitutive kinase activity** → increased proliferation, reduced apoptosis, and growth advantage, suppressing normal hematopoiesis. Signalling proceeds via **RAS, MAP kinases, STAT, PI3K and MYC** through adapter proteins (GRB-2, CRK, CRK-L, SHC). Most TKIs bind the **ATP-binding domain**; **asciminib** uniquely binds the **myristoyl pocket** (*STAMP* — Specifically Targeting the ABL1 Myristoyl Pocket).
- Transformation is associated with **additional chromosomal abnormalities** (double Ph, trisomy 8, isochromosome 17/17p loss of TP53, 3q26) and mutations (*TP53, RB1, RUNX1, ASXL1*). >100 **ABL1 kinase-domain mutations** drive TKI resistance; **T315I** is the "gatekeeper" mutation conferring resistance to imatinib and all second-generation TKIs.

Clinical features and phases

- **~90% present in chronic phase.** In settings with screening, 50–60% are diagnosed incidentally on a routine blood count with minimal symptoms (fatigue).
- Symptomatic disease reflects **anemia and splenomegaly**: fatigue, malaise, weight loss, early satiety, left-upper-quadrant pain. **Splenomegaly is the commonest physical sign** (20–70%); hepatomegaly 5–10%, lymphadenopathy 5%.
- Less common: leukostasis/hyperviscosity from extreme leukocytosis or thrombocytosis (priapism, visual disturbance, MI, CVA, dyspnea); basophilia-related histamine excess (pruritus, flushing, diarrhea, GI ulcers).
- **Phase definitions (key marks):**

Phase	Defining features (Harrison 22e)
Chronic	Blasts ≤5%; controllable counts; >90% present here
Accelerated	≥15% peripheral blasts; ≥30% blasts + promyelocytes; ≥20% peripheral basophils; cytogenetic **clonal evolution** (ACAs other than Ph); platelets <100 × 10^9/L (therapy-unrelated)
Blastic	≥30% blasts in peripheral blood or marrow, **or** sheets of blasts in extramedullary disease

- Blastic phase is **myeloid in ~60%** and **lymphoid in ~25%** (lymphoblasts TdT-positive, peroxidase-negative; CD10/19/20/22, often co-express myeloid markers). The newest WHO classification proposes eliminating "accelerated phase," reclassifying such patients as **high-risk CML**.

Diagnostic approach and investigations

- **Peripheral blood:** leukocytosis (10–500 × 10^9/L), left-shifted granulocytosis with all maturation stages and blasts usually ≤5%; **basophilia/eosinophilia**; thrombocytosis common

(thrombocytopenia suggests acceleration). **Low leukocyte alkaline phosphatase (LAP)** score; high vitamin B_{12}, uric acid, LDH and lysozyme.

- **Bone marrow:** hypercellular with myeloid hyperplasia, **myeloid:erythroid ratio 15–20:1**, blasts ≤5%; reticulin fibrosis (grade 3–4 in 30–40%).
- **Cytogenetics/molecular — confirm the diagnosis:** the diagnosis depends on documenting **t(9;22)** by **G-banding** (positive in ~90%). **FISH** quantifies Ph-positive cells; **RT-PCR** detects/quantifies BCR::ABL1 transcripts (can be done on peripheral blood). Diagnosis should rest on a **marrow with routine cytogenetics** (detects ACAs that FISH misses); the **transcript type must be documented at diagnosis** to avoid spuriously "undetectable" follow-up PCR. ~10% have complex/variant or "masked" Ph; ~5–10% have additional chromosomal abnormalities.
- **Response milestones (standardised on the International Scale, IS) — the basis of monitoring:**

Response	Definition
Partial cytogenetic	≤35% Ph-positive metaphases (≈ IS ≤10%)
Complete cytogenetic (CCyR / **MR2**)	0% Ph-positive (≈ IS ≤1%)
Major molecular (**MMR / MR3**)	BCR::ABL1 (IS) ≤0.1% (≥3-log reduction)
Deep molecular (**DMR / MR4**)	BCR::ABL1 (IS) ≤0.01%
MR4.5	BCR::ABL1 (IS) ≤0.0032% (≥4.5-log reduction)

- **Resistance** = BCR::ABL1 (IS) **>10% at 6 months** or **>1% at ≥12 months**. Pre-TKI prognostic scores (**Sokal, Hasford, EUTOS**) have lost much impact; **achievement of CCyR/MR2** is now the key prognostic endpoint, while MMR/DMR reduces relapse and enables treatment-free remission.

Management — frontline TKI therapy

The goal of management is durable disease control with TKIs; **achievement of CCyR by 12 months** is the principal therapeutic endpoint. Six oral BCR::ABL1 TKIs are FDA-approved.

TKI (brand)	Generation / indication	Frontline dose	Notable toxicities
Imatinib (Gleevec/Glivec)	1st; all phases	400 mg once daily	Fluid retention, periorbital edema, myelosuppression, rashes, cramps
Dasatinib (Sprycel)	2nd; all phases	100 mg daily (50 mg as effective, less toxic)	**Pleural/pericardial effusions, pulmonary hypertension**, myelosuppression
Nilotinib (Tasigna)	2nd; all phases except blastic	300 mg twice daily (empty stomach)	Hyperglycemia, pancreatitis, **arterio-occlusive events**, hypertension, QT/hyperbilirubinemia
Bosutinib (Bosulif)	2nd; all phases	400 mg daily (with dose escalation)	Diarrhea/colitis, liver and renal toxicity

TKI (brand)	Generation / indication	Frontline dose	Notable toxicities
Ponatinib (Iclusig)	3rd; **T315I**, failure of ≥2 TKIs	45 mg daily (reduce to 15 –30 mg on response)	Highest **arterio-occlusive events**, hypertension (50–60%), pancreatitis
Asciminib (Scemblix)	3rd (**STAMP** inhibitor); third-line, T315I	40 mg twice daily or 80 mg daily; T315I 200 mg twice daily	Generally well tolerated

- **All four of imatinib, dasatinib, bosutinib and nilotinib are acceptable frontline.** Second-generation TKIs give faster/deeper molecular responses (ENESTnd, DASISION, BFORE) and lower early transformation, but **no overall-survival advantage** over imatinib. Choice is individualised by: (1) **treatment aim** (survival vs treatment-free remission, linked to age); (2) **cost/affordability** (generic imatinib ~US$500/year); (3) **comorbidities** — avoid dasatinib with lung disease, nilotinib with diabetes/pancreatitis/vascular disease, bosutinib with hepatic/renal/GI disease. If survival is the aim, **generic imatinib** is appropriate; if TFR is the aim, a **second-generation TKI** (e.g., dasatinib) is preferred, as in high-risk disease.
- **Omacetaxine mepesuccinate, hydroxyurea (0.5–10 g/day, cytoreductive bridge), low-dose cytarabine, decitabine and leukapheresis** (for leukostasis) are adjuncts; **interferon-α** is used in pregnancy.

Resistance, transformation, transplant and treatment-free remission

- **Resistance:** before switching, perform **BCR::ABL1 kinase-domain mutation analysis** (Sanger sequencing; ~50% of resistant patients have mutations). Mutation-guided salvage: **Y253H, E255K/V, F359V/C/I → dasatinib or bosutinib; V299L, T315A, F317L → nilotinib; T315I → ponatinib or asciminib** and consider allogeneic HSCT.
- **TKI toxicity management:** in patients already in good molecular response, **dose reduction** (rather than switching) is acceptable for reversible toxicity; switch for prohibitive toxicities (recurrent pleural effusion/dasatinib; vaso-occlusive events/ponatinib, nilotinib; pulmonary hypertension; pancreatitis; immune-mediated pneumonitis/myocarditis/hepatitis treated with steroids).
- **Allogeneic HSCT** — the only proven *curative* modality, now a **later-line** option: indicated for resistance to a second-generation TKI, **T315I** disease, or advanced phase. Chronic-phase long-term survival 50–70% (1-year mortality 5–30%); accelerated phase cure 30–50%; **blastic phase ≤20%.**
- **Accelerated/blastic phase:** TKIs (2nd/3rd generation) ± chemotherapy to reduce burden, **bridging to allogeneic HSCT**. **Lymphoid blast crisis** — anti-ALL chemotherapy (**hyper-CVAD**) + TKI (CR ~70%, median survival ~3 years); **myeloid blast crisis** — anti-AML chemotherapy + TKI (CR 30–50%).
- **Treatment-free remission (TFR):** discontinuation after durable **DMR (MR4) for >2–3 years** yields TFR in 40–60% (≥5 years DMR → 80%+). Eligibility: low/intermediate Sokal risk, first chronic phase, quantifiable transcripts (e13a2/e14a2), ≥5 years of TKI, sustained DMR >2–5 years; restart the TKI only if BCR::ABL1 (IS) rises **>0.1%** (confirmed twice).

- **Pregnancy:** TKIs are teratogenic (malformations 2–10%); **discontinue immediately** on confirmed pregnancy and manage with leukapheresis/hydroxyurea (and interferon-α if needed).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **The Philadelphia chromosome / BCR::ABL1 fusion.** Labels: *Chromosome 9 — ABL1 locus (q34.1)*; *Chromosome 22 — BCR gene (q11.2)*; *Reciprocal translocation t(9;22)*; *Derivative 22q⁻ = Philadelphia chromosome*; *Fusion BCR::ABL1 gene → p210 oncoprotein (constitutive tyrosine kinase)*.
- **Natural history / phase flow with response monitoring.** Labels: *Chronic phase (blasts ≤5%) → Accelerated phase (≥15% blasts / clonal evolution) → Blastic phase (≥30% blasts)*; alongside, the response ladder *Hematologic → Cytogenetic (CCyR/MR2) → Molecular (MMR/MR3 → DMR/MR4 → MR4.5)*.

Clinical / Diagnostic significance

- Sustained unexplained **leukocytosis with splenomegaly and a low LAP score** should prompt marrow examination and cytogenetics — the screen that uncovers CML.
- Demonstrating **BCR::ABL1** (G-banding/FISH/RT-PCR) is both diagnostic and the substrate for monitoring; **quantitative RT-PCR on the International Scale** drives every therapeutic decision (response, resistance, TFR).
- A "**masked Ph**" (morphologic CML, Ph not seen on karyotype) still responds to TKIs if FISH/PCR confirm BCR::ABL1 — do not exclude CML on G-banding alone.
- TKIs have made **CCyR achievement** the dominant prognostic factor, displacing the older Sokal/Hasford/EUTOS scores.

High-yield exam pointers

- **Hallmark:** Ph chromosome, t(9;22)(q34.1;q11.2), **BCR::ABL1** → p210 tyrosine kinase.
- **Diagnostic triad:** neutrophilic leukocytosis with full myeloid spectrum + basophilia, **low LAP**, splenomegaly; confirm with cytogenetics/FISH/PCR.
- **Three phases:** chronic (≤5% blasts) → accelerated (≥15% blasts / clonal evolution) → blastic (≥30% blasts).
- **Frontline:** imatinib 400 mg OD, dasatinib 100 mg OD, nilotinib 300 mg BD, bosutinib 400 mg OD — all acceptable; second-gen = deeper responses, no survival edge.
- **T315I** = gatekeeper mutation → only **ponatinib / asciminib** (± allo-HSCT) work.
- **Asciminib = STAMP inhibitor** (myristoyl pocket); ponatinib inhibits VEGFR → hypertension.
- **Monitoring milestones:** CCyR/MR2 (IS ≤1%), MMR/MR3 (IS ≤0.1%), DMR/MR4 (IS ≤0.01%). Resistance: IS >10% at 6 mo or >1% at 12 mo.
- **Allo-HSCT** = only curative option, reserved for TKI failure / T315I / advanced phase.
- **TFR** possible after durable DMR ≥2 years; **stop TKIs in pregnancy** (teratogenic).

SOURCE & COVERAGE

Harrison 22e — Ch 110 "Chronic Myeloid Leukemia" (Kantarjian & Jabbour). Fully covered by the provided chapter; no coverage gap. Standard textbook adjuncts (LAP score, hyper-CVAD regimen composition) are corroborated by the chapter text.

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Coagulation cascade and DIC

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

Definition / Introduction — The **coagulation cascade** is the sequence of reactions in which inactive plasma serine-protease zymogens are sequentially activated on phospholipid (activated platelet) surfaces, culminating in **thrombin** generation and conversion of soluble **fibrinogen to an insoluble cross-linked fibrin clot**. It functions as one limb of the hemostatic system, balanced against natural anticoagulants and fibrinolysis. **Disseminated intravascular coagulation (DIC)** is, per the ISTH (2001), *"an acquired syndrome characterised by intravascular activation of coagulation with loss of localisation arising from different causes that can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction"* — i.e., uncontrolled thrombin generation causing simultaneous microvascular thrombosis and consumptive bleeding.

Steps of Normal Haemostasis

- **Primary haemostasis (platelet plug):** vascular injury exposes subendothelial collagen; **von Willebrand factor (VWF)** acts as molecular glue mediating platelet adhesion under high shear; adhesion via Gp Ib-IX-V and collagen receptors triggers activation, the release reaction (ADP, serotonin, thromboxane A2), and aggregation through the **Gp IIb/IIIa (αIIbβ3)** receptor binding fibrinogen/VWF (≈50,000 sites/platelet).
- **Secondary haemostasis (fibrin formation):** the coagulation cascade stabilises the platelet plug with fibrin.
- **Fibrinolysis & remodelling:** plasmin degrades fibrin to restore vessel patency once bleeding is arrested.

The Coagulation Cascade — Cell-Based ("Waterfall") Model

Originally described as **extrinsic (tissue factor)** and **intrinsic (contact)** pathways converging on a **common pathway**; the modern view is that coagulation is *initiated* by tissue factor with *amplification* through intrinsic elements. All reactions require **calcium (Ca^{2+})** and occur on activated phospholipid surfaces.

- **Initiation (extrinsic):** vascular damage exposes **tissue factor (TF)**, constitutively expressed on subendothelial smooth muscle/fibroblasts and on circulating microparticles. TF binds **factor VIIa**; the TF/VIIa complex activates **FX→FXa** (directly) and **FIX→FIXa** (indirectly).
- **Amplification (intrinsic loop): Tissue factor pathway inhibitor (TFPI)** rapidly switches off the TF/VIIa/FXa complex, making sustained coagulation dependent on the amplification loop —

thrombin feeds back to activate **FXI, FVIII and FV**. FXIa is thus important in *propagation/amplification*, not initiation.

- **Common pathway: FXa**, with cofactor **FVa** on phospholipid, converts **prothrombin (FII)→thrombin (FIIa)** — the pivotal protease. Thrombin converts **fibrinogen→fibrin** and activates **FXIII→FXIIIa**, which covalently cross-links fibrin to stabilise the clot.
- **Note: FXII, prekallikrein and high-molecular-weight kininogen (HMWK)** (contact phase) prolong the aPTT but cause *no bleeding*, because thrombin can directly activate FXI — explaining why FXII deficiency is asymptomatic.

Pathway	Key factors	Screening test
Extrinsic	TF, **FVII**	**PT**
Intrinsic (contact)	FXII, FXI, FIX, FVIII, PK, HMWK	**aPTT**
Common	FX, FV, FII (prothrombin), fibrinogen (FI)	PT + aPTT
Fibrin formation	thrombin → fibrinogen; FXIII cross-link	**Thrombin time (TT)**

Natural Anticoagulants and the Fibrinolytic System

- **Antithrombin (AT):** major plasma inhibitor of thrombin and other proteases; activity accelerated several-thousand-fold by **heparin/heparan sulfate**. Deficiency → lifelong VTE risk.
- **Protein C / Protein S pathway:** thrombin bound to endothelial **thrombomodulin** (with the **endothelial protein C receptor, EPCR**) activates **protein C**; **activated protein C (APC)** with cofactor **protein S** cleaves and inactivates **FVa and FVIIIa**. Resistance to APC due to **Factor V Leiden** causes a hypercoagulable state.
- **TFPI:** inhibits the TF/FVIIa/FXa initiation complex.
- **Fibrinolysis: tPA** and **urokinase (uPA)** convert **plasminogen→plasmin**, which digests fibrin to fibrin degradation products (FDPs); complete lysis of cross-linked fibrin releases **D-dimer** (a specific marker of clot formation/breakdown). Regulated by **PAI-1/PAI-2** (inhibit tPA/uPA), **α2-antiplasmin** (inhibits plasmin), and **TAFI** (thrombin-activatable fibrinolysis inhibitor).

DIC — Aetiology and Pathophysiology

DIC is always **secondary** to an underlying trigger; common causes (ISTH/Harrison):

Category	Examples
Sepsis/infection	Gram-negative bacilli, staph/strep/pneumococci/meningococci; viral, fungal, parasitic, rickettsial
Trauma/tissue injury	Brain injury, extensive burns, fat embolism, rhabdomyolysis
Obstetric	Abruptio placentae, amniotic-fluid embolism, dead-fetus (retained), septic abortion, **HELLP**
Malignancy	Mucin-producing **adenocarcinoma** (prostate, pancreas), **acute promyelocytic leukaemia (APL/M3)**
Vascular	Giant haemangioma (**Kasabach-Merritt**), large-vessel/aortic aneurysm

Category	Examples
Others	Snake/insect **envenomation**, acute haemolytic transfusion reaction, transplant rejection/GVHD, fulminant hepatic failure, shock, ARDS, massive transfusion

- **Central mechanism — uncontrolled thrombin generation.** Inflammatory activation (sepsis) → increased **TF expression**, neutrophil/monocyte activation, cytokine release, **neutrophil extracellular traps (NETs)** and polyphosphates → **thrombo-inflammation** and excess thrombin.
- Simultaneous **loss of endothelial antithrombotic properties** and disrupted natural anticoagulants + abnormal fibrinolysis.
- → **Systemic fibrin deposition** in small/midsize vessels → microvascular thrombosis → **ischaemic multi-organ damage** (lung→ARDS, kidney, liver, brain) and **microangiopathic haemolysis** (schistocytes).
- → **Consumption of platelets and clotting factors** + **secondary hyperfibrinolysis** (late) → **diffuse bleeding**.
- **Purpura fulminans:** severe DIC with extensive cutaneous thrombosis, in children after viral/bacterial infection and in **homozygous protein C deficiency** neonates.

DIC — Clinical Features and Diagnosis

- **Bleeding:** petechiae, ecchymoses, oozing from venepuncture/catheter/incision sites, GI/pulmonary/CNS haemorrhage; **purpura fulminans**.
- **Thrombosis:** microvascular occlusion → organ failure; large-vessel thrombosis, cerebral embolism; cancer-associated DIC may present chiefly as thrombosis (**Trousseau syndrome**).
- **Acute DIC:** haemodynamic instability/shock; mortality **30 to >80%**, largely determined by the underlying disease.
- **Laboratory hallmark:** ↓platelets, **prolonged PT and aPTT**, **low/falling fibrinogen**, **raised D-dimer/FDPs**, schistocytes on smear. Serial testing (every 6–8 h) is essential as values evolve.

ISTH scoring system for overt DIC (validated; uses platelet count, D-dimer, PT prolongation, fibrinogen):

Parameter	Value	Points
Platelets	>100 $\times 10^9$/L / >50–<100 / <50	0 / 1 / 2
D-dimer	Normal / Moderate ↑ / Severe ↑	0 / 2 / 3
PT prolongation	<3 s / 3–<6 s / >6 s	0 / 1 / 2
Fibrinogen	>1 g/L / <1 g/L	0 / 1

- **Score ≥5 → overt DIC** (repeat labs daily); **<5 → non-overt/low-grade DIC** (repeat every 1–2 days). *Not to be used in pregnancy* (a separate obstetric tool exists).
- **Chronic (compensated) DIC:** giant haemangioma, metastatic carcinoma, late fetal demise; D-dimer/FDP elevated but PT/aPTT/fibrinogen often normal, mild/no thrombocytopenia.
- **Differential: severe liver disease** (similar abnormalities but change slowly, not rapidly) and **TTP** (acute thrombocytopenia + schistocytes + organ failure, but distinguished by **ADAMTS13 deficiency/inhibitor**).

DIC — Management

- **Treat the underlying cause** — this is the cornerstone (antimicrobials for sepsis, chemotherapy, surgery, evacuation of uterus/delivery for obstetric DIC).
- **Blood-product support for active bleeding / high bleeding risk** (not merely to correct numbers):
  - **Platelets** for count <10,000–20,000/μL (goal >20 $\times 10^9$/L; **>50 $\times 10^9$/L** for serious/intracranial bleeding).
  - **Cryoprecipitate or fibrinogen concentrate** to keep **fibrinogen >100–150 mg/dL** (correct fibrinogen *before* giving FFP for prolonged PT/aPTT).
  - **FFP** for prolonged PT/aPTT *with* bleeding (target PT/aPTT <1.5× normal).
  - **Vitamin K** should be given.
- **Heparin** (low-dose continuous infusion, e.g., **5–10 U/kg/h, no bolus**): for **low-grade/chronic DIC** with solid tumour or APL, for recognised thrombosis, and for **purpura fulminans**. *Aggravates bleeding in acute haemorrhagic DIC*; contraindicated if platelets cannot be kept >20,000–30,000/μL, in CNS/GI bleeding, placental abruption, or imminent surgery. No proven survival benefit in severe DIC.
- **Antifibrinolytics** (tranexamic acid/EACA): only in **primary hyperfibrinolytic DIC** with severe bleeding (e.g., APL, giant haemangioma) — use cautiously (thrombosis risk), often with heparin and only with haematology input.
- **Antithrombin / thrombomodulin concentrates:** post-hoc benefit suggested in sepsis-associated DIC; require further study. (Recombinant activated protein C was withdrawn.)
- **Special situations: APL-associated DIC** needs immediate treatment (start ATRA early) within ~24 h; **Trousseau syndrome** is treated with **heparin/LMWH** (warfarin less effective); **HELLP** requires delivery/evacuation of the uterus.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Cell-based coagulation cascade:** vessel injury → **TF + FVIIa** → activate **FIX→FIXa** and **FX→FXa**; cofactors **FVIIIa** and **FVa**; **prothrombin (FII)→thrombin (FIIa)**; **fibrinogen→fibrin**; **FXIIIa cross-linking**; thrombin feedback arrows to **FXI, FVIII, FV**; **TFPI** inhibiting TF/FVIIa/FXa. Bracket-label the **PT (extrinsic)**, **aPTT (intrinsic)** and **common pathway**.
- **DIC pathophysiology flowchart:** *Trigger* → **Uncontrolled thrombin generation** → branch 1: **fibrin deposits in microcirculation** → ischaemic tissue damage + **RBC damage/haemolysis** + multi-organ failure; branch 2: **consumption of platelets & clotting factors** → **diffuse bleeding**; with **secondary fibrinolysis** → **↑FDP/D-dimer**.

Clinical / Diagnostic significance

- **PT** screens the extrinsic/common pathway (FVII, X, V, II, fibrinogen) and underpins the **INR** for warfarin monitoring and liver-disease assessment; **aPTT** screens the intrinsic/common pathway and monitors unfractionated heparin.
- **Mixing studies** distinguish factor deficiency (corrects) from an inhibitor/lupus anticoagulant (fails to correct).

- **D-dimer** is a sensitive marker to *exclude* DVT/PE (age-adjusted thresholds) and is raised in DIC.
- A combined **prolonged PT + aPTT with falling fibrinogen, thrombocytopenia, raised D-dimer and schistocytes** in a sick patient is the classic DIC signature — always search for the underlying trigger.

High-yield exam pointers

- Coagulation is **initiated by tissue factor**, **amplified by the intrinsic loop**, occurs on **phospholipid surfaces**, and needs **Ca^{2+}**; **thrombin** is the pivotal enzyme.
- **FXII deficiency** → long aPTT but **no bleeding**; **FXIII deficiency** → normal PT/aPTT but **abnormal clot solubility** and bleeding.
- Vitamin K–dependent factors = **II, VII, IX, X + protein C and S**.
- **DIC is always secondary**; commonest triggers = **sepsis, trauma, obstetric complications, malignancy (APL, mucinous adenocarcinoma)**.
- **ISTH overt-DIC score ≥5** (platelets, D-dimer, PT, fibrinogen).
- **Schistocytes** in 10–20%; **D-dimer/FDP raised**, **fibrinogen low**.
- **HELLP** = severe peripartum DIC variant; **Trousseau** = cancer DIC presenting as thrombosis; **Kasabach-Merritt** = haemangioma-associated.
- **Treat the cause first**; products only if bleeding; **low-dose heparin** for thrombotic/chronic DIC and purpura fulminans, *not* for acute haemorrhagic DIC.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bleeding and Thrombosis" (coagulation cascade physiology, natural anticoagulants, fibrinolysis, PT/aPTT correlation) and "Coagulation Disorders" (DIC definition, causes, pathophysiology, ISTH scoring, management; differential vs liver disease and TTP).
- **CMDT 2026** — "Disorders of Hemostasis, Thrombosis & Antithrombotic Therapy" (DIC essentials of diagnosis, management table, HELLP, Trousseau syndrome, APL-associated DIC, heparin thresholds).
- Coverage note: The DeVita oncology text was screened for the APL/malignancy-associated DIC angle; the substantive exam-grade DIC detail is fully covered by Harrison and CMDT, which were used as the primary sources.

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Megaloblastic anaemia

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Megaloblastic anaemias are a group of disorders characterised by a distinctive morphological abnormality of the developing red cells in the bone marrow (megaloblasts), arising from **defective DNA synthesis** with relatively preserved RNA and cytoplasmic (haemoglobin) maturation — i.e. **nuclear–cytoplasmic asynchrony**. The marrow is typically hypercellular, yet the anaemia results from **ineffective erythropoiesis** (intramedullary death of haemopoietic precursors by apoptosis). The overwhelming majority are due to deficiency of **cobalamin (vitamin B12)** or **folate (vitamin B9)**, or to drugs/genetic defects impairing their metabolism or DNA synthesis directly.

Etiology

Cobalamin (B12) deficiency	Folate deficiency	Independent of B12/folate
Nutritional: strict vegans (large at-risk Indian/Hindu vegetarian population)	**Nutritional (commonest):** old age, infancy, poverty, alcoholism, chronic invalids; scurvy/kwashiorkor	Antimetabolite drugs: cytarabine, hydroxyurea, 6-mercaptopurine, AZT
Pernicious anaemia (PA) — commonest severe cause in the West; autoimmune gastric atrophy with IF lack	**Malabsorption:** tropical sprue, coeliac (gluten-induced enteropathy), specific folate malabsorption (PCFT mutation)	Methotrexate / antifolates (DHF-reductase inhibitors)
Gastric: total/partial gastrectomy, congenital IF deficiency	**Increased utilisation/loss:** pregnancy & lactation, prematurity, chronic haemolysis (sickle cell, spherocytosis), myelofibrosis, malignancy, exfoliative dermatitis, haemodialysis	Orotic aciduria (responds to uridine)
Intestinal: stagnant/blind-loop syndrome, ileal resection (≥1.2 m) or Crohn's, tropical sprue, fish tapeworm (*Diphyllobothrium latum*), Imerslund-Gräsbeck syndrome	**Antifolate/anticonvulsant drugs:** phenytoin, primidone, barbiturates, sulfasalazine; alcohol	Thiamine-responsive (*SLC19A2*), myelodysplasia, acute myeloid leukaemia
Metabolic: transcobalamin (TC) II deficiency; N2O inactivation of methylcobalamin		

- **B12 stores** are 2–3 mg (3–4 years' reserve); deficiency develops slowly. **Folate stores** are only ~10 mg (3–4 months' reserve), so folate deficiency develops rapidly.
- B12 is **synthesised only by microorganisms**; human source is food of animal origin (meat, fish, dairy). Folate is abundant in liver, yeast and green vegetables but is **destroyed by cooking**.

Pathogenesis — biochemical basis

- The common final lesion is **impaired conversion of deoxyuridine monophosphate (dUMP) → deoxythymidine monophosphate (dTMP)**, the rate-limiting step of DNA synthesis, which requires **5,10-methylene-tetrahydrofolate (THF)** as coenzyme (thymidylate synthase). The shortage of dTTP slows DNA replication; replicons fail to join, producing single-stranded breaks → **megaloblastic change and apoptotic intramedullary cell death**.

- **Only two reactions in humans require cobalamin:**
- **Methionine synthase** (uses **methylcobalamin** + 5-methyl-THF): homocysteine → methionine; methionine → **S-adenosyl-methionine (SAM)**, the universal methyl donor.
- **L-methylmalonyl-CoA mutase** (uses **adenosyl-cobalamin**): methylmalonyl-CoA → succinyl-CoA.
- **Methylfolate trap (THF starvation):** In B12 deficiency, methionine synthase fails, so folate is trapped as 5-methyl-THF in plasma (high serum folate) and cannot be converted to THF/polyglutamates inside the cell (low cell folate). This explains why B12 deficiency produces a **functional intracellular folate deficiency** and why the anaemia partly responds to large doses of folic acid (which bypass the trap) — but giving folate alone allows the **neuropathy to progress**.
- **Neuropathy** is attributed to defective methionine/SAM synthesis (impaired methylation of myelin), not to the megaloblastic process; methylmalonic acid (MMA) accumulates only with the mutase (B12) defect, not with TC II deficiency or N2O exposure.

Clinical features

- **General/anaemia:** insidious pallor, fatigue; "lemon-yellow" tint from combined pallor and mild **unconjugated jaundice** (ineffective erythropoiesis); anorexia, weight loss, low-grade fever; mild splenomegaly may occur.
- **Epithelial/GI: glossitis** (beefy-red, sore tongue), **angular cheilosis/stomatitis**, diarrhoea or constipation; reversible **melanin skin hyperpigmentation**; cervical smear abnormalities.
- **Neurological (B12 only) — subacute combined degeneration (SCD) of the cord:** symmetrical demyelination of the **posterior (dorsal) and lateral (pyramidal) columns** of the cervico-thoracic cord. Presents (more often in males) with **distal paraesthesiae**, loss of **vibration and proprioception**, positive **Romberg** and **Lhermitte** signs, ataxic-spastic gait with **hyperreflexia and extensor plantars**. Also peripheral neuropathy, optic atrophy, autonomic dysfunction (postural hypotension, incontinence, impotence). **Crucially, neuro-psychiatric features can occur with a normal CBC/MCV.**
- **Neuropsychiatric:** dementia, depression, psychosis, cognitive impairment, anosmia/loss of taste ("megaloblastic madness").
- **Reproductive/obstetric:** infertility (both sexes); maternal folate deficiency → prematurity, recurrent fetal loss and **neural-tube defects (NTDs)**.
- **Infantile B12 deficiency** (B12-deficient mother, breast-fed): megaloblastic anaemia at 3–6 months with growth retardation, hypotonia and delayed myelination.

Haematological & laboratory findings / Diagnosis

- **Peripheral smear: oval macrocytes**, marked anisopoikilocytosis, **MCV usually >100 fL** (often 110–140 fL); **hypersegmented neutrophils (>5 lobes)** — an early, characteristic sign. Mild leucopenia and thrombocytopenia in severe cases (pancytopenia possible).
- **Reticulocyte count** is low/inappropriately normal (ineffective erythropoiesis).
- **Bone marrow:** hypercellular; **megaloblasts** with open, sieve-like ("stippled") nuclear chromatin despite haemoglobinised cytoplasm (nuclear-cytoplasmic dissociation); **giant metamyelocytes/giant bands** and hypersegmented megakaryocytes.

- **Ineffective erythropoiesis markers:** raised **unconjugated bilirubin** and **serum LDH** (often markedly), raised urine urobilinogen, **reduced haptoglobin** (may mimic haemolysis/AIHA).
- **Vitamin assays:** serum B12 deficient if <74 pmol/L (~100 ng/L) — symptomatic patients <100 pg/mL; serum/RBC folate low (RBC folate <150 ng/mL is diagnostic, and reflects stores better). **Note:** serum folate is *high* in B12 deficiency (methylfolate trap).
- **Metabolite confirmation (for borderline values): MMA raised in B12 deficiency only**; **homocysteine raised in both** B12 and folate deficiency. (MMA also rises in renal failure.)
- **Establish the cause of B12 deficiency (PA work-up):** anti-**intrinsic-factor antibody** (specific; blocking type I ~55%, binding type II ~35%), anti-**parietal-cell antibody** (sensitive ~90%, less specific), raised **serum gastrin**, low **pepsinogen I**, gastric endoscopy/biopsy (body-fundus atrophy). The Schilling test is now obsolete.

Complications

- **Neurological:** irreversible SCD/peripheral neuropathy and dementia if B12 deficiency is untreated or if folate is given alone.
- **Obstetric/fetal:** NTDs (anencephaly, meningomyelocele, spina bifida), cleft lip/palate, prematurity, fetal loss.
- **Vascular:** hyperhomocysteinaemia → increased risk of arterial and **venous thrombosis** (including unusual sites e.g. cerebral venous sinus); severe homocystinuria causes premature vascular disease.
- **Malignancy:** PA carries an increased long-term risk of **gastric carcinoma** (and gastric carcinoid).
- **Haematological:** symptomatic anaemia, high-output failure; risk of severe **hypokalaemia and thrombocytosis** during early treatment.

Management / Treatment

- **Principle:** identify and treat the *correct* deficiency. In a critically ill patient, take samples for B12/folate (± marrow) and then treat with **both** vitamins; **never give folate alone until B12 deficiency is excluded/corrected** (precipitates/worsens neuropathy).
- **Cobalamin replacement (PA / B12 deficiency):**
  - **Hydroxocobalamin** 1000 µg IM × 6 doses at 3–7 day intervals to replenish stores; **maintenance 1000 µg IM every 3 months**, usually lifelong. (Cyanocobalamin needs higher/more frequent dosing, e.g. monthly, due to poorer retention.)
  - CMDT regimen: 100–1000 µg IM/SC daily for 1 week, weekly for a month, then monthly.
  - **High-dose oral cyanocobalamin 1000–2000 µg/day** is effective even in PA (≈1% absorbed passively, IF-independent); ensure compliance. Parenteral preferred where neuropathy or severe anaemia is present.
  - Give B12 routinely after total gastrectomy or ileal resection; screen patients on long-term PPIs/metformin or after bariatric surgery.
- **Folate replacement: oral folic acid 1–5 mg daily** (Harrison: 5–15 mg/day; CMDT: 1 mg/day), continued ~4 months (until folate-deficient cells are replaced) or long-term if the cause is irreversible (haemolysis, dialysis). **Folinic acid (5-formyl-THF)** is the antidote to methotrexate/antifolates.

- **Response & monitoring:** sense of well-being within days; **reticulocytosis at 5–7 days**; haematology normalises in ~2 months. Watch for **hypokalaemia** (give K^+ supplements) and a rebound thrombocytosis — consider antiplatelet therapy if platelets rise >800 × 10^9/L. Transfusion is rarely needed and is hazardous (precipitates failure); if essential give packed cells slowly, 1–2 units, with diuretic cover.
- **Prophylaxis:** periconceptional **folic acid 400 µg/day** (5 mg/day in previous NTD, diabetes, sickle cell, on antiepileptics) reduces NTDs by ~80%; routine folate in chronic dialysis, prematurity, chronic haemolysis; food fortification programmes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Methylfolate trap / one-carbon metabolism loop** — label: *dietary folate → 5-methyl-THF (plasma)*; *methionine synthase (methylcobalamin)*; *homocysteine → methionine → SAM*; *THF → 5,10-methylene-THF*; *dUMP → dTMP (thymidylate synthase) → DNA*; *L-methylmalonyl-CoA → succinyl-CoA (adenosyl-cobalamin)*; arrows showing the block in B12 deficiency trapping folate as 5-methyl-THF.
- **Peripheral smear & marrow montage** — label: *oval macrocyte*, *hypersegmented neutrophil (>5 lobes)*, *megaloblast with open/stippled chromatin (nuclear-cytoplasmic asynchrony)*, *giant metamyelocyte*. Optional cord cross-section labelling *posterior columns* and *lateral (pyramidal) tracts* for subacute combined degeneration.

Clinical / Diagnostic significance

- **MCV + smear + hypersegmented neutrophils** give a rapid bedside diagnosis; confirm with B12/folate and, if borderline, **MMA (B12-specific) and homocysteine**.
- A **normal CBC does not exclude B12 neuropathy** — measure B12/MMA in any unexplained myelopathy, dementia or peripheral neuropathy.
- Distinguish from **non-megaloblastic macrocytosis** (alcohol, liver disease, hypothyroidism, MDS, reticulocytosis) — these lack megaloblastic marrow and hypersegmentation.
- Coexistent **iron deficiency** (common in PA from atrophic gastritis) can mask macrocytosis ("dimorphic" picture) — check iron studies.
- PA mandates a **single endoscopy** (atrophic gastritis, gastric carcinoma/carcinoid surveillance) and screening for associated autoimmune disease (thyroid, type 1 DM, Addison's, vitiligo).

High-yield exam pointers

- Hallmark = **nuclear-cytoplasmic asynchrony** from defective DNA synthesis; anaemia is from **ineffective erythropoiesis** in a *hypercellular* marrow.
- **Two B12-dependent enzymes:** methionine synthase (methyl-B12) and methylmalonyl-CoA mutase (adenosyl-B12). **MMA ↑ → B12; homocysteine ↑ → both.**
- **Methylfolate trap** explains high serum folate + low cell folate in B12 deficiency.
- **Hypersegmented neutrophil (>5 lobes)** = earliest, most characteristic peripheral clue.
- **Never treat with folate alone** before excluding B12 — risk of subacute combined degeneration.
- **Pernicious anaemia:** elderly, anti-IF (specific) + anti-parietal-cell (sensitive) antibodies, ↑gastrin, ↓pepsinogen I; gastric carcinoma risk.

- Treatment response: **reticulocytosis day 5–7**; beware **hypokalaemia** and rebound **thrombocytosis** early.
- **Folic acid 400 µg periconception (5 mg high-risk)** prevents neural-tube defects.
- B12 store lasts **3–4 years**; folate store only **3–4 months**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Megaloblastic Anemias" (A.V. Hoffbrand)**: aetiology tables, cobalamin/folate biochemistry, methylfolate trap, clinical and haematological features, pernicious anaemia, diagnosis and treatment regimens (hydroxocobalamin 6 × 1000 µg then 3-monthly; folate 5–15 mg).
- **CMDT 2026 — "Blood Disorders" (Vitamin B12 Deficiency; Folic Acid Deficiency)**: current diagnostic cut-offs (B12 <200/<100 pg/mL; RBC folate <150 ng/mL), MMA/homocysteine confirmation, parenteral and oral 1 mg replacement schedules, reticulocyte/hypokalaemia response.
- **Coverage note:** The assigned specialty text (DeVita's *Cancer: Principles & Practice of Oncology*) covers haematological *malignancies*, not nutritional megaloblastic anaemia, and therefore was not a relevant source for this topic; grounding is from Harrison 22e and CMDT 2026, which cover it fully. The term *subacute combined degeneration* and the standard 400 µg/5 mg NTD-prophylaxis doses are universally accepted internal medicine, consistent with Harrison's description of posterior/lateral-column demyelination and periconceptional folate.

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Paraneoplastic neurological syndromes

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

Definition / Introduction — Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect **any level of the neuraxis** — brain, brainstem, cerebellum, spinal cord, dorsal root ganglia, peripheral nerve, neuromuscular junction or muscle — and are caused by **remote immune effects of a tumour, not by metastasis, direct infiltration, infection, metabolic derangement or treatment toxicity**. Most are autoimmune, triggered by neuronal proteins ectopically expressed by the tumour. Clinically disabling PNDs occur in **0.5–1% of all cancer patients**, but in **2–3% of small-cell lung cancer (SCLC) and neuroblastoma** and **30–50% of thymoma**. Crucially, in **~60% of patients the neurologic syndrome precedes the cancer diagnosis**, develops subacutely producing severe deficits, and prompt tumour control improves outcome — making early recognition vital.

Pathogenesis and antibody-based risk classification

- PNDs arise when tumour cells aberrantly express neuronal antigens; antigen is processed by antigen-presenting cells → CD4+ helper T-cell activation → B-cell differentiation and autoantibody production, with CD8+ cytotoxic T cells for intracellular targets.
- **Two immunopathological groups** with prognostic and therapeutic relevance:

- **Antibodies to intracellular antigens** (e.g., Hu, Yo, Ri, CRMP5, Ma2, amphiphysin): antibody is a *marker*; injury is **cytotoxic T-cell mediated** → extensive neuronal loss → **strong cancer association, poor response to immunotherapy**.
- **Antibodies to neuronal cell-surface/synaptic antigens** (e.g., NMDAR, LGI1, GABA-B, AMPAR, Caspr2): antibody is **directly pathogenic** (receptor cross-linking/internalisation, functional block) → **more often respond to immunotherapy**, may occur without cancer and in children/young adults.

- Modern (Graus 2021) terminology abandons "onconeural antibody" for **probability of underlying cancer**: high-risk >70%, intermediate 30–70%, low <30%.

Risk / antibody	Classic neurologic phenotype	Commonest tumour
Anti-Hu (ANNA-1)	Encephalomyelitis, sensory neuronopathy	SCLC
Anti-Yo (PCA-1)	Rapidly progressive cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynaecologic, SCLC
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, neuropathy	SCLC, thymoma
Anti-Ma2	Limbic, hypothalamic, brainstem encephalitis	Testicular germ cell
Anti-Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Anti-SOX1	LEMS (± cerebellar)	SCLC
Anti-KLHL11	Brainstem encephalitis, ataxia, sensorineural deafness	Seminoma/germ-cell
Anti-NMDAR *(intermediate)*	Anti-NMDAR encephalitis	Ovarian teratoma
Anti-AMPAR / GABA-B *(intermediate)*	Limbic encephalitis (± seizures)	SCLC, thymoma, breast
Anti-Caspr2 *(intermediate)*	Morvan syndrome, neuromyotonia	Thymoma
Anti-VGCC (P/Q) *(intermediate)*	LEMS, cerebellar degeneration	SCLC
Anti-LGI1 *(low)*	Limbic encephalitis, hyponatraemia, faciobrachial dystonic seizures	Rarely thymoma
Anti-GAD65 *(low)*	Stiff-person, cerebellar ataxia, epilepsy	Usually none

CNS and dorsal-root-ganglion syndromes (high-risk "classic" phenotypes)

- **Paraneoplastic encephalomyelitis** — multifocal inflammation; combinations of cortical encephalitis (*epilepsia partialis continua*), limbic, brainstem, cerebellar, myelitic and autonomic

involvement. Usually SCLC with **Hu antibodies**; death may result from cardiac arrhythmia, postural hypotension or central hypoventilation.

- **Limbic encephalitis** — subacute confusion, agitation, anxiety/depression, **profound short-term (anterograde) memory loss** and temporal-lobe seizures; MRI shows **unilateral/bilateral medial temporal-lobe T2/FLAIR hyperintensity**. Antibodies: Hu, Ma2, AMPAR, GABA-B, LGI1, Caspr2.
- **Paraneoplastic cerebellar degeneration (rapidly progressive cerebellar syndrome)** — prodrome of dizziness, oscillopsia, nausea → dysarthria, gait and limb ataxia, **downbeating nystagmus**; due to extensive **Purkinje-cell loss**; MRI normal early, **cerebellar atrophy** later. Tumours: SCLC, breast/ovary (anti-Yo), Hodgkin (anti-Tr/DNER).
- **Opsoclonus-myoclonus syndrome** — chaotic, involuntary multidirectional saccades + myoclonus + ataxia from **disinhibition of the cerebellar fastigial nucleus**; **neuroblastoma in children (≥50%)**, lung/breast (± anti-Ri) in adults; in children with hypotonia, irritability and "dancing eyes–dancing feet".
- **Paraneoplastic sensory neuronopathy (dorsal root ganglionopathy)** — immune attack on **dorsal root ganglia**; asymmetric/symmetric sensory loss in all modalities (including face/trunk), painful dysesthesias, sensory ataxia, areflexia; **absent/reduced SNAPs with preserved motor conduction**; Hu antibodies, SCLC.
- **Paraneoplastic stiff-person syndrome / PERM** — progressive axial and limb rigidity with painful stimulus-triggered spasms, continuous motor-unit activity on EMG; **amphiphysin antibodies = paraneoplastic** (breast, SCLC), whereas GAD65 is usually non-paraneoplastic.
- Myelopathy (longitudinally extensive), paraneoplastic visual syndromes (cancer-associated retinopathy with anti-recoverin in SCLC; melanoma-associated retinopathy), and autonomic neuropathy (anti-ganglionic α3-AChR) also occur.

Neuromuscular junction, nerve and muscle syndromes

- **Lambert-Eaton myasthenic syndrome (LEMS)** — antibodies to **presynaptic P/Q-type voltage-gated calcium channels** reduce ACh release. Triad of **proximal lower-limb weakness, hyporeflexia/areflexia and autonomic features** (dry mouth, constipation, impotence); strength and reflexes transiently **improve after brief exercise (post-tetanic facilitation)**. >50% have SCLC. Electrodiagnosis: **low resting CMAP amplitude, decrement on low-rate (2–3 Hz) repetitive nerve stimulation, and >100% increment after high-rate stimulation or brief exercise**.
- **Peripheral nerve hyperexcitability (neuromyotonia / Isaacs syndrome)** — cramps, myokymia/fasciculations, pseudomyotonia; Caspr2 antibodies; thymoma/SCLC. **Morvan syndrome** adds encephalopathy, insomnia (*agrypnia excitata*) and dysautonomia (Caspr2, thymoma in ~50%).
- **Dermatomyositis** (and, weakly, polymyositis) and **immune-mediated necrotizing myopathy** (anti-HMGCR or seronegative carry higher cancer risk); subacute sensorimotor neuropathies and POEMS/paraproteinaemic neuropathies; paraneoplastic **myasthenia gravis** with thymoma.

Autoimmune encephalitides with neuronal surface antibodies

- **Anti-NMDAR encephalitis** — young women/children: viral-like prodrome → psychiatric symptoms, reduced speech, memory loss, **orofacial/limb dyskinesias**, seizures, decreased consciousness, **autonomic instability and central hypoventilation**. ~46% of females ≥12 yr have an **ovarian teratoma**; ~85–90% improve substantially; relapses 12–24%. Diagnosis: CSF antibodies to the **GluN1 subunit** of NMDAR.
- **Anti-LGI1 encephalitis** — older men: limbic encephalitis with **hyponatraemia** and pathognomonic **faciobrachial dystonic seizures** (brief unilateral arm/face contractions preceding amnestic syndrome).
- **Anti-GABA-B** (prominent early seizures, SCLC), **anti-AMPAR** (relapsing limbic encephalitis), **anti-GABA-A** (refractory seizures/status), **anti-mGluR5** (Ophelia syndrome with Hodgkin lymphoma) and **anti-IgLON5** (NREM/REM parasomnia, stridor, tauopathy).

Diagnostic approach

- **Exclude mimics first**: metastasis/leptomeningeal disease (contrast MRI brain + spine, CSF cytology), infection, metabolic and treatment-related causes.
- **CSF** typically shows mild–moderate lymphocytic pleocytosis (<200 cells), raised protein and oligoclonal bands. **Test paired serum and CSF antibodies** (CSF essential and more specific for NMDAR).
- Only ~60–70% of CNS PNDs and <20% of PNS-PNS have a detectable antibody — **a negative panel does not exclude PND.**
- **Tumour hunt**: CT chest/abdomen + whole-body **FDG-PET**; testicular/pelvic ultrasound and MRI for germ-cell tumours/teratoma; **mammography for anti-Yo/Ri**. If initial screen negative in a high-risk phenotype/antibody, **repeat every 4–6 months for ≥2 years**.
- **PNS-Care Score** (Graus 2021): grades phenotype (high 3 / intermediate 2), antibody (high 3 / intermediate 2) and cancer findings (present/consistent 4) → **Definite ≥8, Probable 6–7, Possible 4–5**.
- **DELTA-P score** predicts SCLC in LEMS: **D**ysarthria/dysphagia/bulbar weakness, **E**rectile dysfunction, **L**oss of weight ≥5%, **T**obacco, **A**ge ≥50 yr, **P**erformance status (Karnofsky <70) — each 1 point; score 0–1 virtually excludes SCLC, ≥3 implies >80% risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Neuraxis "site map" of PNDs**: a sagittal CNS + peripheral nerve/muscle outline with labels — *Limbic encephalitis (medial temporal lobe), Brainstem encephalitis, Cerebellar degeneration (Purkinje cells), Opsoclonus-myoclonus (fastigial nucleus), Myelitis, Dorsal root ganglion → sensory neuronopathy, Neuromuscular junction → LEMS, Muscle → dermatomyositis*.
- **NMJ in LEMS**: presynaptic terminal with **P/Q-type VGCC blocked by antibody**, reduced ACh-vesicle release into the cleft, postsynaptic nicotinic AChR. Labels: *autoantibody, P/Q VGCC, Ca^{2+} influx ↓, ACh vesicles, post-tetanic facilitation*.

Clinical / Diagnostic significance

- A subacute, otherwise unexplained neurologic syndrome in a smoker or older adult should trigger **antibody testing and a tumour search** — the PND often unmasks an occult, frequently still-curable cancer.
- **Antibody specificity guides the cancer search**: anti-Yo → breast/ovary, anti-Ma2 → testis, anti-Tr → Hodgkin, anti-NMDAR → ovarian teratoma, anti-Hu/VGCC/SOX1 → SCLC.
- **Management** = treat the tumour + immunotherapy. **First line**: IV methylprednisolone 1 g/day × 3–5 days, IVIG (≈2 g/kg over 5 days) and/or plasma exchange. **Second line**: rituximab 375 mg/m^2 weekly × 4, cyclophosphamide, azathioprine/mycophenolate; refractory NMDAR encephalitis — tocilizumab or bortezomib. **Symptomatic**: diazepam/baclofen for stiff-person; **amifampridine (3,4-diaminopyridine)** and pyridostigmine for LEMS.
- Surface-antibody syndromes respond well; intracellular-antibody (Hu, Yo) syndromes often stabilise at best — **early treatment before irreversible neuronal loss is key**.
- Immune-checkpoint inhibitors can precipitate neurologic immune-related adverse events clinically identical to PNDs.

High-yield exam pointers

- **60% of PNDs present before the cancer is found**; SCLC is the commonest associated tumour.
- **Intracellular antigen = T-cell mediated, marker antibody, poor response; surface antigen = directly pathogenic, treatment-responsive.**
- **Anti-Hu** = encephalomyelitis + sensory neuronopathy + SCLC; **Anti-Yo** = pure cerebellar degeneration + breast/ovary.
- **LEMS** = proximal weakness + areflexia + autonomic features, facilitation on exercise, **incremental RNS at high rate**, P/Q VGCC antibodies, SCLC.
- **Anti-NMDAR encephalitis** = young woman, psychiatric → dyskinesia → seizures → dysautonomia, **ovarian teratoma**, CSF GluN1 antibody, good recovery.
- **Anti-LGI1** = limbic encephalitis + **hyponatraemia + faciobrachial dystonic seizures**.
- **Opsoclonus-myoclonus** = "dancing eyes" + neuroblastoma (child); **stiff-person** = amphiphysin/GAD65, EMG continuous motor-unit activity.
- Diagnostic tools: paired serum/CSF antibodies, MRI, **whole-body PET-CT**, PNS-Care score, DELTA-P score; rescreen for cancer every 4–6 months for ≥2 years.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis" (Dalmau & Graus): pathogenesis, high/intermediate/low-risk antibody tables, individual syndromes, MRI/CSF, treatment.
- **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — "Paraneoplastic Syndromes": Graus 2021 revised criteria, PNS Euronetwork epidemiology, high/intermediate-risk antibody table, **PNS-Care Score, DELTA-P score**, and immunotherapy regimens/doses.
- **CMDT 2026** — "Cancer" / Lung cancer: frequency of paraneoplastic syndromes and LEMS in clinical practice.

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Paroxysmal nocturnal haemoglobinuria

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

Definition / Introduction — Paroxysmal nocturnal hemoglobinuria (PNH) is an **acquired, clonal hematopoietic stem-cell disorder** caused by a somatic mutation in the X-linked *PIGA* gene, leading to deficiency of the **glycosylphosphatidylinositol (GPI) anchor** and of the GPI-linked complement-regulatory proteins **CD55 and CD59** on the surface of blood cells. The result is a chronic, complement-mediated **intravascular hemolytic anemia** with recurrent exacerbations. The classic clinical triad is **(1) intravascular hemolysis, (2) a marked tendency to venous thrombosis, and (3) a variable degree of bone marrow failure (pancytopenia)** — a combination that makes PNH a uniquely recognisable entity. It is a rare disease (estimated prevalence **5–10 per million**, perhaps somewhat commoner in Southeast Asia and the Far East), affects men and women equally, is **never inherited/congenital**, and usually presents in young adults. It is the prime example of a *clonal but non-malignant* disorder.

Molecular pathogenesis — the PIGA mutation and GPI anchor

- The fundamental lesion is an **acquired somatic mutation of the *PIGA* gene** (located on the X chromosome) in a hematopoietic stem cell. *PIGA* encodes an enzyme needed for an **early step in GPI biosynthesis**.
- Because the gene is X-linked, a single inactivating hit (one active X in each cell) abolishes function, producing a clone of progeny cells deficient in the GPI glycolipid.
- GPI is a glycolipid that, through a peptide bond, **anchors numerous proteins to the cell-surface membrane**; these proteins possess only an extracellular domain. Loss of GPI therefore removes a whole family of surface proteins, the critical ones being the **complement regulators CD55 and CD59**.
  - **CD55** (*decay-accelerating factor*) — prevents assembly/accelerates decay of the C3 and C5 convertases, i.e., limits C3-fragment deposition.
  - **CD59** (*membrane inhibitor of reactive lysis / protectin*) — the **most important** regulator; it blocks insertion of C9 polymers, preventing formation of the **membrane attack complex (MAC, C5b-9)**.

- The marrow becomes a **mosaic** of mutant (GPI-negative, "PNH") and normal (GPI-positive) cells; the peripheral blood always contains both populations, and in most patients the PNH clone predominates.
- Rarely, PNH arises from **biallelic mutations of the autosomal *PIGT* gene (chromosome 20q)** without a *PIGA* mutation; here GPI is made but cannot bind proteins, and the picture is complicated by a **chronic inflammatory state**.

Mechanism of hemolysis — complement on an unprotected cell

- Hemolysis is **mainly intravascular** and results from the *intrinsic* hypersensitivity of CD55/CD59-deficient red cells to **activated complement**.
- **Alternative pathway** activation (continuous low-grade "tick-over") drives the **chronic** baseline hemolysis; **classical pathway** activation (antigen–antibody) during **infection or inflammation** triggers the dramatic acute **exacerbations** ("paroxysms").
- Without CD59, the MAC inserts freely into the membrane → lysis → **hemoglobinemia and hemoglobinuria**.
- Free plasma hemoglobin **scavenges nitric oxide**, producing smooth-muscle dystonia — **esophageal spasm/dysphagia, abdominal pain, erectile dysfunction**, and contributing to thrombotic risk and kidney damage.

Relationship with bone marrow failure (PNH–aplastic anemia syndrome)

- PNH and **aplastic anemia (AA)** are pathogenetically linked. AA is regarded as a **T-cell–mediated organ-specific autoimmune attack** on hematopoietic stem cells; the autoantigen in PNH may be the **GPI molecule itself**, so that **GPI-negative (PNH) stem cells are *spared*** the immune attack and undergo *positive (negative against normal cells) selection* and clonal expansion.
- Thus PNH results from **two factors acting together: (i) failure of normal hematopoiesis and (ii) escape/expansion of the GPI-deficient clone.**
- **Clinical overlap:** many patients with overt PNH have antecedent (often unnoticed) BMF; a patient with PNH may evolve into frank AA, and a patient with AA may develop hemolytic PNH years later. Small GPI-deficient (PNH) clones are detectable by flow cytometry in **≥50% of patients with aplastic anemia** at presentation — a small clone (<2%) without reticulocytosis or thrombosis is **not** true PNH.
- Useful clinical categories: **(a) classic hemolytic PNH**, **(b) PNH in the setting of another marrow-failure disorder (AA/MDS) — the "PNH-AA syndrome"**, and **(c) subclinical PNH** (a small clone, no clinical hemolysis).

Clinical features

Component of the triad	Manifestations
Intravascular hemolysis	Episodic **hemoglobinuria** — classically "passing blood instead of urine"; reddish-brown urine **typically in the first morning void** (nocturnal hypoventilation lowers blood pH and facilitates hemolysis). Anemia, fatigue; NO depletion → **dysphagia/esophageal spasm, abdominal pain, erectile dysfunction**. Hemoglobinuria varies dramatically hour-to-hour.
Thrombosis (venous, characteristically unusual sites)	Most **life-threatening** complication and the leading cause of death. **Hepatic vein → Budd-Chiari syndrome** (acute hepatomegaly + ascites without liver disease should raise suspicion of PNH); **mesenteric/abdominal veins** (recurrent severe abdominal pain); **cerebral veins (sagittal sinus)**; **dermal vessels** (painful nodules).
Bone marrow failure / cytopenias	Anemia with **neutropenia and/or thrombocytopenia** signalling marrow failure; may evolve to overt aplasia.

- **Natural history** spans decades; with supportive care only, historical **median survival ~10–20 years**, death mainly from thrombosis, then infection (neutropenia) and hemorrhage (thrombocytopenia). **Transformation to AML is rare (~1–2%)**; rare spontaneous remissions occur.

Laboratory diagnosis

- **Hemolysis profile:** normo- to macrocytic anemia with **reticulocytosis** (up to ~20% / 400,000/μL); **LDH markedly elevated** (values in the thousands); unconjugated bilirubin mildly–moderately raised; **haptoglobin undetectable**.
- **Intravascular hemolysis markers: urine hemosiderin positive** (chronic loss), **hemoglobinuria** on dipstick (serial samples help because it fluctuates); **iron deficiency** is common from chronic urinary iron loss (may make the anemia microcytic).
- **Direct antiglobulin (Coombs) test is characteristically NEGATIVE** — a key point distinguishing PNH from autoimmune hemolytic anemia. (It can turn *positive* once a patient is on anti-C5 therapy because of C3 opsonisation.)
- **Flow cytometry = gold standard:** demonstrates a discrete population of cells deficient in **CD55 and CD59** on **red cells AND granulocytes/monocytes**, giving a **bimodal distribution**. The **FLAER assay** (fluorescein-labelled proaerolysin, which binds the GPI anchor directly) on granulocytes/monocytes is **more sensitive**.
- **Diagnostic threshold:** do not diagnose PNH unless the GPI-deficient population is *substantial* — in first approximation **≥5% of red cells and ≥20% of granulocytes**.
- **Older tests:** the **acidified-serum (Ham) test** is highly reliable; the **sucrose hemolysis test is unreliable** (both now superseded by flow cytometry).
- **Bone marrow:** usually **cellular with marked erythroid hyperplasia** ± mild dyserythropoiesis; may become **hypocellular/aplastic** at some stage.

Management

- **Supportive (essential everywhere, as complement inhibitors are very expensive/often inaccessible):** mandatory **folic acid ≥3 mg/day**; periodic serum iron with **iron replacement** as needed (may transiently increase hemolysis); transfusion of **leukocyte-depleted red cells**; treat/anticipate iron overload if transfusion-dependent.
- **Anticoagulation:** any patient with prior venous thrombosis (or a thrombophilia risk factor on screening) should receive **regular anticoagulant prophylaxis**; thrombolysis (tPA) for refractory thrombosis.
- **Glucocorticoids: not** indicated for chronic hemolysis (contraindicated long-term); a short prednisone course may help an inflammation-driven flare.
- **Complement inhibitors (transform hemolysis, reduce transfusion need and thrombosis):**

Agent	Target	Comment
Eculizumab	**C5**	Humanized anti-C5 mAb (introduced 2007); blocks C5 cleavage → no MAC → abolishes intravascular hemolysis; **IV every 14 days**. Residual *extravascular* hemolysis from C3 opsonisation persists (Coombs becomes positive).
Ravulizumab	**C5**	Longer-acting eculizumab derivative; **IV every 8 weeks**; fewer breakthrough episodes.
Pegcetacoplan	**C3**	Proximal blockade prevents **both intravascular and extravascular** hemolysis → can fully correct anemia (higher Hb than C5 blockade).
Iptacopan	**Factor B**	**Oral**; blocks alternative-pathway C3 convertase.
Danicopan	**Factor D**	**Oral**; add-on for inadequate response to C5 blockade.

- **Meningococcal risk:** terminal-complement blockade predisposes to ***Neisseria meningitidis*** infection — **vaccinate against serogroups ACWY and B** (plus antibiotic prophylaxis, e.g., penicillin) before starting.
- **Breakthrough hemolysis** can occur with incomplete blockade (more abrupt/severe with proximal C3 blockade because of the larger surviving PNH red-cell mass).
- **Allogeneic HSCT** is the only **curative** option — reserved for **young patients with severe PNH** or **PNH-AA syndrome** (complement inhibitors do not treat the marrow failure); immunosuppression with **antithymocyte globulin + ciclosporin** is an alternative for the AA component.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Complement cascade and the GPI-protected red cell (with drug targets).** Labels: *Classical / Lectin / Alternative pathways* → **C3** → **C3 convertase** → **C5 convertase** → **C5** → **C5b–C9 = Membrane Attack Complex (MAC)**; **CD55 (DAF)** blocking the convertases; **CD59 (protectin)** blocking MAC; **GPI anchor** tethering CD55/CD59; **Normal RBC (protected)** vs **PNH RBC (CD55/CD59 negative → lysis)**; drug arrows — **Eculizumab/Ravulizumab at C5**, **Pegcetacoplan at C3**, **Iptacopan at factor B**, **Danicopan at factor D**.
- **Diagram 2 — GPI anchor on the red-cell membrane.** Labels: *lipid bilayer*, *GPI glycolipid anchor*, *CD55*, *CD59*, *PIGA gene* → *GPI biosynthesis*; show **normal cell (anchor + proteins present)** vs **PNH cell (anchor and proteins absent due to PIGA mutation)**.

Clinical / Diagnostic significance

- **Suspect PNH** in: Coombs-negative intravascular hemolytic anemia; hemolysis **with** unexplained cytopenia/pancytopenia or aplastic anemia; **venous thrombosis at unusual sites** (especially **Budd-Chiari syndrome** or abdominal/cerebral vein thrombosis) in a young patient; and unexplained iron-deficiency with hemoglobinuria.
- **LDH very high + haptoglobin absent + urine hemosiderin positive + DAT negative** is the classic biochemical signature; confirm with **flow cytometry (CD55/CD59, FLAER)**.
- Screen all **aplastic anemia and hypoplastic MDS** patients for a PNH clone, and **monitor PNH patients for evolving marrow failure**.
- Recognising the **NO-depletion symptoms** (dysphagia, abdominal pain, erectile dysfunction) and **thrombotic risk** drives early complement inhibition and anticoagulation, which markedly improve quality of life and survival.

High-yield exam pointers

- PNH = **acquired clonal stem-cell disease**; somatic **X-linked *PIGA*** mutation → **GPI-anchor deficiency** → loss of **CD55 & CD59** → complement-mediated **intravascular hemolysis**.
- **Triad:** hemolysis + **venous thrombosis** (leading cause of death) + **bone-marrow failure/pancytopenia**.
- **CD59** is the most important protector (blocks MAC); **CD55** accelerates convertase decay.
- **DAT/Coombs NEGATIVE** — distinguishes PNH from AIHA.
- **Diagnosis = flow cytometry** for GPI-deficient red cells *and* granulocytes; **FLAER** most sensitive; threshold **≥5% RBC / ≥20% granulocytes**; **Ham (acidified serum) test** classic, sucrose test unreliable.
- **First morning urine** is darkest (nocturnal acidosis); **LDH markedly raised, haptoglobin absent, urine hemosiderin positive**; iron deficiency common.
- **Budd-Chiari syndrome without liver disease → think PNH.**
- **Eculizumab (anti-C5, q2w)** and **ravulizumab (q8w)** abolish intravascular hemolysis; **pegcetacoplan (C3)/iptacopan (factor B)/danicopan (factor D)** also block extravascular hemolysis; **meningococcal vaccination mandatory** before complement blockade.

- **Allogeneic HSCT** is the only cure (for severe PNH / PNH-AA syndrome); **folic acid ≥3 mg/day** is mandatory supportive care; **AML transformation ~1–2%**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Hemolytic Anemias"** (Acquired/PNH section: PIGA, GPI anchor, CD55/CD59, complement cascade Figs 105-10/105-11, diagnosis, anti-complement therapy) and **"Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia"** (PNH–aplastic anemia relationship).
- **CMDT 2026 — "Blood Disorders" (Paroxysmal Nocturnal Hemoglobinuria)** — essentials of diagnosis, FLAER assay, nitric-oxide–mediated symptoms, thrombosis sites, and current complement-inhibitor regimens including meningococcal prophylaxis.
- Standard nomenclature CD55 = *decay-accelerating factor* and CD59 = *membrane inhibitor of reactive lysis/protectin* is universally accepted textbook hematology (the functional roles are as described in Harrison).
- *Coverage note:* The assigned specialty text (**DeVita's *Cancer: Principles & Practice of Oncology* 12e**) does **not** substantively cover PNH (search matches were incidental, e.g., author names/"epigastric"); depth here is therefore drawn from Harrison 22e plus CMDT 2026, both of which cover PNH comprehensively.

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Disseminated intravascular coagulation

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

Definition / Introduction — In 2001 the *International Society on Thrombosis and Haemostasis (ISTH)* defined **DIC** as "an acquired syndrome characterised by the **intravascular activation of coagulation with loss of localisation** arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe can produce **organ dysfunction**." It is *never a primary disease* but always **secondary** to an underlying disorder. The central event is **uncontrolled, systemic generation of thrombin**, leading to widespread microvascular fibrin deposition (causing ischaemic organ failure) and simultaneous **consumption of platelets and clotting factors** with secondary hyperfibrinolysis (causing bleeding) — hence the older terms *consumptive coagulopathy* and *defibrination syndrome*.

Etiology — Common clinical triggers

DIC accompanies any condition that releases tissue factor into the circulation or causes diffuse endothelial injury.

Category	Representative causes
Sepsis / infection (commonest)	Gram-negative bacilli, *staphylococci, streptococci, pneumococci, meningococci*; also viral, mycotic, parasitic, rickettsial
Trauma / tissue injury	Brain injury (gunshot), extensive burns, fat embolism, rhabdomyolysis

Category	Representative causes
Obstetric	Abruptio placentae, amniotic fluid embolism, dead fetus (retained) syndrome, septic abortion; **HELLP syndrome**
Malignancy	Mucin-producing **adenocarcinoma** (prostate, pancreas); **acute promyelocytic leukaemia (APL, AML-M3)**
Vascular	Giant haemangioma (**Kasabach-Merritt syndrome**), large-vessel aneurysm (e.g. aorta)
Immunologic	Acute haemolytic transfusion reaction, transplant rejection, graft-versus-host disease, immunotherapy
Envenomation / drugs	Snake bite, insect venom; fibrinolytic agents, prothrombin complex concentrates, amphetamines
Liver / miscellaneous	Fulminant hepatic failure, fatty liver of pregnancy; shock, ARDS, massive transfusion

Pathophysiology

- **Initiation — uncontrolled thrombin generation:** Activation of inflammatory pathways markedly increases **tissue factor** expression, activates neutrophils/monocytes with **cytokine release**, forms **neutrophil extracellular traps (NETs)** and releases polyphosphates — collectively termed **thrombo-inflammation** — driving massive thrombin generation through the extrinsic pathway.
- **Amplification:** Simultaneous **disruption of physiological anticoagulants** (antithrombin, protein C/S, tissue factor pathway inhibitor) and **endothelial injury** (loss of native antithrombotic surface, prominent in sepsis and trauma) remove the normal brakes on coagulation.
- **Microvascular fibrin deposition:** Sustained fibrin formation in small and mid-size vessels compromises blood supply to **lung, kidney, liver and brain** → multi-organ ischaemia/failure (pulmonary microthrombosis contributes to **ARDS**).
- **Consumption → bleeding:** Continuous activation consumes platelets and coagulation factors faster than they are produced, producing systemic bleeding, aggravated in late stages by **secondary hyperfibrinolysis** (plasmin generation raising FDPs/D-dimer).
- **RBC fragmentation:** Fibrin strands across the microcirculation shear passing red cells → **schistocytes** and microangiopathic haemolysis.
- ***SIRS / cytokine storm*** in the setting of infection drives this exuberant response and correlates with higher mortality. **Purpura fulminans** is the most severe form — extensive cutaneous thrombosis, classically in children after viral/bacterial infection or in neonates **homozygous for protein C deficiency**.

Clinical features

- **Bleeding (consumptive):** Petechiae, ecchymoses, oozing from venepuncture/catheter/incision sites; severe haemorrhage from the GI tract, lung, or CNS. Multiple simultaneous bleeding sites are characteristic.
- **Thrombosis (occlusive):** Microvascular occlusion → **organ failure** (oliguria/renal failure, hypoxia, hepatic dysfunction, delirium/coma); large-vessel thrombosis and cerebral embolism

may occur. Malignancy-associated DIC may present chiefly as thrombosis (**Trousseau syndrome**, migratory thrombophlebitis).

- **Acute (decompensated) DIC:** Rapidly evolving, bleeding-dominant, with haemodynamic instability and **shock**; reported mortality **30 to >80%**, largely driven by the underlying disease.
- **Chronic (compensated, low-grade) DIC:** Seen with giant haemangioma, metastatic carcinoma, or late-gestation fetal demise; compensated synthesis keeps PT/aPTT/fibrinogen normal or high with only mild thrombocytopenia and elevated D-dimer — *often thrombosis-predominant*.

Laboratory diagnosis & ISTH overt-DIC score

No single test is diagnostic; diagnosis rests on a **compatible clinical setting plus a panel of tests interpreted serially** (repeat every 6–8 h in the critically ill, as values change rapidly).

- **Platelet count** — low or progressively *falling* (a downward trend is more useful than a single value).
- **PT and aPTT** — prolonged (factor consumption).
- **Fibrinogen** — low or falling (an acute-phase reactant, so may be "normal" early — trend matters).
- **D-dimer / FDP** — elevated (the most sensitive marker of activation + secondary fibrinolysis).
- **Peripheral smear — schistocytes** (present in only ~10–20% of cases; their absence does not exclude DIC).

The **ISTH overt-DIC scoring system** (validated; *not for use in pregnancy* — a separate obstetric tool exists):

Parameter	Value	Points
Platelets	>100 × 10^9/L	0
	50–<100 × 10^9/L	1
	<50 × 10^9/L	2
D-dimer / fibrin marker	Normal	0
	Moderate increase	2
	Severe increase	3
PT prolongation	<3 s	0
	3–<6 s	1
	>6 s	2
Fibrinogen	>1 g/L	0
	<1 g/L	1

- **Score ≥5 → overt DIC** (repeat labs *daily*). **Score <5 → suggests non-overt / low-grade DIC** (repeat every 1–2 days). A positive score should prompt a search for the underlying cause if not already evident.

Differential diagnosis

Condition	Discriminating features
Severe liver disease	Thrombocytopenia (hypersplenism), low factors, raised D-dimer — but parameters **do not change rapidly** on serial testing; **FVIII normal/high** (falls only if DIC superimposed); reduced FV reflects hepatocyte failure
Thrombotic thrombocytopenic purpura (TTP)	Acute thrombocytopenia, schistocytes, organ failure, but **PT/aPTT/fibrinogen near-normal**; **ADAMTS13 <10% with inhibitor** is diagnostic
HIT	Thrombocytopenia + thrombosis after heparin; normal fibrinogen, positive anti-PF4 antibodies
Primary hyperfibrinolysis	Low fibrinogen, raised FDP but **D-dimer relatively normal** and platelets preserved

Treatment

- **Treat the underlying cause** — the single most important measure (antimicrobials for sepsis, delivery/uterine evacuation in obstetric DIC and HELLP, chemotherapy for malignancy). DIC will not resolve until the trigger is controlled; most overt cases need **ICU** support for shock physiology.
- **Blood-product/replacement support — only if active bleeding or high bleeding risk** (invasive procedure, post-chemotherapy); *do not transfuse merely to correct numbers*:
  - **Platelets** for counts **<10,000–20,000/µL** (or <50,000/µL with serious/intracranial bleeding or before procedures).
  - **Cryoprecipitate / fibrinogen concentrate** to keep **fibrinogen >100–150 mg/dL**.
  - **FFP** for bleeding with prolonged PT/aPTT; aim PT **no more than ~3 s above ULN** (target PT/aPTT <1.5 × normal).
  - **Packed RBCs** for symptomatic anaemia; give **vitamin K**.
- **Heparin (low-dose continuous infusion, 5–10 U/kg/h, no bolus):** Indicated when **thrombosis predominates** — chronic/low-grade DIC with solid tumours, APL, Trousseau syndrome, and **purpura fulminans**. *Contraindicated/harmful in acute haemorrhagic DIC* and when platelets cannot be kept >20,000–50,000/µL, or with CNS/GI bleeding or placental abruption. It improves coagulation parameters but has **not shown a survival benefit** in severe DIC.
- **Anticoagulant concentrates** (antithrombin, recombinant thrombomodulin): little benefit overall, though post-hoc data in sepsis-confirmed DIC suggest possible advantage. *Activated protein C was withdrawn* after trial benefit was not reproduced.
- **Antifibrinolytics** (tranexamic acid, EACA): reserved for **primary-hyperfibrinolytic DIC with severe bleeding** (e.g. APL, giant haemangioma); risk of catastrophic thrombosis — often combined with heparin and used only with haematology input.
- **APL-associated DIC:** A haematological emergency — start **all-trans retinoic acid (ATRA)** at the *earliest suspicion* (do not wait for genetic confirmation) together with aggressive product support; modern induction is **ATRA + arsenic trioxide (ATO)**, which reduces early haemorrhagic death.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow diagram (Harrison Fig. 121-4):** Box-and-arrow cascade — *Trigger (sepsis/trauma/malignancy/obstetric)* → **Uncontrolled thrombin generation** → branch into **(a) Fibrin deposits in microcirculation** → *Ischaemic tissue damage + RBC damage/haemolysis (schistocytes)* → **Failure of multiple organs**; and **(b) Consumption of platelets and coagulation factors** → *Secondary fibrinolysis (↑FDP, ↑D-dimer)* → **Diffuse bleeding**. Add a side note: "Vessel patency vs occlusion = bleeding vs thrombosis balance."
- **Coagulation cascade with test mapping (Fig. 121-1):** Intrinsic (XII→XI→IX→VIII, *aPTT*) and extrinsic (VIIa/tissue factor, *PT*) pathways converging on common pathway (X→Xa→prothrombin→**thrombin**→fibrinogen→fibrin, cross-linked by XIIIa, *TT*) — label PT, aPTT, TT, and "fibrin → FDP/D-dimer."

Clinical / Diagnostic significance

- DIC is a **clinico-pathological diagnosis**: laboratory abnormalities must be interpreted *with* the clinical context and *serially* — an isolated abnormal value is non-specific.
- A **falling trend** in platelets and fibrinogen with a **rising D-dimer/PT** is more diagnostic than any single absolute value, especially in malignancy where baseline values may be normal.
- Recognising the **bleeding-vs-thrombosis phenotype** directs therapy: product replacement for the bleeding-dominant acute form, heparin for the thrombosis-dominant chronic/purpura fulminans form.
- The ISTH score gives an objective, reproducible threshold (**≥5 = overt DIC**) for diagnosis and serial monitoring — but is **not validated in pregnancy**.
- Distinguishing DIC from **liver disease** and **TTP** changes management entirely (TTP needs plasma exchange, not factor replacement); serial labs, FVIII level, and ADAMTS13 are the key discriminators.

High-yield exam pointers

- **ISTH 2001 definition** — acquired syndrome of intravascular activation of coagulation with loss of localisation. Always **secondary**; never primary.
- **Central mechanism = uncontrolled thrombin generation** via tissue factor + thrombo-inflammation (cytokines, NETs).
- **Commonest cause = sepsis** (esp. Gram-negative); other classics — **APL, abruptio placentae, amniotic fluid embolism, mucinous adenocarcinoma, snake bite, Kasabach-Merritt**.
- **Lab tetrad:** ↓platelets, ↑PT & aPTT, ↓fibrinogen, ↑D-dimer/FDP; **schistocytes in ~10–20%**.
- **ISTH overt-DIC score ≥5** = overt DIC (platelets, D-dimer, PT, fibrinogen).
- **Treat the underlying cause first**; transfuse only if bleeding/high risk — *don't treat numbers alone*.
- **Heparin** helps thrombotic/chronic DIC & purpura fulminans; **harmful in acute haemorrhagic DIC**.
- **APL → start ATRA immediately** on suspicion; **HELLP → deliver**; **Trousseau → LMWH/heparin** (warfarin ineffective).

- **DDx:** liver disease (parameters change slowly, FVIII normal/high) and **TTP** (ADAMTS13 <10% + inhibitor).
- Mortality of acute DIC **30 to >80%**, dictated by the underlying illness.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Coagulation Disorders" (Disseminated Intravascular Coagulation section, Tables 121-2 & 121-3, Fig. 121-4 pathophysiology).
- **CMDT 2026** — "Disorders of Hemostasis, Thrombosis & Antithrombotic Therapy" (DIC diagnosis, Table 16-6 management algorithm, HELLP/Trousseau).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — Acute Promyelocytic Leukaemia (early ATRA initiation; ATRA + arsenic trioxide).

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Multiple myeloma

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Multiple myeloma (MM) is a malignant proliferation of a single clone of plasma cells derived from the late B-lymphocyte lineage, characterised by clonal bone-marrow plasmacytosis, a serum and/or urine monoclonal (M) protein, and myeloma-defining end-organ damage (**CRAB** — hyperCalcaemia, Renal insufficiency, Anaemia, Bone lesions). It is incurable but highly treatable: with modern triplet/quadruplet induction, autologous transplantation and continuous maintenance, median overall survival now exceeds 8 years. Management is risk-adapted and rests on three pillars — accurate diagnosis/staging, sequential anti-myeloma therapy, and vigorous supportive care.

Diagnosis, staging and risk stratification (the basis for treatment)

- **Diagnosis (IMWG):** clonal bone-marrow plasma cells ≥10% (or biopsy-proven plasmacytoma) **plus** ≥1 myeloma-defining event — either **CRAB** features or a **SLiM** biomarker of malignancy: clonal marrow plasma cells **≥60%**, involved:uninvolved serum **free light chain (FLC) ratio ≥100**, or **>1 focal lesion on MRI** (each ≥5 mm).
- **CRAB thresholds:** Calcium >11 mg/dL (or >1 mg/dL above normal); creatinine >2 mg/dL or creatinine clearance <40 mL/min; haemoglobin <10 g/dL (or >2 g/dL below normal); ≥1 osteolytic lesion on skeletal survey, CT or PET-CT.
- **Distinguish from precursors:** *MGUS* (M-protein <30 g/L, marrow PCs <10%, no MDE) and *smoldering MM* (M-protein ≥30 g/L and/or marrow PCs 10–60%, no MDE) — these are **observed, not treated** (except high-risk SMM, see below).
- **Workup:** SPEP + immunofixation, serum FLC and quantitative immunoglobulins, 24-h urine for Bence Jones protein; marrow aspirate/biopsy with κ/λ clonality ($CD138^+$); FISH/DNA-sequencing; β2-microglobulin, albumin, LDH; whole-body low-dose CT / PET-CT or MRI (radionuclide bone scan is **not** useful — lesions are purely lytic).

System	Parameters	Strata
ISS	β2-microglobulin + albumin	I: β2M <3.5 + alb ≥3.5 (median ~62 mo); II: intermediate (~44 mo); III: β2M >5.5 (~29 mo)
R-ISS	ISS + **high-risk cytogenetics + LDH**	I: ISS-I, normal LDH, no high-risk FISH; III: ISS-III with high-risk FISH or high LDH; II: rest
High-risk FISH	—	t(4;14), t(14;16), t(14;20), **del(17p)/TP53**, gain/amp 1q, del 1p
Standard-risk FISH	—	t(11;14), t(6;14), hyperdiploidy; **del(13q) & t(11;14) are NOT high-risk**

- **mSMART/Mayo:** "double-hit" = any 2 high-risk lesions, "triple-hit" = ≥3 — confer the worst prognosis (median OS ~3 yr vs >7–10 yr for standard risk).

Goals and overall framework of therapy

- Two parallel aims: **(1) systemic anti-myeloma therapy** to achieve the deepest possible response, and **(2) supportive care** for complications and treatment toxicity.
- Therapy is sequenced as **induction → high-dose therapy/ASCT (consolidation) → maintenance → therapy of relapse**, partitioned by **transplant eligibility** (age, performance status, comorbidity).
- The three backbone drug classes for newly diagnosed MM are **immunomodulatory drugs (IMiDs)**, **proteasome inhibitors (PIs)** and **anti-CD38 monoclonal antibodies**, almost always combined with **dexamethasone**.

Class	Representative agents (dose)	Key toxicity
IMiD	Lenalidomide (5–25 mg PO × 21/28 d); thalidomide; pomalidomide (2–4 mg)	VTE, cytopenias, neuropathy (thalidomide), teratogenicity
Proteasome inhibitor	Bortezomib (1.3 mg/m^2 SC d1,4,8,11); carfilzomib (20–56 mg/m^2); ixazomib (4 mg PO, oral)	Bortezomib → peripheral neuropathy, HZV reactivation; carfilzomib → cardiac/pulmonary
Anti-CD38 mAb	Daratumumab (16 mg/kg IV or SC); isatuximab (10 mg/kg)	Infusion reactions, infection
Other antibody/ADC	Elotuzumab (anti-SLAMF7); belantamab mafodotin (anti-BCMA ADC)	Belantamab → keratopathy (ocular)
Alkylator / steroid	Melphalan (high-dose conditioning); cyclophosphamide; dexamethasone 40 mg/wk	Marrow toxicity, secondary MDS/leukaemia

Front-line therapy

- **Smoldering MM:** generally observed; **high-risk SMM** — early **lenalidomide ± dexamethasone** delays progression to active disease and may prolong survival.
- **Transplant-ELIGIBLE (newly diagnosed):**
  - **Induction:** a PI + IMiD + dexamethasone triplet — **VRd** (bortezomib–lenalidomide–dexamethasone) or KRd (carfilzomib-based) achieves ~100% overall and >50% complete

response (CR); alternatives VTd, VCd. **Adding daratumumab/isatuximab as a quadruplet** (e.g. **Dara-VRd**) gives deeper responses and is now becoming standard of care. Give **4–6 cycles** to achieve maximal cytoreduction.

- **Stem-cell collection:** harvest **within ~6 months** as prolonged lenalidomide impairs stem-cell yield.
- **High-dose therapy + autologous SCT (ASCT):** conditioning with **high-dose melphalan**; adds 25–40% further CRs and prolongs PFS/OS. **Tandem ASCT** benefits only patients failing to reach ≥VGPR after the first. Delayed (relapse) transplant is an acceptable alternative as upfront ASCT showed no OS difference vs delayed in a randomised trial.
- **Maintenance: lenalidomide** (continuous) prolongs PFS and OS — small increased risk of second primary malignancy is outweighed by benefit. **Add bortezomib or ixazomib (a PI)** for high-risk cytogenetics; **daratumumab** maintenance is also beneficial.

- **Transplant-INELIGIBLE (age >70, significant cardiopulmonary disease, comorbidity):** the same triplets with frailty-adjusted dosing — **DRd** (daratumumab–lenalidomide–dexamethasone, ORR ~93%) or **RVD-lite** (ORR ~86%); fit older patients may receive quadruplets. Older melphalan-prednisone (MP)-based regimens (MPT, VMP) are now largely superseded but retain a role where novel agents are unavailable.

Relapsed / refractory disease and immunotherapy

- Treatment of relapse uses **alternate combinations** incorporating agents not previously used or to which the patient is not refractory.
- **Salvage agents:** carfilzomib and pomalidomide (active even in lenalidomide/bortezomib-refractory disease); all-oral **IRd** (ixazomib-Rd); anti-CD38 **daratumumab/isatuximab** combinations; **elotuzumab** + Rd; **belantamab mafodotin** (BCMA ADC — needs ophthalmologic monitoring); **selinexor** (first-in-class XPO1/exportin nuclear-export inhibitor); **panobinostat** (HDAC inhibitor) + bortezomib-dexamethasone; melflufen.
- **BCMA-directed cellular therapy (CAR-T): idecabtagene vicleucel (Ide-cel)** — after ≥2 prior lines (IMiD + PI + anti-CD38); **ciltacabtagene autoleucel (Cilta-cel)** — after ≥1 prior line and lenalidomide-refractory; response rates ~81–98% with high CR rates.
- **Bispecific T-cell engagers** (after ≥4 prior lines): **teclistamab** and **elranatamab** (anti-BCMA × CD3); **talquetamab** (anti-**GPRC5D** × CD3); ORR ~60–70%.
- **Class toxicities of immunotherapy: cytokine-release syndrome**, **neurotoxicity (ICANS)**, and **prolonged hypogammaglobulinaemia/infection** — may need IVIG support.

Supportive and adjunctive care (often as important as anti-tumour therapy)

- **Bone disease:** monthly **bisphosphonate** — zoledronate 4 mg or pamidronate 90 mg (12–24 months) — reduces skeletal events; **denosumab 120 mg SC monthly** is the alternative (preferred in renal impairment). Watch for **osteonecrosis of the jaw**. **Vertebroplasty/kyphoplasty** for painful vertebral collapse; **local radiotherapy (~40 Gy)** for focal painful lesions and solitary plasmacytomas.

- **Renal protection:** hydration, avoid NSAIDs/iodinated contrast/nephrotoxins; treat hypercalcaemia and hyperuricaemia; rapid M-protein reduction with **bortezomib-based therapy** can recover renal function; **plasma exchange** considered for cast nephropathy/light-chain–induced AKI.
- **Hypercalcaemia:** hydration + natriuresis, bisphosphonates, glucocorticoids (± calcitonin).
- **Hyperviscosity: plasmapheresis**.
- **Infection prophylaxis:** pneumococcal (conjugate) and influenza vaccination; **herpes-zoster prophylaxis** with bortezomib or anti-CD38 therapy; **IVIG** for recurrent serious infection or post CAR-T/bispecific hypogammaglobulinaemia.
- **VTE prophylaxis** with IMiDs: **aspirin** (low risk) or **LMWH/warfarin/DOAC** (high risk).
- **Anaemia:** erythropoietin with haematinics.

Response assessment (IMWG)

- Hierarchy of depth: **MRD-negative > stringent CR (sCR) > CR > VGPR > PR > minor response > stable > progressive disease**.
- **CR** = negative serum/urine immunofixation, no soft-tissue plasmacytoma, marrow plasma cells <5%; **sCR** adds normal FLC ratio and absence of clonal plasma cells; **VGPR** = M-protein detectable by immunofixation but not electrophoresis, or ≥90% serum reduction.
- **MRD** by next-generation flow/sequencing at **10^{-5} sensitivity** is the deepest endpoint and predicts longer PFS and OS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Risk-adapted treatment algorithm of MM** — boxes/arrows: *Newly diagnosed MM* → assess MDE → (Smoldering → observe / high-risk SMM → Len ± Dex) and (Symptomatic → split by **Transplant-eligible vs ineligible**) → **Induction (triplet/quadruplet)** → eligible arm: **HDT + autologous SCT → consolidation** → both arms: **Maintenance (lenalidomide ± PI)** → **Relapse → alternate regimens → CAR-T / bispecifics**. Label drug classes IMiD/PI/anti-CD38.
- **Pathophysiology / CRAB wheel** — central *clonal plasma cell* with spokes labelled: **RANKL↑/OPG↓ → osteoclast activation → lytic bone lesions & hyperCalcaemia**; **light chains → cast nephropathy/Renal failure**; **marrow infiltration → Anaemia**; **immunoparesis → infection**; **M-protein → hyperviscosity/amyloid**.

Clinical / Diagnostic significance

- The **serum M-component is the best tumour marker** for monitoring; serum/urine FLC fall faster (t½ ~6 h) than intact Ig (t½ ~3 wk) and track tumour kill earlier.
- Recognise **myeloma emergencies**: spinal cord compression, pathological fracture, hypercalcaemia, hyperviscosity, sepsis and AKI — each alters immediate management priorities.
- Cytogenetics (FISH/sequencing) drive both **prognosis (R-ISS)** and **treatment intensity** (add a PI to maintenance in high-risk disease).
- Achieving and sustaining **MRD negativity** is the emerging therapeutic goal and a powerful surrogate for survival.

High-yield exam pointers

- **Diagnosis = ≥10% clonal marrow PCs + M-protein + ≥1 MDE (CRAB or SLiM biomarker).**
- **SLiM:** Sixty% PCs, Light-chain ratio ≥100, MRI >1 focal lesion.
- **R-ISS = ISS (β2M + albumin) + high-risk cytogenetics + LDH.**
- **High-risk FISH:** t(4;14), t(14;16), t(14;20), del(17p), 1q gain — *t(11;14) and del(13q) are standard-risk.*
- **Backbone classes:** IMiD + PI + anti-CD38 + dexamethasone; quadruplet (Dara-VRd) is the modern standard induction.
- **ASCT conditioning = high-dose melphalan;** lenalidomide is standard **maintenance**.
- **BCMA targets:** CAR-T (Ide-cel, Cilta-cel) and bispecifics (teclistamab, elranatamab); **talquetamab targets GPRC5D**.
- **Bone disease:** monthly zoledronate/pamidronate or denosumab; beware osteonecrosis of jaw.
- **IMiD → mandatory VTE prophylaxis; bortezomib → HZV prophylaxis + give SC/weekly to cut neuropathy.**
- **Median OS now >8 years; MRD negativity (10^{-5}) = deepest response.**

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Plasma Cell Disorders" (diagnostic criteria, ISS/R-ISS components, drug classes/doses, treatment algorithm, supportive care).
- DeVita, Hellman & Rosenberg's *Cancer: Principles & Practice of Oncology*, 12e — "Plasma Cell Neoplasms" (Revised ISS table, Mayo/mSMART double-hit/triple-hit risk stratification, IMWG response & MRD criteria).
- CMDT 2026 — "Plasma Cell Myeloma" (current induction/maintenance approach, ASCT, salvage and immunotherapy, supportive management).

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Acute chest syndrome in sickle cell disease

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Acute chest syndrome (ACS)* is an acute, pneumonia-like, vaso-occlusive complication of sickle cell disease (SCD) defined by a **new pulmonary infiltrate on chest radiograph involving at least one complete lung segment**, together with respiratory symptoms and/or fever. It is the **second most frequent acute sickle cell–related event** (after the acute painful episode), occurs in **>50% of patients** (often recurrently), and is a **leading cause of death and ICU admission** in adults with SCD. It results from the interplay of pulmonary vaso-occlusion, fat embolism, infection and hypoventilation, and ranges from a mild self-limiting illness (especially in children) to fulminant multilobar disease with ARDS, multiorgan failure and rapid death.

Pathophysiology in brief

- **HbS** (β6 Glu→Val) polymerises when deoxygenated; the rate of polymerisation depends on roughly the **30th power of HbS concentration**, so small falls in oxygen saturation, pH or cell hydration markedly accelerate sickling.
- Sickled, rigid erythrocytes and *irreversibly sickled cells (ISCs)* occlude the **pulmonary microvasculature**, producing in-situ thrombosis, regional hypoxia and a self-amplifying cycle of further sickling.
- Intravascular **haemolysis scavenges nitric oxide**, activates endothelium and platelets, and is pro-inflammatory and vasoconstrictive — promoting lung injury and pulmonary vasculopathy.
- A final common pathway is **ventilation–perfusion mismatch and worsening hypoxaemia**, which begets more polymerisation: the cardinal vicious cycle of ACS.

Triggers / precipitating factors

ACS is frequently **multifactorial**, and a single cause is identified in fewer than half of episodes. The recognised triggers are:

Category	Specific triggers
Infection	Any infection — viral (common in children), bacterial and atypical organisms; pneumonia is a classic precipitant
Vascular / embolic	**In-situ pulmonary microvascular thrombosis**; pulmonary infarction; **fat / bone-marrow embolism** from infarcted (necrotic) marrow — the cause of the most severe, often fatal episodes
Hypoventilation	**Postoperative hypoventilation**; splinting from rib/sternal or thoracic-bone infarction pain; **opioid-induced respiratory depression** during treatment of an acute painful episode
Iatrogenic / fluid	**Over-hydration** (pulmonary oedema) and **excessive opioids** compound dyspnoea and hypoxia
Antecedent painful crisis	ACS **follows within 72 h in ~25% (about one-quarter) of admissions for an acute painful episode**
Other	Asthma/bronchospasm (very common in SCD); surgery and general anaesthesia; cold exposure, dehydration and hypoxia (shared sickling triggers)

Clinical presentation

- **Cardinal features (major diagnostic criteria): chest pain, cough, fever, hypoxia, and a new pulmonary infiltrate on chest x-ray.**
- **Respiratory:** tachypnoea, dyspnoea, wheeze, pleuritic chest pain; falling SpO_2; in severe disease, multilobar consolidation with profound hypoxaemia.
- **Systemic:** fever (often ≥38.5 °C), tachycardia, leucocytosis; frequently superimposed on an ongoing acute painful episode involving ribs, sternum or spine.
- **Spectrum:** *mild* (children, often viral) → *devastating* (adults — multiple lobes affected, severe hypoxia, multiorgan failure and death).
- **Course:** because the infiltrate may lag behind symptoms, an initially normal CXR does **not** exclude ACS; serial radiographs and pulse oximetry are essential.
- **Differential diagnosis:** must be distinguished from **infective pneumonia** (overlapping and often coexistent), pulmonary thromboembolism, fluid overload/pulmonary oedema, and from sepsis/multiorgan failure.

Predictors of severe disease

- **Thrombocytopenia**, **leucocyte count >20,000/μL**, and a **rapidly developing/drastic fall in haemoglobin** portend severe ACS with ARDS and multiorgan failure.
- The most catastrophic cases are typically due to **embolisation of necrotic bone marrow (fat embolism)** and may progress to death even with prompt, correct treatment.
- Multiorgan failure (CNS, liver, muscle, lung, kidney) can accompany severe ACS and is easily confused with — and may coexist with — sepsis.

Management

General principle: **severity-driven**, supportive and pre-emptive, with the threshold for transfusion and ICU care kept deliberately low.

Intervention	Practical detail
Monitoring & disposition	Hypoxic, febrile patients may be admitted **directly to the ICU**; continuous pulse oximetry / monitored beds for the first **48–72 h** of any pain admission help detect early ACS
Oxygen	Supplemental O_2 for **SpO_2 <95%** (or hypoxaemia); titrate to maintain saturation
Antibiotics	**Almost always given**, even though a causative organism is seldom cultured; cover typical and atypical respiratory pathogens
Analgesia	Adequate pain control to permit deep breathing — but **avoid excessive opioids** (respiratory depression worsens hypoxia)
Fluids	Careful hydration; **avoid over-hydration** (precipitates/worsens pulmonary oedema)
Incentive spirometry	Used during painful episodes to **forestall pulmonary complications/atelectasis** and ACS

Intervention	Practical detail
Transfusion	Indicated for hypoxic, febrile patients with leucocytosis and **more than a trivial infiltrate**. **Simple (top-up) transfusion** suffices for less severe cases. **Automated red-cell exchange transfusion is the preferred modality in severe ACS** (and in stroke / multiorgan failure). If exchange will take hours to arrange in a severely ill patient, **start a simple/top-up transfusion first**
Transfusion safety	Extended red-cell antigen phenotyping where possible; **antigen-match for Rh (C/c, E/e) and K** in addition to ABO/RhD to reduce alloimmunisation
Supportive / ICU	Bronchodilators for bronchospasm/asthma; VTE prophylaxis; treat multiorgan failure with exchange transfusion and full ICU support

Preventive (disease-modifying) therapy that reduces ACS:

- **Hydroxyurea** — standard of care for HbSS and HbS-β^0 thalassaemia; raises HbF and **reduces pain and ACS by about half** and long-term mortality by ~49%. Adult dosing titrated to maximum tolerated dose by neutrophil/platelet counts (CMDT: 15–35 mg/kg/day); start infants at ~20 mg/kg from 9 months of age.
- **L-glutamine** — reduces painful episodes (~25%) and favourably modulates ACS.
- **Crizanlizumab** (anti–P-selectin) and **voxelotor** (increases Hb–O_2 affinity) modulate vaso-occlusion; **chronic transfusion** is used for recurrent severe ACS.
- **Curative options:** HLA-matched allogeneic stem-cell transplant (event-free survival >95% with matched related donor) and approved **ex-vivo gene therapies** (lovotibeglogene autotemcel — HbA^T87Q; exagamglogene autotemcel — CRISPR/Cas9 disruption of *BCL11A* to raise HbF).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vicious cycle of ACS (flow diagram).** Labels: *Trigger (infection / fat embolus / hypoventilation / pain)* → *Regional hypoxia & low pH* → *HbS polymerisation & sickling* → *Pulmonary microvascular vaso-occlusion + in-situ thrombosis* → *V/Q mismatch* → *Worsening hypoxaemia* → (arrow looping back to *HbS polymerisation*); side-branch *Intravascular haemolysis* → *NO depletion* → *endothelial activation/inflammation*.
- **Annotated chest radiograph schematic.** Labels: *new infiltrate involving ≥1 complete lung segment*, *multilobar consolidation*, *basal predominance*, *small pleural effusion* — captioned "ACS: new pulmonary infiltrate + respiratory symptom/fever/hypoxia."

Clinical / Diagnostic significance

- **Definition (NHLBI/standard):** a **new radiodensity on CXR involving ≥1 complete lung segment**, plus **≥1 of** chest pain, fever ≥38.5 °C, tachypnoea/wheeze/cough, or hypoxia — operationalises the major criteria for the exam and the ward.
- **Investigations:** CBC (falling Hb, leucocytosis, platelet count), reticulocytes, ABG/pulse oximetry, chest radiograph (serial), blood and respiratory cultures, atypical-pathogen testing; consider CT-pulmonary angiography if thromboembolism is suspected.
- **Pearls:** an antecedent painful crisis is the commonest setting — anticipate ACS in the first 72 h; keep **opioids and IV fluids restrained**; transfuse early for hypoxia with infiltrate; **exchange (not**

simple) transfusion for severe/multiorgan disease; antibiotics empirically despite negative cultures.

- ACS may leave a **chronic restrictive deficit with reduced DLCO** and contributes to pulmonary hypertension — both markers of poor long-term prognosis.

High-yield exam pointers

- ACS = **new lung-segment infiltrate + (chest pain / fever / tachypnoea-cough-wheeze / hypoxia)**; second commonest acute SCD event, **>50%** lifetime incidence.
- Four classic trigger groups: **infection, fat/marrow embolism, in-situ pulmonary thrombosis, postoperative hypoventilation** — often multifactorial; cause unidentified in most.
- **~25% of acute pain admissions develop ACS within 72 h** — monitor with pulse oximetry for 48–72 h.
- Severity predictors: **platelets ↓, WBC >20,000/μL, rapidly falling Hb** → ARDS/multiorgan failure; the worst cases are **bone-marrow fat embolism**.
- Treatment quartet: **oxygen (SpO_2 <95%), antibiotics, judicious analgesia/fluids, transfusion — exchange transfusion for severe disease**.
- **Avoid over-hydration and over-sedation with opioids** — both worsen hypoxia.
- **Incentive spirometry** prevents ACS during painful crises; **hydroxyurea halves ACS** as long-term prophylaxis.
- Transfuse with **Rh (C/c, E/e) and K antigen-matched** units to limit alloimmunisation.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Disorders of Hemoglobin"** (sickle cell disease; complications — Acute Chest Syndrome; transfusion and disease-modifying therapy).
- **CMDT 2026 — "Blood Disorders" (Sickle Cell Anemia)** for current management, drug regimens and the hemoglobin-distribution table.

Coverage note: The dedicated specialty text listed in the spec (DeVita's Cancer — haematological malignancies) contains only a single passing mention of ACS and is not the appropriate subspecialty source for this benign-haematology topic; depth was therefore drawn from Harrison 22e supplemented by CMDT 2026. The precise NHLBI consensus definition ("new radiodensity involving ≥1 complete lung segment plus a respiratory symptom/fever/hypoxia") and the naming of atypical organisms (*Mycoplasma*, *Chlamydophila*) are universally accepted standard internal medicine stated for completeness beyond Harrison's exact "major diagnostic criteria" phrasing.

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Flow cytometry — principle and applications

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

Definition / Introduction — Flow cytometry is a laser-based technique that simultaneously measures multiple physical and antigenic characteristics of single cells as they flow, one at a time, in a fluid stream past a focused beam of light. Each cell is interrogated for its **size, internal complexity (granularity), and the panel of surface/intracytoplasmic molecules** bound by fluorochrome-labelled monoclonal antibodies — its *antigen footprint* or **immunophenotype**. Because it can characterise thousands of cells per second across several parameters at once (*multiparametric analysis*), it is indispensable in haematology for diagnosing and sub-classifying leukaemias and lymphomas, detecting paroxysmal nocturnal haemoglobinuria (PNH), enumerating CD4 T-cells and CD34 stem cells, and tracking minimal residual disease (MRD). When the instrument also physically deflects and collects cells of interest it is called **fluorescence-activated cell sorting (FACS)**.

Principle and instrumentation

- **Pre-requisite — a single-cell suspension:** prepared from peripheral blood, bone marrow, body fluids (CSF, pleural/peritoneal), or *disaggregated solid tissue*; cells are stained with **fluorochrome-conjugated monoclonal antibodies** directed against the chosen antigens.
- Three integrated systems make up the cytometer:
  - **Fluidics** — *hydrodynamic focusing*: a fast outer sheath fluid constrains the sample core so cells file past the laser in **single line, one cell at a time**.
  - **Optics** — one or more **lasers** (e.g., 488 nm argon-blue) illuminate each cell; lenses, dichroic mirrors and band-pass filters separate the emitted light by wavelength onto detectors.
  - **Electronics** — **photodiodes/photomultiplier tubes (PMTs)** convert light pulses into digital voltage signals proportional to the parameter measured.
- **Two scatter (intrinsic) signals — require no antibody:**
  - **Forward scatter (FSC)** — light scattered in the direction of the beam; proportional to **cell size**.
  - **Side scatter (SSC)** — light scattered at ~90°; proportional to **internal complexity/granularity** (e.g., high in granulocytes, low in lymphocytes).
- **Fluorescence (extrinsic) signals:** each bound fluorochrome absorbs laser light and re-emits at a longer wavelength; common dyes excited at 488 nm include **FITC (green), PE (orange), PerCP and PE-Cy5/APC tandems (red)** — allowing several antigens to be measured on one cell simultaneously.
- **Gating & display:** populations are electronically "gated" on dot-plots/histograms (classically **CD45 vs SSC** to resolve blasts, lymphocytes, monocytes and granulocytes), then analysed for their marker profile.
- **Cell sorting (FACS):** charged droplets containing target cells are deflected by electrostatic plates into collection tubes — used to purify CD34 stem cells or rare tumour cells (e.g., flow-sorting Hodgkin/Reed-Sternberg cells for sequencing).

Immunophenotyping — the antigen footprint

- The immunophenotype is *valuable diagnostically because it distinguishes specific tumour subtypes*, even though "stage of differentiation" itself does not predict natural history (Harrison).
- **Clonality** is the key malignant signature detectable by flow:
  - **B-cell clonality** — *surface immunoglobulin light-chain restriction* (skewed **kappa : lambda** ratio) instead of the polyclonal mix of reactive lymphocytes.
  - **T-cell clonality** — aberrant antigen loss or an abnormal CD4:CD8 pattern (TCR clonality usually needs PCR).
- Antibodies may target **surface, cytoplasmic** (e.g., cytoplasmic CD3, CD79a, MPO) or **nuclear** antigens (e.g., TdT) after permeabilisation.

Lineage	Characteristic CD / marker profile
Haematopoietic stem/progenitor	CD34, CD117 (c-Kit), CD90 (Thy-1), CD133; **TdT** (lymphoblasts)
B-lymphoid	CD19, CD20, CD22, CD79a; surface Ig (kappa/lambda)
T-lymphoid	CD3, CD2, CD5, CD7, CD4, CD8
NK cell	CD16, CD56, CD57
Myeloid/monocytic	CD13, CD33, CD117, MPO; CD14, CD64 (monocytic)
Erythroid / megakaryocytic	CD71, glycophorin A; CD41, CD61
Plasma cell	CD138, CD38, CD56; cytoplasmic light-chain restriction
Common leucocyte / gating	CD45 (bright on lymphocytes, dim on blasts)

Applications in haematology and beyond

- **Acute leukaemia** — distinguishes **AML (CD13, CD33, CD117, MPO+)** from **ALL**, and B-ALL (**CD19, CD10, TdT, cyto-CD79a**) from T-ALL (**cyto-CD3, CD7**); identifies mixed-phenotype/biphenotypic acute leukaemia and acute promyelocytic leukaemia.
- **Chronic lymphocytic leukaemia (CLL)** — diagnostic immunophenotype is **CD5+ CD19+ CD20(dim) CD23+** with light-chain restriction; a monoclonal B-cell count ≥5 × 10^9/L defines CLL; flow confirms monoclonality in marrow/blood (DeVita).
- **Non-Hodgkin lymphoma sub-typing:**
  - *Follicular lymphoma* — CD19, CD20, **CD10, BCL6 positive**, CD5 and CD23 negative.
  - *Marginal-zone/MALT lymphoma* — CD19, CD20, CD22, CD79a positive; **negative for CD5, CD10, CD23 and cyclin D1**; light-chain restriction separates it from reactive infiltrates.
  - *Mantle cell* — CD5+, cyclin D1/t(11;14) (corroborated by FISH/IHC).
- **Hodgkin lymphoma** — flow-sorted Hodgkin/Reed-Sternberg cells express **bright CD30, CD15, CD40, CD95, CD64 but NOT CD20** (DeVita, Fig 66.4).
- **Paroxysmal nocturnal haemoglobinuria (PNH)** — flow is the **gold-standard** diagnostic test (replaces the old Ham/acidified-serum and sucrose lysis tests); see below.

- **Multiple myeloma / plasma-cell disorders** — peripheral-blood flow detects and quantifies **circulating plasma cells**; multiparametric flow estimates the **plasma-cell proliferative (S-phase) rate**; "absence of clonal plasma cells by 2- to 4-colour flow" is part of stringent CR; sensitive MRD assessment.
- **Minimal residual disease (MRD)** — multiparameter flow (alongside PCR/NGS) detects sub-microscopic residual leukaemia/lymphoma; uMRD status is independently prognostic in CLL and ALL.
- **CD4+ T-cell enumeration in HIV/AIDS** — flow cytometry is the standard method to count CD4 T-cells for staging (AIDS = CD4 <200/μL) and monitoring antiretroviral therapy.
- **CD34+ haematopoietic stem-cell enumeration** — quantifies the graft for autologous/allogeneic transplantation and apheresis adequacy.
- **DNA content / cell-cycle analysis** — DNA-binding dyes measure **ploidy (aneuploidy)** and **S-phase fraction** as prognostic markers in tumours.
- **Other uses** — lymphocyte subset quantitation in primary immunodeficiency (e.g., absent B and NK cells in GATA2 deficiency); **CSF flow cytometry** for lymphomatous/leukaemic meningitis; reticulocyte counting; fetomaternal haemorrhage (fetal Hb cells); platelet function/receptor disorders (CD41/CD61 in Glanzmann, CD42 in Bernard-Soulier); HLA-B27 typing; flow-based crossmatch in transplantation; increasing the sensitivity of antibody detection in autoimmune haemolytic anaemia to as few as 30–40 molecules per red cell.

PNH — the model "flow cytometry diagnosis"

- PNH arises from a somatic **PIGA** mutation → shortage of the **GPI anchor** → loss of GPI-linked complement-regulatory proteins **CD55 (DAF)** and **CD59 (MIRL)** from blood cells, causing complement-mediated intravascular haemolysis.
- Flow shows a **bimodal distribution**: a discrete population of cells that is **CD55 and CD59 negative** alongside normal cells.
- Run on **both granulocytes and red cells** (granulocytes avoid the confounding effect of haemolysis/transfusion on red cells); **FLAER** (fluorescein-labelled aerolysin, which binds GPI) is the preferred reagent for white cells.
- A diagnosis of PNH requires a *substantial* clone — roughly **≥5% of red cells and ≥20% of granulocytes** GPI-deficient (Harrison).
- Small PNH clones are detected by sensitive flow in **half or more of aplastic-anaemia patients** at presentation and signal an immune (immunosuppression-responsive) pathophysiology.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of a flow cytometer (label exactly):** *Sample (single-cell suspension) → Sheath fluid → Flow cell / hydrodynamic focusing → Laser beam (488 nm) → Forward scatter detector (FSC = size) → Side scatter detector (SSC = granularity, 90°) → Dichroic mirrors/filters → Fluorescence PMTs (FITC / PE / APC) → Computer (dot-plot & histogram) → (FACS) charged-droplet deflection plates → collection tubes.*
- **A CD45-vs-SSC gating dot-plot** labelling *lymphocytes (CD45-bright, low SSC), monocytes, granulocytes (high SSC), and the blast gate (CD45-dim, low SSC)*; OR a **PNH histogram** showing the *bimodal CD59-positive (normal) vs CD59-negative (PNH) red-cell populations*.

Clinical / Diagnostic significance

- Provides **rapid, objective, quantitative** lineage assignment and clonality that, combined with morphology, cytochemistry, cytogenetics/FISH and molecular studies, completes the modern WHO classification of leukaemias and lymphomas.
- Works on **tiny / hypocellular samples** (CSF, fine-needle aspirates, "dry-tap" marrows) where histology may be insufficient.
- Enables **prognostication and MRD-guided therapy** (CLL, ALL, myeloma), **CD4-based HIV staging**, **stem-cell graft quantification**, and definitive, non-invasive diagnosis of **PNH**.
- Limitations: needs a viable single-cell suspension (poor for sclerotic/Hodgkin-rich tissue with few tumour cells), cannot show architecture (complementary to immunohistochemistry), is operator/panel-dependent, and degrades with delayed/old samples.

High-yield exam pointers

- **FSC = cell size; SSC = granularity/internal complexity** — the two antibody-independent parameters.
- **Hydrodynamic focusing** lines cells up singly; lasers + PMTs + fluorochromes (FITC/PE/APC) give multiparametric data.
- **CD45 vs SSC** is the standard gating plot; **light-chain (kappa:lambda) restriction** = B-cell clonality.
- **PNH** = flow is gold standard → **CD55 & CD59 negative**, bimodal, use **granulocytes + FLAER**; clone ≥5% RBC / ≥20% granulocytes.
- **CLL** = CD5+CD19+CD23+; **AML** = CD13/CD33/CD117/MPO; **B-ALL** = CD19/CD10/TdT.
- **Hodgkin/RS cells** = CD30+ CD15+ CD20− (flow-sorted).
- Flow enumerates **CD4 T-cells (HIV)** and **CD34 stem cells (transplant)**; tracks **MRD**.
- **FACS** = the sorting variant (charged-droplet deflection); also measures **DNA ploidy & S-phase**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Non-Hodgkin's Lymphoma" (immunophenotype/antigen footprint, single-cell suspension method, FL/MZL markers, light-chain restriction); "Hemolytic Anemias" (PNH flow cytometry, CD55/CD59, bimodal clone, ≥5%/≥20% thresholds, AIHA antibody sensitivity); "Bone Marrow Failure Syndromes including Aplastic Anemia and Myelodysplasia" (PNH-clone detection, GATA2); "Hematopoietic Stem Cells" (CD34/CD90/CD117/CD133); "Hematopoietic Cell Transplantation"; "HIV Disease/AIDS" (CD4 staging).
- **DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — CLL immunophenotype (CD5/CD19/CD23) and MRD by flow; Hodgkin/Reed-Sternberg flow immunophenotype (CD30/CD15/CD40/CD95/CD64, not CD20); multiple-myeloma circulating plasma cells, S-phase and clonal-PC CR criteria; CSF flow cytometry in leptomeningeal disease; DNA/ploidy analysis.
- **CMDT 2026** — "Blood Disorders" (PNH: flow cytometry demonstrates deficiencies of CD55 and CD59).
- *Coverage note:* This is a laboratory-technique topic and Harrison/DeVita cover it **applied within disease chapters** rather than as a stand-alone "method" section. The detailed instrument physics (hydrodynamic focusing, FSC/SSC definitions, named fluorochromes FITC/PE/APC, PMTs, droplet-based FACS) and a few standard application specifics (**FLAER** reagent for PNH white cells; CD41/CD61 and CD42 in platelet disorders; CD4 counting "by flow cytometry"; reticulocyte/fetomaternal-haemorrhage assays) are **universally accepted standard laboratory/internal-medicine knowledge** included to satisfy the "principle" half of the question, as they are not described verbatim in the available corpus. All disease-specific marker panels, the PNH thresholds, and the clonality concepts are corpus-grounded as cited above.

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Hereditary spherocytosis

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

Definition / Introduction — Hereditary spherocytosis (HS) is the commonest inherited haemolytic anaemia due to a **defect of the red-cell membrane–cytoskeleton complex**, in which mutations affecting the *vertical* anchoring proteins (ankyrin, band 3, spectrin, band 4.2) uncouple the lipid bilayer from the underlying cytoskeleton. The resulting loss of membrane surface area produces rigid, poorly deformable **spherocytes** that are selectively trapped and destroyed in the spleen (extravascular haemolysis). It was first described by *Minkowski and Chauffard* in the late 19th century, who recognised spherocytes in the peripheral blood and their abnormal susceptibility to lysis in hypotonic media. Estimated prevalence is **1:2000–1:5000** in populations of European ancestry, making it the most common HS of this group.

Molecular basis and genetics

- The red-cell cytoskeleton is built on the **spectrin tetramer** (head-to-head association of two α-spectrin/β-spectrin heterodimers), linked to the overlying membrane through two multiprotein

bridges: the **ankyrin complex** (ankyrin + band 3 [AE1] + band 4.2) and the **junctional complex** (band 4.1R + actin + adducin + dematin).

- The ankyrin complex provides mainly **vertical (radial)** connections; the junctional complex provides **horizontal (tangential)** connections. Pathogenic changes that weaken *vertical* links cause **spherocytosis**, whereas defects of *horizontal* links cause elliptocytosis; spectrin defects can cause either.
- **Band 3** (anion exchanger, ~1.2 million copies/cell) is the most abundant membrane protein; its surface exposure with ageing creates the antigenic signal for macrophage clearance — a process accelerated in HS.
- HS is **genetically heterogeneous** — a single phenotype arising from mutations in any one of several genes. Inheritance is most often **autosomal dominant** (heterozygous), but the most severe forms are **autosomal recessive** (homozygous). A negative family history may reflect either a **de novo mutation** or a recessive form.

Gene	Protein	Inheritance in HS	Approx. share / comment
ANK1 (8p11.2)	Ankyrin	Dominant	May account for the **majority** of HS
SLC4A1 (17q21)	Band 3 (AE1)	Dominant	~**25%** of HS
SPTB (14q23–q24)	β-spectrin	Dominant	Rare
SPTA1 (1q22–q23)	α-spectrin	Recessive	Rare; severe biallelic forms
EPB42 (15q15–q21)	Band 4.2	Recessive	~**3%** of HS

Pathophysiology

- A *vertical* anchoring defect leaves regions of the lipid bilayer unsupported by the cytoskeleton → the membrane **vesiculates and is shed** → progressive **loss of surface area relative to volume** → the biconcave disc becomes a **spherocyte**.
- Spherocytes have reduced **deformability**. As they traverse the narrow fenestrations of the **splenic** red pulp cords, the metabolically stressed, low-glucose, acidic environment promotes further membrane loss ("splenic conditioning"), and the cells are ultimately phagocytosed by splenic macrophages.
- The spleen therefore plays a **dual role**: it both *worsens* the membrane lesion (vesiculation on transit) and is the *major site of destruction*. This explains why splenectomy is therapeutically effective even though it does not correct the underlying defect.
- Chronic extravascular haemolysis → unconjugated hyperbilirubinaemia, raised LDH, reduced haptoglobin, reticulocytosis, and a tendency to **pigment (bilirubinate) gallstones** and **splenomegaly**.

Clinical presentation

- **Wide spectrum of severity.** Severe cases present in **infancy** with neonatal jaundice or transfusion-dependent anaemia; mild cases may present in young adults or even later, sometimes only when gallstones are detected.

- The classic triad is **anaemia, jaundice and splenomegaly**; the discovery of **gallstones in a young person** frequently triggers diagnostic work-up.
- Haemolysis is often **compensated** (no anaemia) but may *decompensate* with intercurrent stress — pregnancy, infection, folate deficiency or renal impairment reducing erythropoietin.
- **Crises:** (1) *Aplastic crisis* from **parvovirus B19** infection causing transient red-cell aplasia and a precipitous fall in haemoglobin; (2) *Haemolytic crisis* with intercurrent infection; (3) *Megaloblastic crisis* from folate depletion. Chronic skull marrow expansion can cause frontal bossing in severe congenital cases.

Diagnosis and investigations

- **Full blood count / film:** normocytic anaemia with **spherocytes** (small, densely staining cells lacking central pallor) on the smear; **reticulocytosis**.
- **Red-cell indices** are highly suggestive: **MCHC >34 g/dL** (cells are dehydrated/spheroidal) with raised **RDW >14%** and a normal or slightly low MCV — a powerful screening clue from a routine blood count.
- **Haemolysis markers:** raised unconjugated bilirubin and AST, raised urinary/faecal urobilinogen; LDH increased and haptoglobin reduced when an intravascular component is present.
- **Confirmatory tests** (when family history is negative or a recessive form is suspected):
  - **Osmotic fragility test** — classically *increased* fragility in hypotonic saline (the historical diagnostic test); sensitivity improves after 24-h incubation.
  - **Acid glycerol lysis test (AGLT)** — accelerated lysis.
  - **Eosin-5′-maleimide (EMA)–binding test** by flow cytometry — *reduced* fluorescence (band 3 / Rh-related membrane protein deficiency); a sensitive, widely used screen.
  - **SDS-PAGE** of membrane proteins — quantifies the specific deficient protein.
  - **Ektacytometry** (osmotic gradient / laser diffraction) — measures deformability and reliably **distinguishes spherocytosis from stomatocytosis**.
  - **Molecular genetic studies** for a definitive answer in ambiguous cases.
- A negative **direct antiglobulin (Coombs) test** is essential to separate HS from **autoimmune haemolytic anaemia**, which can also produce spherocytes.

Treatment

- **No causal therapy** exists; management is supportive and directed at the spleen and its complications.
- **Splenectomy** abolishes or markedly reduces haemolysis. Current recommendations: perform at **age 4–6 years in severe cases**, **delay to puberty in moderate cases**, and **avoid in mild cases**; **partial (subtotal) splenectomy** is an option that preserves some splenic immune function. Knowledge of outcomes in affected relatives helps guide the decision.
- **Pre-splenectomy vaccination** against encapsulated organisms — *Streptococcus pneumoniae* and *Neisseria meningitidis* (and *Haemophilus influenzae* type b) — is **imperative**; **penicillin prophylaxis** afterwards is recommended in children though its value in older patients is debated.

- **Cholecystectomy** (usually laparoscopic) should be done — often at the same sitting as splenectomy — **only when gallstones are symptomatic/clinically indicated**, not automatically.
- **Supportive care: folic acid** supplementation for the increased erythropoietic demand; blood transfusion during aplastic/haemolytic decompensation; in the **<10%** of most severe (transfusion-dependent) infants, **erythropoietin** may be transfusion-sparing, and recurrent transfusion mandates **iron-overload surveillance and chelation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Red-cell membrane–cytoskeleton complex (schematic).** Labels: *lipid bilayer*; *band 3 (anion exchanger AE1)*; *glycophorin A*; *ankyrin*; *protein band 4.2*; *α-spectrin* and *β-spectrin* (tetramer); *actin*; *band 4.1R*; *adducin*; *dematin*; mark the **ankyrin (vertical) complex** vs the **junctional (horizontal) complex** — annotate "vertical-link defect → spherocytosis."
- **Peripheral blood smear / surface-area concept.** Draw a normal **biconcave disc** beside a **spherocyte** (small, round, loss of central pallor); annotate "membrane vesiculation → ↓ surface-area-to-volume ratio → ↓ deformability → splenic trapping." Optionally an **osmotic fragility curve** with the HS curve shifted *left* (lysis at higher NaCl concentration).

Clinical / Diagnostic significance

- **Triad** to recognise: haemolytic anaemia + splenomegaly + pigment gallstones in a young patient with autosomal-dominant family history.
- The **MCHC >34 g/dL + spherocytes + reticulocytosis + negative DAT** quartet is effectively diagnostic at the bedside; EMA-binding/osmotic fragility confirm it.
- **Parvovirus B19** is the classic cause of aplastic crisis — anticipate it during any abrupt fall in haemoglobin.
- Splenectomy decisions balance haemolysis control against lifelong risk of **overwhelming post-splenectomy infection (OPSI)** and thrombosis — hence vaccination, prophylaxis and age thresholds.
- Distinguish from **AIHA** (DAT-positive), **G6PD/pyruvate-kinase deficiency**, and from **dehydrated/overhydrated stomatocytosis** (ektacytometry), in which splenectomy is *contraindicated* due to thrombo-embolic risk.

High-yield exam pointers

- HS = **vertical** membrane-protein defect (ankyrin/band 3/spectrin/4.2); elliptocytosis = horizontal (band 4.1/spectrin) defect.
- **ANK1 (ankyrin)** = commonest gene; **band 3 (SLC4A1)** ~25%; mostly **autosomal dominant**.
- Hallmark lab clue: **MCHC >34 g/dL**, **RDW >14%**, normal/low MCV, spherocytes, reticulocytosis.
- Best screening confirmatory tests today: **EMA-binding (flow cytometry)** and **osmotic fragility**; **ektacytometry** separates HS from stomatocytosis.
- **DAT (Coombs) is NEGATIVE** — separates HS from immune spherocytosis.
- **Splenectomy** at **4–6 yr (severe)** / puberty (moderate); avoid in mild — vaccinate against pneumococcus, meningococcus, Hib first.

- Haemolysis is **extravascular** → unconjugated bilirubin↑, LDH↑, haptoglobin↓, **pigment gallstones**, splenomegaly.
- Complications: **aplastic crisis (parvovirus B19)**, gallstones, folate-deficiency megaloblastic crisis; give **folic acid**.
- No curative therapy; **erythropoietin** may spare transfusions in severe infants; the most severe ~**<10%** are transfusion-dependent.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Hemolytic Anemias"** (red-cell membrane–cytoskeleton complex; Hereditary Spherocytosis section, Table of inherited membrane-cytoskeleton diseases, diagnostic tests and treatment). Primary source for this answer.
- **CMDT 2026 — "Blood Disorders"** (haemolytic-anaemia classification and supportive context).
- *Coverage note:* The dedicated specialty text listed in the spec (**DeVita's Cancer**) covers haematologic *malignancies* and does **not** address hereditary spherocytosis, so it was not used. CMDT covers HS only briefly within its haemolysis classification; depth is therefore drawn from Harrison. Universally accepted standard points not stated verbatim in the corpus — *H. influenzae* type b vaccination, negative direct Coombs test, and folate/gallstone associations — are included as established internal-medicine teaching.

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Hypoproliferative anaemias

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

Definition / Introduction — *Hypoproliferative (underproduction) anemias* are those in which anemia results from **inadequate red-cell production by the bone marrow** rather than from blood loss or accelerated destruction. They are characterised by an **inappropriately low reticulocyte response** for the degree of anemia (low absolute reticulocyte count; reticulocyte production index <2–2.5) with a marrow that fails to amplify erythropoiesis. They are the **largest group of anemias — at least 75% of all cases** — the commonest being iron deficiency and anemia of inflammation. The functional erythron requires three things: **renal erythropoietin (EPO), a competent erythroid marrow, and adequate substrate (iron, folate, vitamin B12)**; a defect in any one produces a hypoproliferative anemia.

Pathophysiology — why production fails

- Erythropoiesis is driven by **EPO**, a glycoprotein made by renal peritubular interstitial cells; its synthesis is governed by **hypoxia-inducible factor (HIF)-1α**. When haemoglobin falls below 100 –120 g/L (10–12 g/dL), plasma EPO rises **logarithmically**.
- The pronormoblast undergoes **4–5 divisions → 16–32 mature red cells**; with EPO stimulation, production can rise **4–5 fold in 1–2 weeks** — but *only if iron supply is adequate*.
- Hypoproliferation occurs when EPO is deficient, when the marrow cannot respond (aplasia, infiltration, dysplasia), or when substrate (chiefly iron) is unavailable or sequestered.

- The reticulocyte count is the **physiological pivot**: an elevated count signals haemolysis/haemorrhage (hyperproliferation), whereas a low/inappropriately normal count defines the **hypoproliferative** mechanisms.

Classification by mechanism (cause-based)

Mechanism	Representative causes
Nutritional / substrate deficiency	Iron, vitamin B12, folate, copper, vitamin C deficiency
Lack of erythropoietin	Chronic kidney disease, anemia of inflammation, anemia of aging; ACE-inhibitor effect
Anemia of inflammation (iron sequestration)	Infection, autoimmunity, malignancy, CHF, CKD — hepcidin-driven
Absence of red-cell precursors	Aplastic anemia (pancytopenia), pure red-cell aplasia (parvovirus B19)
Marrow replacement (myelophthisis)	Metastatic carcinoma, lymphoma/myeloma, granuloma (TB, histoplasmosis), myelofibrosis
Stem-cell / clonal defects	Myelodysplastic syndrome, acute/chronic leukemia

- A complementary morphological scheme (Wintrobe) groups anemia by **MCV**: *microcytic* (iron deficiency, thalassemia, sideroblastic, inflammation), *normocytic* (renal, aplastic, marrow invasion, endocrine), and *macrocytic* (B12/folate deficiency, MDS, alcohol/liver disease). Most hypoproliferative anemias are **normocytic-normochromic** or microcytic.

Iron-restricted hypoproliferation: deficiency vs inflammation

- **Iron metabolism** is governed by **hepcidin**, a 25-amino-acid hepatic peptide that degrades the iron exporter **ferroportin**, throttling iron release from enterocytes, macrophages and hepatocytes. Hepcidin is **suppressed** in iron deficiency (maximising absorption) and **raised by IL-6 (STAT3 pathway)** in inflammation.
- **Iron-deficiency anemia (IDA):** absolute store depletion → low ferritin → iron-restricted erythropoiesis → **microcytic, hypochromic** cells with **high RDW**. Clues: pica, koilonychia, cheilosis, atrophic glossitis, and oesophageal webs (**Plummer-Vinson syndrome**). Severe IDA may cause **reactive thrombocytosis**.
- **Anemia of inflammation (chronic disease):** the second commonest anemia worldwide; mild–moderate, **normocytic-normochromic** (microcytic if long-standing) with **low reticulocytes**. It is fundamentally a **disorder of iron distribution** — high hepcidin sequesters iron in macrophages (functional iron deficiency) with **reduced EPO production and blunted EPO response** (IL-1β, TNF-α, IFN-γ).

Parameter	Iron deficiency	Anemia of inflammation	Thalassemia trait
Serum ferritin	**Low (≤15–30 µg/L)**	Normal–high (>100)	Normal–high
Serum iron	Low	Low	Normal–high
Transferrin saturation	Low (<15–20%)	Low (<20%)	Normal–high

Parameter	Iron deficiency	Anemia of inflammation	Thalassemia trait
MCV	Low (<80 fL)	Low–normal	Low
RDW	High	Normal	Low–normal
Soluble transferrin receptor (sTfR)	High	Low–normal	Normal–high
Hepcidin	Very low	Normal–high	Low–normal

(Normal serum iron 50–150 µg/dL; TIBC 300–360 µg/dL; transferrin saturation 25–50%; ferritin <30 µg/L = depleted stores, sensitivity 92% / specificity 98%.)

Selected entities of marrow failure

- **Aplastic anemia:** bone-marrow failure from stem-cell injury/immune (T-cell) suppression → **pancytopenia with a hypocellular marrow** and no abnormal cells. Causes: idiopathic/autoimmune, drugs (chloramphenicol, sulfonamides, phenytoin, carbamazepine, gold), benzene/toluene, radiation, viral hepatitis, parvovirus/EBV/CMV, PNH, pregnancy; inherited telomere/DNA-repair defects (**Fanconi anemia, dyskeratosis congenita**). **Severe aplastic anemia (Camitta criteria):** marrow cellularity <20% **plus** ≥2 of — neutrophils <500/µL, platelets <20,000/µL, reticulocytes <1%.
- **Pure red-cell aplasia:** isolated erythroid precursor loss with severe reticulocytopenia; classic trigger **parvovirus B19** (also thymoma, autoimmune, drugs).
- **Anemia of CKD:** EPO deficiency once >50% renal function is lost; anemia is near-universal at **GFR <30 mL/min/1.73 m²**, compounded by absolute and functional iron deficiency.
- **Anemia of aging:** roughly **one-third nutritional (iron), one-third inflammation/CKD, one-third "unexplained"** (low EPO-for-Hb; associated with clonal hematopoiesis of indeterminate potential, **CHIP**).
- **Marrow infiltration / clonal disease:** carcinoma, lymphoma, myeloma, myelofibrosis or leukemia produce a **leukoerythroblastic (myelophthisic) smear** — nucleated RBCs, teardrop cells and immature myeloid forms — mandating marrow examination. **MDS** may present as an isolated macrocytic anemia or pancytopenia.

Diagnostic approach

- **Step 1 – CBC + reticulocyte count:** correct the percentage for anemia — *Corrected reticulocyte count = measured retic × (patient Hct / 45)*; a low/inappropriately normal value confirms hypoproliferation.
- **Step 2 – Blood smear:** microcytic-hypochromic (IDA), macro-ovalocytes + hypersegmented neutrophils (megaloblastic), teardrop/nRBC (myelophthisis), dimorphic with basophilic stippling (sideroblastic).
- **Step 3 – MCV-guided tests:** *low MCV* → ferritin/iron studies (IDA vs inflammation vs thalassemia, RDW helps); *normal MCV* → renal function, EPO level, SPEP/light chains; *high MCV* → B12/folate, then marrow for suspected MDS.

- **Step 4 – Bone marrow aspirate + biopsy** (biopsy first) for pancytopenia, very low reticulocytes (<0.1%), nRBC/teardrops, or suspected infiltration/aplasia/MDS; assess cellularity, **myeloid:erythroid ratio (normal ≈2.5:1, range 2:1–5:1)** and iron stores (Perls stain — absent stainable iron is the gold standard for iron deficiency).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Physiological classification algorithm:** box "Anemia → CBC + reticulocyte count" branching to "**High absolute reticulocyte count → haemolysis / haemorrhage**" and "**Low absolute reticulocyte count → HYPOPROLIFERATIVE → assess MCV**"; under MCV draw three arms — *Low → Ferritin (low = iron deficiency; normal/high = inflammation, thalassemia, sideroblastic)*, *Normal → EPO level, BUN/creatinine, SPEP, marrow exam*, *High → smear (hypersegmentation? Yes = B12/folate deficiency; No = MDS / drug effect)*. Labels: *CBC, reticulocyte count, MCV, ferritin, EPO, marrow exam*.
- **Hepcidin–ferroportin axis:** liver hepcidin acting on ferroportin in **duodenal enterocyte, splenic macrophage, hepatocyte**; arrows "IL-6 → ↑hepcidin → ↓iron release (anemia of inflammation)" and "iron deficiency/erythroferrone → ↓hepcidin → ↑iron release." Labels: *Hepcidin, Ferroportin, Transferrin, IL-6/STAT3, Erythroferrone*.

Clinical / Diagnostic significance

- The **reticulocyte count is the single most useful triage test** — it separates underproduction from increased destruction before any expensive workup.
- A **low ferritin is diagnostic of iron deficiency**, but ferritin is an acute-phase reactant; in inflammation use a higher cut-off (<100 µg/L) and transferrin saturation <20%.
- In **males and postmenopausal women**, IDA mandates GI evaluation (endoscopy) to exclude occult malignancy/bleeding.
- A **leukoerythroblastic smear or unexplained pancytopenia** is an absolute indication for bone-marrow biopsy.
- Distinguish **aplastic anemia (hypocellular marrow)** from **MDS and hypocellular leukemia** by morphology, blast percentage and cytogenetics.

Treatment (cause-directed)

- **Iron deficiency:** oral iron salts (iron sulfate, 65–100 mg elemental iron); **alternate-day single morning dose maximises absorption** (avoids the hepcidin peak of daily dosing) and is better tolerated; continue ≥3 months to refill stores. **IV iron** (ferric carboxymaltose, derisomaltose, ferumoxytol) for intolerance, malabsorption, severe anemia (Hb ≤8 g/dL), CKD, CHF, pregnancy 2nd–3rd trimester, or surgery within 6 weeks; watch for **hypophosphataemia** (FGF-23, with carboxymaltose).
- **Anemia of inflammation:** treat the underlying disorder; ESAs in CKD targeting Hb **<11.5 g/dL**, with IV iron to keep transferrin saturation 30–40% and ferritin 200–700 µg/L; HIF prolyl-hydroxylase inhibitors are an oral alternative.
- **Megaloblastic anemia:** replace B12/folate.

- **Aplastic anemia: allogeneic HSCT** for patients <40 yr with an HLA-matched donor; otherwise **immunosuppression — equine ATG 40 mg/kg/day ×4 days + cyclosporine 6 mg/kg BID + eltrombopag 150 mg/day** (response ~90%) with corticosteroid cover for serum sickness.
- **Transfusion** is reserved for haemodynamic instability or symptomatic anemia; use **restrictive thresholds (7–8 g/dL)** in stable patients. IDA itself should not be transfused unless decompensated.

High-yield exam pointers

- Hypoproliferative = **low reticulocyte response**; constitutes **≥75% of all anemias**.
- **Reticulocyte production index <2–2.5** = inadequate marrow response = hypoproliferative.
- Commonest two causes: **iron deficiency and anemia of inflammation**.
- **Ferritin <30 µg/L** = absolute iron deficiency; **high hepcidin + hyperferritinaemia + hypoferremia** = functional iron deficiency of inflammation.
- **Plummer-Vinson** = IDA + dysphagia + oesophageal web; **koilonychia, pica, atrophic glossitis** are IDA signs.
- **Severe aplastic anemia (Camitta):** cellularity <20% + 2 of (ANC <500, platelets <20,000, retics <1%).
- **Parvovirus B19** → pure red-cell aplasia / transient aplastic crisis.
- **CKD anemia** = EPO deficiency, prominent once GFR <30 mL/min.
- **Leukoerythroblastic (myelophthisic) smear** → suspect marrow infiltration → biopsy.
- Normal **M:E ratio ≈ 2.5:1**; absent marrow stainable iron is the gold standard for iron deficiency.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Anemia and Polycythemia"* (physiological classification, reticulocyte interpretation, smear morphology, marrow indications) and *"Iron Deficiency and Other Acquired Anemias Due to Decreased Erythrocyte Production"* (iron metabolism, hepcidin, iron studies, anemia of inflammation, CKD and aging).
- **CMDT 2026** — *"Blood Disorders"* (aplastic anemia causes, Camitta severity criteria, ATG/cyclosporine/eltrombopag regimen; iron-restricted anemia management).
- Coverage note: The dedicated specialty text assigned in the spec (**DeVita's Cancer: Principles & Practice of Oncology**) is oriented to haematological malignancies and contributes only peripherally here — to the *marrow-replacement / clonal stem-cell* causes (MDS, leukemia, lymphoma, myeloma). The spine of this benign-haematology topic is Harrison's two hematology chapters supplemented by CMDT 2026 for management; this is reflected in the citations above.

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Light chain amyloidosis (AL)

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

Definition / Introduction — *Amyloidosis* is a group of protein-misfolding disorders defined by the **extracellular deposition of insoluble, antiparallel β-pleated-sheet–rich protein fibrils** that distort tissue architecture and impair organ function. **AL (light-chain) amyloidosis** is the form in which the fibril precursor is a **monoclonal immunoglobulin light chain** produced by a clonal bone-marrow plasma-cell (or B-lymphoproliferative) disorder; it was formerly called *primary systemic amyloidosis*. It is the **most common systemic amyloidosis in North America** and is rapidly progressive and fatal if untreated. (The term *amyloid* was coined around 1854 by **Rudolf Virchow**, who thought the deposits resembled starch — Latin *amylum*.)

Classification & nomenclature context

- Amyloid diseases are named by the convention **A + X**, where *A* = amyloid and *X* = the fibril precursor protein; they are classed as **systemic vs localized** and **acquired vs inherited**.
- AL sits among the **systemic amyloidoses**; the major systemic types are contrasted below.

Type	Precursor protein	Clinical setting	Typical organ involvement
AL	Immunoglobulin **light chain**	Primary / myeloma-associated (plasma-cell dyscrasia)	**Renal, heart**, nerve, GI, soft tissue
AH	Immunoglobulin heavy chain	Rare variant of primary/myeloma-associated	Renal
AA	Serum amyloid A (SAA)	Secondary / reactive (chronic inflammation, infection, FMF)	Hepatic, renal
Aβ2M	β2-microglobulin	Long-term dialysis–associated	Synovium, bone, carpal tunnel
ATTR	Transthyretin (mutant / wild-type)	Familial / age-related	Cardiac, peripheral & autonomic nerve

- **Localized AL** can occur in skin, conjunctiva, urinary bladder and the tracheobronchial tree, produced by *local* clonal plasma cells.

Etiopathogenesis

- A **clonal plasma-cell expansion** secretes a **monoclonal light chain** whose primary sequence (and other genetic/epigenetic factors) predisposes it to **misfold** rather than fold normally; the misfolded protein forms oligomers → higher-order polymers → fibrils that deposit in tissues.
- The **amyloid hypothesis** holds that soluble **oligomeric intermediates are the most toxic species** (direct proteotoxicity, reactive oxygen species, stress signalling), while fibrillar deposits cause architectural disruption.
- Fibrils are composed of **full-length 23-kDa monoclonal light chains** plus fragments; **λ (lambda) subtypes predominate** (λ light chains are more amyloidogenic and more nephrotoxic than κ — *Ch 116*).

- Accessory molecules co-deposited with fibrils: **serum amyloid P component, apolipoproteins E and A-IV, glycosaminoglycans, and metal ions**.
- May coexist with **multiple myeloma, non-Hodgkin lymphoma, or Waldenström macroglobulinemia**. Estimated incidence **8–12 per 100,000**; usually presents **after age 40**.

Clinical features (multisystem, pleiotropic)

Recognition of the *constellation* of syndromes — unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, macroglossia — is the key to early diagnosis.

Organ system	Frequency / features
Kidney	60–70%; **proteinuria, often nephrotic-range** → hypoalbuminemia, secondary hyper-cholesterolemia/triglyceridemia, edema/anasarca. Interstitial (vs glomerular) deposition → **azotemia without proteinuria**
Heart	70–80%; **leading cause of death**. ECG: **low limb-lead voltage with pseudo-infarct pattern**. Echo: concentrically thickened ventricles, **diastolic dysfunction, abnormal global longitudinal strain**, "sparkly" myocardium; poor atrial contractility (atrial thrombi/thromboembolism even in sinus rhythm). Cardiac MRI: increased wall thickness, **delayed subendocardial gadolinium enhancement**
Nervous system	Peripheral **sensorimotor neuropathy** and/or **autonomic dysfunction** — orthostatic hypotension, GI dysmotility (early satiety, diarrhea, constipation), dry eyes/mouth, impotence, neurogenic bladder
GI / liver / spleen	Hepatomegaly with **cholestasis** (raised alkaline phosphatase, preserved transaminases/synthetic function); splenic involvement with **functional hyposplenism**
Skin / soft tissue	**Periorbital ecchymoses ("raccoon-eye" sign)** and easy bruising (capillary amyloid ± **acquired factor X deficiency**); **macroglossia** (~10%); nail dystrophy, alopecia, amyloid arthropathy of wrists/shoulders

- **Macroglossia** and **periorbital "raccoon-eye" ecchymoses** are **pathognomonic** (each seen in a minority of patients).
- Endocrine deposition may cause **hypothyroidism, hypoadrenalism, or hypopituitarism**.

Diagnosis & investigations

Diagnosis requires (1) **histologic proof of amyloid**, (2) **accurate typing**, and (3) demonstration of an **underlying clonal plasma-cell disorder + a clonal light chain**.

- **Tissue biopsy + Congo red stain → apple-green birefringence under polarized light**; 10-nm fibrils on electron microscopy. **Abdominal subcutaneous fat aspirate** (16-gauge needle) is positive in **>80%** of systemic cases and avoids organ biopsy.
- **Typing** (essential — wrong type = wrong treatment): **laser-capture microdissection + tandem mass spectrometry is the diagnostic standard** (sensitivity **88%**, specificity **96%**); immunoelectron microscopy is more reliable than routine immunohistochemistry (commercial antibodies may mistype).
- **Plasma-cell / light-chain workup:**

- **SPEP/UPEP are poor screening tests** in AL (an M-spike is often absent). >**90%** have monoclonal light chain/immunoglobulin detectable by **serum/urine immunofixation (SIFE/UIFE)** or by **serum free light-chain (FLC) nephelometry**.
- Assess **both the κ:λ FLC ratio AND the absolute FLC level** — renal insufficiency reduces clearance and non-specifically raises both isotypes.
- **Bone marrow** shows clonal plasma cells (typically **5–30%** of nucleated cells in ~90%); demonstrate **κ or λ restriction** by flow cytometry, immunohistochemistry, or *in situ* hybridization.

- A monoclonal protein alone is **not** diagnostic (MGUS is common in the elderly) — but in biopsy-proven amyloid, AL must be **actively excluded/confirmed**.

Staging & prognosis

- **Mayo 2004 cardiac stage** — based on **NT-proBNP and cardiac troponin** (European modification identifies very-high-risk patients); most widely used.
- **Mayo 2012 stage** — adds **dFLC** (difference between involved and uninvolved circulating free light chains) as an independent survival predictor; **dFLC <50 mg/L** confers a better outcome regardless of cardiac stage.
- **Boston University stage** — incorporates **BNP and troponin I**.
- A validated **renal staging system** (24-h urine protein + eGFR) predicts progression to dialysis at 2 years.
- **High-risk** patients (~**15–20%**): advanced **cardiac stage IIIb** or severe heart failure (**NYHA III–IV**).

Treatment

Therapy targets the **clonal plasma cells** (myeloma-style regimens) to abolish the amyloidogenic light chain; **organ-function recovery lags 6–12 months** behind hematologic response.

- **High-dose IV melphalan + autologous stem-cell transplant (HDM/SCT)** — complete hematologic response in ~**40%**; durable remissions (sometimes >15 years). Only ~**20–30%** are eligible (cardiac stage, performance status limit candidacy).
- **Transplant-ineligible (standard):** FDA-approved **CyBorD (cyclophosphamide + bortezomib + dexamethasone) plus daratumumab (anti-CD38)**.
- **Bortezomib + melphalan-dexamethasone (MDex)** can overcome the adverse genetics of **gain of 1q21** and **t(11;14)**.
- If **bortezomib is contraindicated** (pre-existing peripheral neuropathy): **MDex** or **immunomodulatory drugs (lenalidomide, pomalidomide)**.
- **Novel antifibril monoclonal antibodies** are in trials, combined with anti–plasma-cell therapy.
- **Localized AL: surgical excision** or **low-dose radiotherapy (~20 Gy)**; systemic chemotherapy is *not* appropriate.
- **Supportive care:**
  - *Nephrotic syndrome*: diuretics, support stockings, albumin infusion to aid diuresis; **ACE inhibitors with caution** (no proven renal benefit).

- *Cardiac*: diuretics are mainstay; **digoxin, calcium-channel blockers and β-blockers are relatively contraindicated** (bind amyloid fibrils → heart block, worsening failure). **Amiodarone** for arrhythmia; **atrial ablation** for AF; **ventricular pacing** for conduction block; AICDs are less effective (thickened myocardium); consider **anticoagulation even without AF** (atrial thrombi).
- *Autonomic*: **midodrine** (α-agonist) for orthostatic hypotension; motility/bulk agents for GI dysmotility; nutritional support.

- **Prognosis:** untreated median survival historically only **~1–2 years**; markedly improved over four decades with modern therapy and earlier diagnosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis flow diagram:** *Clonal plasma cells → monoclonal λ/κ light chain → misfolding → oligomers (toxic) → β-pleated-sheet fibrils → tissue deposition.* Labels: **Clonal plasma cell, Free light chain, Misfolded monomer, Toxic oligomer, Amyloid fibril (β-sheet), Tissue deposit (heart/kidney/nerve), Serum amyloid P component**.
- **Clinical signs sketch (face/hand):** label **Macroglossia, Periorbital "raccoon-eye" ecchymoses, Nail dystrophy** — alongside **ECG strip showing low-voltage + pseudo-infarct pattern**.

Clinical / Diagnostic significance

- Suspect AL in any patient with **unexplained nephrotic-range proteinuria, "hypertrophic" cardiomyopathy with low ECG voltage, peripheral/autonomic neuropathy, hepatomegaly, or macroglossia** — especially when **multiple** systems are involved.
- **Fat-pad aspirate + Congo red + mass-spectrometry typing + serum FLC + bone marrow** is the practical diagnostic quartet.
- **Cardiac biomarkers (NT-proBNP, troponin) and dFLC** drive staging, prognosis and monitoring — remember renal failure falsely elevates them.
- An **acquired factor X deficiency** explains the bleeding/bruising and must be checked before biopsy.

High-yield exam pointers

- AL = **monoclonal light chain**, formerly *primary systemic amyloidosis*; **λ > κ**, fibril = **23-kDa light chain**.
- **Congo red → apple-green birefringence**; **abdominal fat-pad aspirate positive in >80%**.
- **Kidney 60–70%, Heart 70–80% (commonest cause of death).**
- **Macroglossia** and **periorbital "raccoon-eye" ecchymoses** = **pathognomonic** signs.
- **ECG low voltage + pseudo-infarct**; echo with **concentric thickening + abnormal global longitudinal strain**.
- **Mass spectrometry** typing is the gold standard (88%/96%); **SPEP/UPEP unreliable — use FLC + SIFE/UIFE.**
- Staging: **Mayo 2004/2012 (NT-proBNP, troponin, dFLC); dFLC <50 mg/L = better outcome**.

- Treatment: **HDM/SCT** (eligible ~20–30%) or **CyBorD + daratumumab**; **β-blockers, CCBs, digoxin relatively contraindicated** in cardiac amyloid.

> **SOURCE & COVERAGE**
>
> Harrison's Principles of Internal Medicine, 22e — **Ch 117 "Amyloidosis"** (Berk & Sanchorawala); cross-reference **Ch 116 "Plasma Cell Disorders"** (light-chain physiology, λ amyloidogenicity, free light-chain ratio). Coverage note: the topic is fully supported by the provided chapters; specific Mayo/BU staging cut-off values (exact NT-proBNP/troponin thresholds, Roman-numeral substages) are referenced by name in Harrison but the numeric thresholds are not tabulated in the provided text, so only the named systems and the dFLC <50 mg/L threshold are stated here.

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Microangiopathic haemolytic anaemia (MAHA)

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

Definition / Introduction — Microangiopathic haemolytic anaemia (MAHA) is a form of acquired, predominantly **intravascular haemolysis** caused by **mechanical fragmentation of red cells** as they are sheared in a microvasculature distorted by platelet/fibrin microthrombi, abnormal endothelium or turbulent flow. It is defined by the combination of **thrombocytopenia and fragmented RBCs (schistocytes)** on the peripheral smear with laboratory evidence of haemolysis (raised LDH and unconjugated bilirubin, low/absent haptoglobin) and microvascular thrombosis. The thrombotic microangiopathies — **thrombotic thrombocytopenic purpura (TTP)** and **haemolytic-uraemic syndrome (HUS)** — are the prototype causes; disseminated intravascular coagulation (DIC), malignant hypertension, pregnancy syndromes, prosthetic-valve haemolysis, drugs and vasculitis also produce a microangiopathic picture.

Pathophysiology — why red cells fragment

- Red cells normally survive ~120 days and are remarkably deformable, squeezing through capillaries narrower than themselves thousands of times. MAHA occurs when they **succumb to shear stress** in an abnormal microcirculation, producing intravascular haemolysis and haemoglobinuria.
- **Mechanical trauma** to the cell membrane generates **schistocytes** (helmet cells, fragmented RBCs) and microspherocytes; the freed haemoglobin saturates haptoglobin and spills into urine (haemoglobinuria ± haemosiderinuria).
- In the thrombotic microangiopathies, **platelet-rich microthrombi** deposited in arterioles/capillaries create the fibrin/platelet strands against which circulating RBCs are lacerated, simultaneously **consuming platelets** (hence thrombocytopenia).
- **TTP mechanism:** the plasma metalloprotease **ADAMTS13** normally cleaves the ultra-large von Willebrand factor (VWF) multimers secreted by endothelium into smaller multimers. Deficiency of, or **antibodies to, ADAMTS13** allow ultra-large VWF multimers to persist, driving pathological platelet adhesion and aggregation and widespread microvascular thrombosis. **ADAMTS13 activity <10% is diagnostic of TTP.** (ADAMTS13 deficiency alone is insufficient —

congenital deficiency causes disease only episodically, e.g., a first pregnancy — so a trigger is required.)

- **HUS mechanism:** endothelial injury — by **Shiga toxin** (E. coli O157:H7) in typical/diarrhoea-associated HUS, or by **uncontrolled complement alternative-pathway activation** in atypical HUS (aHUS) — initiates the microangiopathy, with the kidney bearing the brunt.
- **Common pathophysiologic theme:** increased red-cell turnover. Chronic intravascular haemolysis causes urinary iron loss (and may need iron replacement), whereas recurrent haemolysis raises folate demand and bilirubin (pigment gallstones).

Classification / Causes of MAHA

- In Harrison's classification of haemolytic anaemias, MAHA falls under **acquired, extracorpuscular** causes — "**Mechanical destruction (microangiopathic)**" — alongside toxic agents, drugs, infection and autoimmune mechanisms (the lone inherited extracorpuscular exception being familial/atypical HUS).

Category	Representative causes
Primary thrombotic microangiopathies	TTP (ADAMTS13 deficiency/inhibitor); HUS (Shiga toxin); atypical HUS (complement dysregulation)
Pregnancy-associated	HELLP syndrome, pre-eclampsia/eclampsia; pregnancy may unmask TTP
Drug-induced	Antibody-mediated: **ticlopidine** (possibly clopidogrel). Direct endothelial toxicity: **cyclosporine, tacrolimus, gemcitabine, mitomycin C**
Infection	Shiga-toxin E. coli O157:H7; systemic sepsis (often with DIC); HIV
Consumptive coagulopathy	Disseminated intravascular coagulation (DIC)
Mechanical / cardiac	Prosthetic (especially leaky/paraprosthetic-regurgitant) heart valves; cardiac haemangioma
Transplant / systemic	Haematopoietic stem-cell (bone-marrow) transplantation; vasculitis; (malignant hypertension, disseminated malignancy — standard textbook additions)

Peripheral smear and laboratory diagnosis

- **Peripheral blood smear is the cornerstone:** schistocytes/fragmented RBCs + thrombocytopenia define MAHA (Fig. 120-1D). Polychromasia, macrocytosis and occasional nucleated RBCs reflect the brisk reticulocyte response.
- **Haemolysis markers** (largely intravascular pattern):

Parameter	Finding in MAHA
Haemoglobin	Reduced (may fall acutely)
Reticulocytes / MCV	Increased
Peripheral smear	**Schistocytes**, helmet cells, low platelets
Bilirubin	Increased, mostly **unconjugated**

Parameter	Finding in MAHA
LDH	Markedly increased (up to ~10× normal with intravascular haemolysis)
Haptoglobin	**Reduced to absent**
Urine	Haemoglobinuria ± haemosiderinuria
Direct antiglobulin (Coombs) test	**Negative** (mechanical, not immune — key distinguishing point)
Platelet count	Low (consumption)

- **Distinguishing MAHA mechanism by coagulation profile:** in **DIC**, although thrombocytopenia and microangiopathy occur, a **coagulopathy predominates** — consumption of clotting factors and fibrinogen prolongs the **PT and often the aPTT**. By contrast, **PT and aPTT are characteristically normal in TTP and HUS**. This single distinction is high-yield.
- A complete diagnostic panel in suspected TTP/MAHA: CBC with platelet count and smear, **ADAMTS13 activity (± inhibitor assay)**, LDH, bilirubin, haptoglobin, PT/aPTT/fibrinogen, direct antiglobulin test and renal function.

Differentiating TTP vs HUS vs DIC

Feature	TTP	HUS (typical)	DIC
Core defect	ADAMTS13 deficiency / inhibitor → ultra-large VWF	Shiga-toxin (E. coli O157:H7) endothelial injury	Systemic coagulation activation
Classic age/setting	Adults; women > men; HIV, pregnancy	Children; preceded by (often bloody) diarrhoea	Sepsis, malignancy, obstetric catastrophe
Predominant organ	CNS (neurologic findings)	Kidney (acute renal failure)	Multi-organ
Renal failure	Variable	Prominent	Variable
PT / aPTT	**Normal**	**Normal**	**Prolonged**
Fibrinogen	Normal	Normal	Low (consumed)
ADAMTS13	**<10%** (diagnostic)	Generally normal	Normal
First-line therapy	Therapeutic plasma exchange	Supportive (± dialysis)	Treat cause; replace factors

- The classic **TTP "pentad"** (first described by *Eli Moschcowitz, 1924*): **microangiopathic haemolytic anaemia, thrombocytopenia, renal failure, neurologic findings and fever**. The full pentad is now seen less often because of earlier diagnosis — do **not** wait for all five before treating.

Specific syndromes and management

- **TTP — a medical emergency.** Inherited TTP is *Upshaw-Schulman syndrome*; idiopathic TTP (more common in women, and in HIV/pregnancy) is autoantibody-mediated against ADAMTS13.
  - **Therapeutic plasma exchange (TPE)** is the mainstay — it transformed mortality from **85–100% down to 10–30%**. Continue TPE until the platelet count normalises and signs of haemolysis resolve for at least **2 days**.
  - **Glucocorticoids** are a reasonable adjunct to TPE. **Rituximab** added to initial therapy reduces relapse. **Caplacizumab** (anti-VWF nanobody) reduces mortality and care burden in patients with ADAMTS13 <10% or high clinical probability. ISTH guidance: start caplacizumab and rituximab in those with diagnostic ADAMTS13 (usually <10%), and rituximab additionally where an inhibitor is demonstrated.
  - **Relapse** is significant: 25–45% within 30 days of remission and 12–40% late relapses, more frequent with severe ADAMTS13 deficiency. Treat suspected relapse **before** confirmatory assays return.
- **HUS.** Triad of acute renal failure, MAHA and thrombocytopenia, typically following haemorrhagic diarrhoea in children (E. coli O157:H7). Treatment is **primarily supportive**; ~40% of diarrhoea-associated cases need dialysis but overall mortality is **<5%**. Non-diarrhoeal HUS carries higher mortality (~26%). Plasma infusion/exchange has **not** been shown to alter the course of HUS/aHUS, **except** where anti-factor-H antibodies are present.
- **Atypical HUS (aHUS).** Due to dysregulation of the **complement alternative pathway** — anti-factor-H autoantibodies in some, but mostly germline mutations in **CFH, CFI, CD46 (MCP), C3, CFB, THBD (thrombomodulin)** — inherited (autosomal dominant) with incomplete penetrance, needing a trigger (usually infection). Shiga-toxin HUS is regarded as a *phenocopy* of aHUS. The anti-C5 inhibitor **eculizumab** markedly ameliorates the microangiopathy, improving platelet counts and renal function and largely abrogating the need for plasma exchange; aHUS remains a **diagnosis of exclusion**.
- **Drug-induced MAHA:** withdrawing or reducing the endothelial-toxic agent usually settles the microangiopathy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Peripheral blood smear in MAHA (label exactly):** *Schistocytes (fragmented RBC) / helmet cells*, *microspherocyte*, *polychromatic macrocyte (reticulocyte)*, *nucleated RBC*, *markedly reduced platelets*. Caption: "Schistocytes + thrombocytopenia = MAHA."
- **Diagram 2 — Pathogenesis of TTP (Fig. 120-4 style; label exactly):** *Endothelial cell*, *ultra-large VWF multimers*, *ADAMTS13 (cleaving protease)*, *normal multimers (protease present)* vs *ultra-large multimers (no protease → TTP)*, *platelet aggregation / microthrombus*, *sheared/fragmented red cell*.

Clinical / Diagnostic significance

- The triad **schistocytes + thrombocytopenia + negative Coombs** in a patient with haemolysis (high LDH, low haptoglobin, unconjugated hyperbilirubinaemia) mandates urgent evaluation for a thrombotic microangiopathy.
- **PT/aPTT** rapidly separate TTP/HUS (normal) from DIC (prolonged, low fibrinogen) — order them early.
- **ADAMTS13 <10%** confirms TTP and predicts relapse risk; send the sample **before** starting plasma exchange but **do not delay TPE** awaiting the result.
- Recognise **secondary settings**: malignant hypertension, HELLP/pre-eclampsia, prosthetic-valve dysfunction, sepsis-DIC and drugs — management is of the cause, not blind plasma exchange.
- Eculizumab has reframed aHUS therapy; correctly distinguishing aHUS from TTP and Shiga-toxin HUS changes treatment entirely (complement blockade vs TPE vs supportive care).

High-yield exam pointers

- **MAHA = mechanical, intravascular haemolysis** → schistocytes + thrombocytopenia + raised LDH + low haptoglobin + **negative direct Coombs**.
- **TTP pentad (Moschcowitz, 1924):** MAHA, thrombocytopenia, renal failure, neurologic signs, fever — treat before the pentad is complete.
- **ADAMTS13 <10% is diagnostic of TTP**; inherited form = **Upshaw-Schulman syndrome**.
- **TTP: TPE is life-saving** (mortality 85–100% → 10–30%); adjuncts rituximab, caplacizumab, steroids.
- **HUS:** children, bloody diarrhoea, **E. coli O157:H7**, kidney-predominant; treatment mainly supportive, mortality <5%.
- **aHUS:** complement alternative-pathway mutations (CFH, CFI, CD46, C3, CFB, THBD) → **eculizumab**.
- **DIC vs TTP/HUS:** PT/aPTT **prolonged in DIC, normal in TTP/HUS**; fibrinogen low in DIC.
- Drug culprits: **ticlopidine** (immune); **gemcitabine, mitomycin C, cyclosporine, tacrolimus** (endothelial toxicity).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 120 "Disorders of Platelets and Vessel Wall" (TTP/HUS/aHUS, MAHA definition, ADAMTS13–VWF pathogenesis, treatment) and Ch 105 "Hemolytic Anemias" (classification, mechanical/microangiopathic destruction, intravascular-haemolysis laboratory features, familial/atypical HUS complement genes). Coverage note: A few standard exam additions not explicitly named as MAHA causes in the provided chapters — HELLP/pre-eclampsia, malignant hypertension, disseminated malignancy and the universally taught point that the **direct Coombs test is negative** in MAHA — are included as accepted textbook internal medicine; all eponyms, drug names, gene names and numerical values are grounded in the two chapters above.

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Myelodysplastic syndromes

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

Definition / Introduction — The myelodysplastic syndromes (MDS) are a heterogeneous group of **acquired clonal haematopoietic stem-cell neoplasms** defined by two hallmarks: (1) peripheral **cytopenias due to ineffective, dysplastic haematopoiesis** (a bone-marrow failure phenotype), and (2) a variable but substantial **risk of progression to acute myeloid leukaemia (AML)**. The marrow is typically normo- or **hypercellular** (hypocellular in ~20%) yet produces too few mature cells, and the disease is characterised by morphological **dysplasia** plus recurrent **cytogenetic and somatic-mutational** abnormalities. MDS is fundamentally a disease of the elderly arising from age-related genomic instability.

Epidemiology and Aetiology

- **Disease of older adults**: mean age at onset **>70 years**, slight male predominance; incidence 35 to >100 per million in the general population and 120 to >500 per million in older adults (~30,000–40,000 new US cases/year). Overall 5-year survival is poor (~30%).
- **Rare in children/young adults** — when MDS occurs before age 40 it is frequently **constitutional/germline**, mandating predisposition gene screening.

Aetiological category	Key features
Primary (de novo)	Most cases; no identifiable exposure or antecedent haematologic disease
Therapy-related (t-MDS)	**Alkylating agents** (busulfan, melphalan, chlorambucil, nitrosourea, procarbazine) — 5–7 yr latency, complex karyotype/−5/−7; **topoisomerase-II inhibitors** — ~2 yr latency, *11q23 (MLL)* lesions. Age-independent, very poor prognosis
Environmental	Ionising radiation (atomic-bomb survivors), **benzene**, tobacco smoking, pesticides
Germline predisposition	**GATA2** deficiency (MonoMAC), familial **RUNX1** (familial platelet disorder), **DDX41**, **SAMD9/SAMD9L** (MIRAGE/ataxia-pancytopenia), ETV6, ANKRD26; inherited marrow-failure syndromes — Fanconi anaemia, telomere biology disorders (dyskeratosis congenita), Shwachman-Diamond

Aetiological category	Key features
Evolution	Acquired aplastic anaemia and other marrow-failure states may transform to MDS

Pathophysiology and Molecular Genetics

- MDS is a **clonal stem-cell disorder** with disordered proliferation, impaired differentiation and aberrant maturation, producing **ineffective haematopoiesis** — cytopenias despite a cellular marrow (intramedullary apoptosis).
- **Cytogenetic abnormalities in ~50%** of patients; non-random and aneuploidy (loss/gain) predominates over translocations — **del(5q), −7/del(7q), del(20q), trisomy 8**; type and number of lesions strongly predict leukaemic transformation and survival.
- **Somatic mutations** are detectable in **80–90%** across ~100 recurrently mutated myeloid genes, grouped by function:

Functional class	Genes (frequency)	Prognostic note
Spliceosome (commonest)	**SF3B1** (20–25%; up to 80% of ring-sideroblast cases), SRSF2 (~20–30% MDS, ~55% CMML), U2AF1, ZRSR2	SF3B1 **favourable**; SRSF2/U2AF1 adverse
DNA methylation / epigenetic	TET2 (~30%), DNMT3A (R882), IDH1/IDH2 (→ 2-hydroxyglutarate oncometabolite)	EZH2/ASXL1 adverse
Chromatin / transcription factors	ASXL1 (20–25%), EZH2 (~10%), RUNX1, ETV6	EZH2, RUNX1, ASXL1 **adverse**
Tumour suppressor	**TP53** (17p13.1)	**Biallelic/"multi-hit" = complex karyotype, very poor**
Signal transduction	FLT3, NRAS, KRAS, CBL	Drive secondary-AML transformation
Cohesin	STAG2	Adverse

- **Genotype–phenotype links**: *SF3B1* → ring sideroblasts; *del(5q)* → heterozygous ribosomal-protein loss mimicking red-cell aplasia. Distinguish **clonal haematopoiesis of indeterminate potential (CHIP)** (mutation without cytopenia/dysplasia, ~10% of those ≥70 yr) and **CCUS** (clonal cytopenia of undetermined significance) from frank MDS.

Clinical Features and Laboratory Diagnosis

- **Anaemia dominates** the early course (fatigue, dyspnoea, pallor); **~50% are asymptomatic**, diagnosed incidentally on a blood count. Bleeding (thrombocytopenia *and* platelet dysfunction; ~50% have a bleeding event) and **infection** (neutropenia + impaired neutrophil function; ~40% of deaths, mostly pneumonia) occur. **Splenomegaly in ~20%.** Fever/weight loss favour a myeloproliferative process.
- **Autoimmune/inflammatory associations** (e.g. *Sweet's syndrome*); MDS with inflammation should prompt consideration of **VEXAS syndrome** (somatic *UBA1* mutation; cytoplasmic vacuoles in myeloid/erythroid precursors).

- **Peripheral blood**: macrocytic anaemia with **macro-ovalocytes**, reticulocytopenia; **pseudo-Pelger-Huët** neutrophils (hypogranular, hyposegmented, Döhle bodies); large hypogranular platelets; circulating blasts mirror marrow blast count.
- **Bone marrow** (hyper- or normocellular; hypocellular in ~20%): **dyserythropoiesis** (nuclear budding/multinuclearity, megaloblastoid change, **ring sideroblasts** on Prussian-blue), **dysgranulopoiesis** (hypogranular/hyposegmented), **dysmegakaryopoiesis** (**micromegakaryocytes**, dwarf megakaryocytes with unilobed nuclei) — megakaryocyte changes are the most reliable. Blast percentage is enumerated manually and by flow cytometry; cytogenetics/FISH and an NGS myeloid panel are integral.
- **Diagnostic criteria**: persistent unexplained cytopenia(s) **plus** dysplasia in **≥10%** of cells in ≥1 myeloid lineage, **or** an MDS-defining cytogenetic lesion, **or 5–19% blasts**. Ring-sideroblast threshold is **≥15%** (or **≥5%** if *SF3B1* mutated). Exclude **B12/folate/copper deficiency**, HIV/parvovirus B19, alcohol, drugs and copper depletion.

Classification

- **FAB (1983)** — five subtypes: refractory anaemia (RA), RA with ring sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukaemia (**CMML**). WHO later moved RAEB-t into AML and reclassified **CMML as an MDS/MPN-overlap (myeloproliferative)** neoplasm (monocytosis >1000/µL).
- Two current schemes — **WHO 5th edition (2022)** and the **International Consensus Classification (ICC 2022)** — both integrate morphology, cytopenias, blast %, cytogenetics and molecular data; **≥20% marrow/blood blasts separates AML from MDS** (ICC adds an **MDS/AML** category at 10–19% blasts, emphasising the continuum).

WHO 2022 category	Blasts / defining feature
MDS with **isolated del(5q)**	<5% BM, <2% PB; del(5q) alone or +1 other (not −7/7q)
MDS with **SF3B1** mutation	<5% BM, <2% PB; ≥15% ring sideroblasts may substitute
MDS with **biallelic TP53** inactivation	<20% blasts; usually complex karyotype
MDS with **low blasts**	<5% BM, <2% PB
MDS, **hypoplastic**	≤25% cellularity
MDS with **increased blasts-1 (IB1)**	**5–9% BM or 2–4% PB**
MDS with **increased blasts-2 (IB2)**	**10–19% BM or 5–19% PB, or Auer rods**
MDS with **fibrosis**	5–19% BM; 2–19% PB

Prognosis — IPSS-R / IPSS-M

- The **IPSS (1997)** was refined to the **Revised IPSS (IPSS-R, 2012)** using: marrow blast %, **five cytogenetic risk subgroups** (very good → very poor), and depth of each cytopenia (Hb <80 / 80–<100 / ≥100 g/L; platelets <50 / 50–100 / ≥100 $\times 10^9$/L; ANC <800 vs ≥800/µL).
- **Five IPSS-R risk categories** with median overall survival:

IPSS-R category	Median OS
Very low	8.8 years
Low	5.3 years
Intermediate	3.0 years
High	1.6 years
Very high	0.8 years

- The **molecular IPSS-M (2022)** adds ~2 dozen genes (notably multi-hit *TP53*) and **re-stratifies ~45%** of patients (mostly upstaged) — now the emerging standard. For management, patients are dichotomised into **lower-risk** (very-low/low/intermediate) vs **higher-risk** (high/very-high) disease.
- **Favourable**: isolated del(5q), *SF3B1*/ring-sideroblast disease. **Adverse**: complex karyotype, chromosome-7 lesions, *TP53*. Most patients die of **cytopenia complications (infection, bleeding)** or comorbidity rather than overt leukaemia.

Risk-adapted Treatment

Setting	Therapy
All patients (supportive)	RBC transfusion (+ **iron chelation** — deferasirox/deferoxamine/deferiprone — when ferritin >2500 ng/mL or ≥20 units); platelet transfusion if <10 $\times 10^9$/L; aggressive infection management
Lower-risk, anaemia	**ESA** (epoetin/darbepoetin) if serum EPO ≤500 U/L (~50% response) ± G-CSF; **luspatercept** (TGF-β/SMAD2-3 ligand trap) after ESA failure, esp. *SF3B1*/RS — RBC-independence ~38%; **imetelstat** (telomerase inhibitor) for transfusion-dependent low/int-1 with EPO >500
Lower-risk, del(5q)	**Lenalidomide** 10 mg/day — 55–80% erythroid response + cytogenetic remission; watch myelosuppression and **VTE** (aspirin prophylaxis)
Lower-risk, hypoplastic/young	**Immunosuppression** — ATG ± cyclosporine; responders <60 yr, absent 5q−, **HLA-DR15**; TPO mimetics (eltrombopag/romiplostim) for thrombocytopenia
Higher-risk	**Hypomethylating agents** — **azacitidine** 75 mg/m^2 ×7 days q28 (AZA-001: median OS **24.5 months**); decitabine; **oral decitabine-cedazuridine**; ± **venetoclax**; **ivosidenib** (IDH1)
Curative	**Allogeneic HSCT** — only curative option (cure ~30–60% by risk); reduced-intensity conditioning extends eligibility to older/fit patients; aim **marrow blasts <5%** pre-transplant

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Dysplasia montage (peripheral smear + marrow)** — label: *pseudo-Pelger-Huët neutrophil (hypogranular, bilobed)*, *ring sideroblast (perinuclear iron granules, Prussian blue)*, *micromegakaryocyte / unilobed "dwarf" megakaryocyte*, *macro-ovalocyte*, *dyserythropoiesis with nuclear budding*, *myeloblast with Auer rod*.
- **Risk-adapted treatment algorithm (flowchart)** — *MDS diagnosis* → *IPSS-R/IPSS-M risk* → **Lower-risk**: ESA / luspatercept / lenalidomide (del5q) / IST / imetelstat → **Higher-risk**: hypomethylating agent (azacitidine) → **allogeneic HSCT** if fit.

Clinical / Diagnostic significance

- A bone-marrow aspirate **plus trephine biopsy with iron stain, cytogenetics/FISH and an NGS myeloid panel** is mandatory; megakaryocyte dysplasia and *SF3B1*/*TP53* status drive both classification and therapy.
- Always **exclude reversible mimics** — B12/folate/copper deficiency, HIV, alcohol, drugs — before labelling MDS; transient dysplasia is common in these.
- **Hypoplastic MDS vs aplastic anaemia**: clonal cytogenetic/molecular lesions and dysplasia favour MDS; some (del13q/del20q, *DNMT3A/ASXL1*) overlap and respond to immunosuppression.
- *TP53* multi-hit and complex karyotype predict transplant relapse; pre-HSCT cytoreduction to <5% blasts improves outcome.

High-yield exam pointers

- MDS = **acquired clonal stem-cell neoplasm** → ineffective haematopoiesis (cytopenias with cellular marrow) + AML risk; mean age **>70**.
- **≥20% blasts = AML**; MDS blast range **5–19%**; **IB1 = 5–9%, IB2 = 10–19%** (or Auer rods).
- **Commonest mutation = SF3B1** (spliceosome) → ring sideroblasts, **good prognosis**; **TP53 / complex karyotype / −7 = worst**.
- **Pseudo-Pelger-Huët** neutrophils, **ring sideroblasts**, **micromegakaryocytes** — classic dysplastic triad.
- **del(5q) syndrome**: macrocytic anaemia, normal/high platelets, hypolobated megakaryocytes → **lenalidomide**; 5-yr survival >90%.
- **IPSS-R** (blasts, cytogenetics, cytopenias) → 5 groups, median OS 8.8 to 0.8 yr; **IPSS-M** adds molecular data.
- Lower-risk → ESA/luspatercept/lenalidomide/IST; higher-risk → **azacitidine**; **allogeneic HSCT is the only cure**.
- Suspect **germline predisposition** (GATA2, RUNX1, DDX41) if MDS at **<40 years** or strong family history; consider **VEXAS** (UBA1) when MDS coexists with systemic inflammation.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia" (WHO 2022 & ICC classification tables, IPSS-R, treatment).
- **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — "Myelodysplastic Syndromes" (molecular pathogenesis by functional gene class, germline predisposition, IPSS-R/IPSS-M risk stratification, risk-adapted therapy and trial data).
- **CMDT 2026** — "Myelodysplastic Neoplasms" (diagnostic essentials, current drug regimens and doses, prognosis).

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Neuroendocrine tumours

Asked in: Paper III May 2022 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Neuroendocrine tumors (**NETs**) are neoplasms arising from cells of the diffuse neuroendocrine system that retain the ability to synthesize and ectopically secrete peptides, growth factors and bioactive amines, giving rise to characteristic clinical syndromes. Gastrointestinal NETs are broadly grouped by site of origin as **extrapancreatic NETs** (historically called *carcinoid tumors*) or **pancreatic NETs**. They classically pursue a more indolent course than most other malignancies, though behavior ranges from benign to highly aggressive. Diagnosed incidence has risen markedly (≈6.4-fold in U.S. SEER data, 1973–2012), partly reflecting improved diagnosis and classification.

Classification

NETs are categorized along three axes — anatomic site, functional status, and histologic differentiation/grade. Histologic grade (mitotic count and Ki-67 index) is the single most important determinant of behavior and treatment.

Axis	Categories
Anatomic	Pancreatic NETs; extrapancreatic GI ("carcinoid") — stomach, small intestine (terminal ileum), appendix, rectum; bronchial/thymic
Functional	*Functional* (hormone-secretion symptoms) vs *non-functional* (≈80% of pancreatic NETs; silent or anatomic symptoms)
Histologic (WHO/Table 89-1)	See grading table below

Tumor	Differentiation	Grade	Mitoses /10 HPF	Ki-67
NET	Well-differentiated	Low (G1)	<2	<3%
NET	Well-differentiated	Intermediate (G2)	2–20	3–20%
NET	Well-differentiated	High (G3)	>20	>20%

Tumor	Differentiation	Grade	Mitoses /10 HPF	Ki-67
Neuroendocrine carcinoma	Poorly differentiated	High (G3)	>20	>20%

- **Histology:** monotonous sheets of small round cells with uniform nuclei; immunostaining positive for **chromogranin A** and **synaptophysin**; ultrastructural electron-dense neurosecretory granules.
- **Molecular:** sporadic pancreatic NETs — *MEN1* mutated in 44%, *DAXX/ATRX* in 43%, mTOR-pathway genes in 15%. Small-intestinal NETs — recurrent *CDKN1B* (p27^Kip1) mutation in 8% and loss of chromosome 18.
- **Inherited syndromes (minority):** MEN 1 (*menin*, 11q13 — commonest), von Hippel–Lindau (*VHL*, 3p25), neurofibromatosis type 1 (*NF1*, von Recklinghausen), tuberous sclerosis (*TSC1* hamartin / *TSC2* tuberin).

Functional pancreatic NET syndromes

Tumor	Syndrome / features	Key marker	Symptom control
Insulinoma (commonest)	Fasting hypoglycemia — confusion, coma, weight gain	↑Fasting insulin + proinsulin + **C-peptide**	**Diazoxide**, everolimus (SSA with caution)
Glucagonoma	*Necrolytic migratory erythema*, glucose intolerance, weight loss; hypercoagulable (≈33%)	Glucagon **>1000 pg/mL**	Somatostatin analogue (SSA)
Gastrinoma	**Zollinger-Ellison syndrome** — peptic ulcers, GERD, diarrhea	Fasting hypergastrinemia	**PPIs**, SSA
VIPoma	**Verner-Morrison / WDHA / pancreatic cholera** — watery diarrhea, hypokalemia, achlorhydria	↑VIP (28-aa peptide)	SSA + fluid/electrolyte replacement
Somatostatinoma	Diabetes, cholelithiasis, diarrhea, steatorrhea	↑Plasma somatostatin	Surgery (SSA value questionable)
ACTHoma	Ectopic Cushing's — hyperglycemia, hypokalemia	↑ACTH/cortisol	Ketoconazole, **metyrapone**, ± adrenalectomy

- **Gastrinomas** mostly arise in the **gastrinoma triangle** (bounded by duodenum, pancreas and confluence of cystic and common bile ducts); 50–90% of sporadic ZES gastrinomas are duodenal; up to **25% of ZES patients have MEN 1**.
- **Insulinomas** are usually <2 cm and best localized by **endoscopic ultrasound (EUS)**; enucleation is the primary surgical option. SSAs may worsen hypoglycemia by suppressing counter-regulatory hormones.

Extrapancreatic ("carcinoid") NETs and the carcinoid syndrome

- **Gastric NETs:** *type 1* (chronic atrophic gastritis/pernicious anemia, high gastrin, multifocal, benign — commonest); *type 2* (gastrinoma/ZES); *type 3* (sporadic, normal gastrin, aggressive).

- **Small-intestinal NETs:** terminal ileum, submucosal, often multifocal; serotonin-driven **mesenteric fibrosis/desmoplasia** → intermittent obstruction and the classic **"spoke-and-wheel"** calcified mesenteric mass on CT.
- **Appendiceal NETs:** <2 cm → appendectomy alone (very low metastatic risk); 2–3 cm ≈20–30% metastatic risk; >3 cm → right hemicolectomy.
- **Rectal NETs:** <1 cm well-differentiated → endoscopic removal; 1–2 cm metastasize in up to one-third; >2 cm metastasize in >70%.
- **Carcinoid syndrome** — driven mainly by **serotonin (5-HT)** (synthesized from tryptophan by **tryptophan hydroxylase**; metabolite **5-HIAA** measurable in 24-h urine), plus histamine and tachykinins (substance P). Usually emerges only after **hepatic metastases** allow vasoactive substances into the systemic circulation. Features: sudden **flushing** (face/neck), secretory **diarrhea**, wheezing/bronchospasm, and tryptophan diversion may cause niacin deficiency (**pellagra**). Most common with appendiceal/small-intestinal primaries.
- **Carcinoid heart disease** (≈two-thirds of carcinoid-syndrome patients): plaque-like fibrous endocardial thickening of the **right heart** mediated by serotonin acting on **5-HT2B receptors**; **tricuspid regurgitation** is near-universal (also tricuspid stenosis, pulmonary regurgitation/stenosis). Left-sided disease in <10% (associated with patent foramen ovale).
- **Carcinoid crisis:** life-threatening release of vasoactive substances (profound hypotension or hypertension) precipitated by tumor manipulation at surgery, embolization, or anesthesia induction — prevented/treated with **somatostatin analogues**.

NETs in MEN syndromes (Ch 400)

Syndrome	Gene (locus)	Key NET-associated tumors
MEN 1 (*Wermer*)	*MEN1* / menin (11q13)	Parathyroid adenoma (90%); enteropancreatic NETs 30–70% (gastrinoma >50%, insulinoma 10–30%, non-functioning/PPoma); anterior pituitary (prolactinoma)
MEN 2A (*Sipple*)	*RET* (10q11.2), codon **634**	Medullary thyroid carcinoma (MTC) 90%, pheochromocytoma >50%, parathyroid 10–25%
MEN 2B / MEN 3	*RET* codon **918** (Met→Thr)	MTC, pheochromocytoma, mucosal neuromas, marfanoid habitus, megacolon (*no* hyperparathyroidism)
FMTC (MTC only)	*RET* codon **618**	MTC alone
MEN 4	*CDKN1B* (p27^Kip1, 12p13)	Parathyroid + pituitary adenoma
MEN 5	*MAX* (14q23.3)	Pheochromocytoma, pituitary, parathyroid

- **Menin** is a 610-amino-acid tumor-suppressor protein; tumorigenesis follows the Knudson **two-hit hypothesis**.
- In MEN 1, pancreatic NETs are typically **multiple**, of earlier onset, and often indolent; gastrinoma/foregut carcinoid is a leading cause of death — favoring conservative/selective surgery.

- In MEN 2, *RET*-mutation carriers are offered **prophylactic total thyroidectomy** (between age <1 and 5 years per codon risk); pheochromocytoma must be excluded before any surgery. Metastatic MTC: TKIs **vandetanib, cabozantinib, selpercatinib**.

Diagnosis and investigations

- **Functional/biochemical:** hormone-specific assays (insulin/C-peptide, gastrin, glucagon, VIP), **urinary 5-HIAA** for carcinoid syndrome; **chromogranin A** as a general (but neither sensitive nor specific) marker — falsely raised by PPIs and renal impairment.
- **Imaging:** CT/MRI for anatomy; **somatostatin-receptor imaging** since >90% of NETs express SSTRs — **Gallium-68 (^68Ga) DOTATATE PET** (also DOTATOC, ^64Cu-dotatate) is highly sensitive. **FDG-PET** is typically negative in low-grade but positive in high-grade tumors.
- **Localization:** EUS for small pancreatic/duodenal tumors; receptor-positivity on DOTATATE PET predicts SSA and PRRT responsiveness.

Management

- **Localized disease:** surgical resection is the mainstay; appendiceal/rectal small tumors may be cured endoscopically or by limited resection. Adjuvant therapy is **not** recommended after resection of well-differentiated NETs.
- **Hormone-symptom control: somatostatin analogues** — octreotide, lanreotide (14-aa somatostatin analogues binding **SSTR subtypes 2 and 5**); **telotristat ethyl** (tryptophan hydroxylase inhibitor) for refractory carcinoid diarrhea; prophylactic cholecystectomy if long-term SSA planned (gallstone risk).
- **Anti-tumor systemic therapy (Table 89-3):**
  - **SSAs** also slow growth — *PROMID* (octreotide LAR, midgut), *CLARINET* (lanreotide; 2-yr PFS 65% vs 33%).
  - **Peptide receptor radioligand therapy (PRRT) — ^177Lu-DOTATATE** (NETTER-1: PFS at 20 months 65.2% vs 10.8%); requires positive SSTR imaging; renal toxicity mitigated by amino-acid co-infusion.
  - **mTOR inhibitor everolimus** 10 mg/day (RADIANT-3 pancreatic 11 vs 4.6 months; RADIANT-4 GI/lung) — stomatitis, rash, pneumonitis.
  - **TKIs** — sunitinib 37.5 mg/day (pancreatic NET 11.4 vs 5.5 months), cabozantinib (CABINET), surufatinib, pazopanib — hypertension, proteinuria.
  - **Chemotherapy — temozolomide + capecitabine** is the preferred regimen for advanced pancreatic NET (has replaced streptozocin).
- **Hepatic-directed therapy** (liver-predominant disease): resection, radiofrequency/cryoablation, hepatic-artery embolization (bland/chemo/radio-embolization), selective transplantation.
- **High-grade neuroendocrine carcinoma:** treated on a small-cell paradigm with **platinum (cisplatin/carboplatin) + etoposide**; response best when **Ki-67 ≥55%**; immune checkpoint blockade (ipilimumab + nivolumab) shows activity in poorly differentiated tumors.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Serotonin pathway in carcinoid (Fig. 89-6):** label *Tryptophan* → *(tryptophan hydroxylase)* → *5-Hydroxytryptophan (5-HTP)* → *(aromatic L-amino acid decarboxylase)* → *Serotonin (5-HT)* → stored in secretory granules → secretion → *(monoamine oxidase, aldehyde dehydrogenase)* → *5-HIAA* → *urine*; mark **telotristat ethyl** inhibiting tryptophan hydroxylase.
- **Carcinoid heart disease (Fig. 89-8):** right heart with fibrous endocardial plaque, retracted **tricuspid valve leaflets**, **tricuspid regurgitation**; label right atrium, right ventricle, pulmonary valve, and "serotonin / 5-HT2B mediated".

Clinical / Diagnostic significance

- Suspect NET in unexplained flushing + secretory diarrhea, refractory peptic ulcers (ZES), fasting hypoglycemia, or necrolytic migratory erythema.
- A diagnosis of gastrinoma or multiple/young-onset pancreatic NETs mandates screening for **MEN 1** (calcium, PTH, gut hormones, pituitary MRI).
- ^68Ga-DOTATATE PET both stages disease and selects patients for SSA/PRRT; chromogranin A is used for monitoring, not screening.
- Grade (Ki-67) dictates therapy: well-differentiated → SSA/PRRT/targeted agents; high-grade carcinoma → platinum–etoposide.

High-yield exam pointers

- Commonest functional pancreatic NET = **insulinoma**; commonest *overall* pancreatic NET = **non-functioning**.
- **Whipple's triad** + ↑insulin/proinsulin/**C-peptide** = insulinoma; normal C-peptide with hypoglycemia suggests exogenous insulin.
- **Gastrinoma triangle**: cystic + common bile duct confluence, 2nd–3rd part duodenum, pancreatic neck/body.
- **WDHA = Verner-Morrison = pancreatic cholera** (VIPoma).
- Carcinoid syndrome needs **hepatic metastases**; diagnostic test = **24-h urinary 5-HIAA**.
- Carcinoid heart disease = **right-sided, tricuspid regurgitation**, via **5-HT2B** receptors.
- **^177Lu-DOTATATE PRRT** for progressive SSTR-positive NETs (NETTER-1/2).
- MEN 2 = **RET**: codon 634 (2A), 918 (2B), 618 (FMTC); prophylactic thyroidectomy in carriers.
- **Temozolomide + capecitabine** = preferred chemo for pancreatic NET.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 89 "Gastrointestinal Neuroendocrine Tumors" (Kulke) and Ch 400 "Multiple Endocrine Neoplasia Syndromes" (Thakker). Coverage note: both asks ("Neuroendocrine tumors") are fully supported; *spec.gap = false*. Bronchial/thymic and lung NETs are covered only briefly in the provided GI/MEN chapters (detailed pulmonary NET pathology lies outside these two chapters). MEN 2 management specifics (vandetanib/cabozantinib/selpercatinib, prophylactic thyroidectomy timing) are from Ch 400 and are standard internal medicine.

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Non-Hodgkin's lymphoma

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

Definition / Introduction — Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of malignancies of mature **B**, **T**, and **natural-killer (NK)** lymphocytes, distinguished from Hodgkin's lymphoma by the *absence of Reed-Sternberg cells* and by their biologically and clinically diverse behaviour. About **85–90%** are of B-cell origin and **10–15%** are T/NK-cell. They span a spectrum from **indolent** (slow-growing, treatable but usually incurable) to **aggressive/highly aggressive** (rapidly fatal if untreated, but potentially curable). NHL is the seventh most common cause of cancer death; incidence rises with age and has been increasing by ~1.5–2% per year, with a 5-year survival of ~74%.

Etiology, risk factors & infectious associations

- **Immunodeficiency** is the strongest predisposer — HIV, post-transplant immunosuppression (~100-fold increased risk, greatest in first post-transplant year), and inherited defects (*ataxia-telangiectasia, Wiskott-Aldrich, X-linked lymphoproliferative, Chédiak-Higashi, common variable immunodeficiency*). Most immunodeficiency-associated NHLs are EBV-driven DLBCLs.
- **Autoimmune disease** — Sjögren's syndrome and Hashimoto's thyroiditis (MALT lymphoma), rheumatoid arthritis, SLE, celiac sprue (enteropathy-associated T-cell lymphoma).
- **Chemical/iatrogenic** — phenoxy herbicides/dioxin, phenytoin, anti-TNF agents, prior chemo-/radiotherapy.
- **Infectious agents** (chronic antigenic stimulation or direct transformation):

Agent	Associated lymphoma
EBV	Burkitt's, post-transplant LPD, primary CNS DLBCL, extranodal NK/T-cell (nasal)
HTLV-1	Adult T-cell leukemia/lymphoma (ATLL)
HIV	Aggressive DLBCL, Burkitt's
Hepatitis C	Lymphoplasmacytic lymphoma, splenic marginal-zone lymphoma
H. pylori	Gastric MALT lymphoma (regresses with eradication)

Agent	Associated lymphoma
HHV-8	Primary effusion lymphoma, multicentric Castleman's disease
Borrelia / C. psittaci / C. jejuni	Cutaneous / ocular adnexal / small-bowel (IPSID) MALT

Classification (WHO-HAEM5, 2022) & cytogenetics

- Lymphoid neoplasms are grouped as **mature B-cell** vs **mature T/NK-cell**, each containing indolent and aggressive entities.
- **B-cell:** follicular lymphoma (FL), DLBCL, Burkitt's, mantle-cell (MCL), marginal-zone (splenic/MALT/nodal), lymphoplasmacytic, primary mediastinal large B-cell, high-grade B-cell with *MYC* + *BCL2* rearrangements.
- **T/NK-cell:** peripheral T-cell lymphoma (PTCL)-NOS, angioimmunoblastic (AITL), anaplastic large-cell (ALCL, ALK±), mycosis fungoides/Sézary, ATLL, extranodal NK/T-cell nasal type.
- ~90% of lymphomas arise from B cells after immunoglobulin gene recombination/somatic hypermutation; the error-prone nature of these processes underlies recurrent translocations:

Translocation	Gene(s)	Lymphoma
t(8;14)(q24;q32)	*MYC / IgH*	**Burkitt's** (also t(2;8), t(8;22))
t(14;18)(q32;q21)	*BCL2 / IgH*	**Follicular**, DLBCL
t(11;14)(q13;q32)	*CCND1 (cyclin D1) / IgH*	**Mantle-cell**
t(11;18)(q21;q21)	*API2 / MALT1*	**MALT** (commonest, up to 50%)
t(2;5)(p23;q35)	*NPM1 / ALK*	**Anaplastic large-cell**
t(3;14) / 3q27	*BCL6 / IgH*	DLBCL, FL

- Gene-expression profiling splits DLBCL into **germinal-centre B-cell (GCB)** type (better prognosis) and **activated B-cell (ABC)** type (worse); the **Hans algorithm** (CD10, BCL6, MUM1 by IHC) approximates this.

Clinical features & staging

- Commonest presentation is **painless lymphadenopathy** (peripheral, central/retroperitoneal, or both); ~85% of indolent NHLs are disseminated at diagnosis with frequent marrow involvement.
- **"B" symptoms** — fever, drenching night sweats, weight loss **>10% of body weight over the preceding 6 months**.
- Extranodal disease is common (GI tract, skin, Waldeyer's ring, marrow, CNS, testis); pace of progression distinguishes aggressive from indolent disease.
- **Diagnosis requires excisional/core tissue biopsy** with histology, immunophenotype (flow cytometry/IHC) and cytogenetics/FISH — *fine-needle aspiration alone is inadequate*.
- **Staging — Ann Arbor system** (adapted for NHL), now applied as the modern **Lugano classification** using **whole-body 18F-FDG PET/CT**:

Stage	Extent
I	Single nodal region (I) or single extranodal site (IE)
II	≥2 nodal regions, same side of diaphragm (± contiguous extranodal IIE)
III	Nodal regions on both sides of diaphragm (± spleen, IIIS)
IV	Diffuse/disseminated extranodal involvement (marrow, liver, etc.)

Suffix **A** = no B symptoms, **B** = B symptoms present; **E** = extranodal extension; **bulky** = mediastinal mass >⅓ chest diameter or any mass >10 cm. Bone-marrow biopsy is not required when PET/CT is performed. Because NHL disseminates non-contiguously, **histology + clinical risk score predict outcome better than anatomic stage**.

Prognostic indices

- **International Prognostic Index (IPI)** for aggressive NHL — 1 point each for: **A**ge ≥60, raised **L**DH, ECOG **P**erformance status ≥2, **A**nn Arbor stage III/IV, **>1 e**xtranodal site (mnemonic *APLES*). Risk groups: low (0–1), low-intermediate (2), high-intermediate (3), high (4–5) → 5-yr OS ~73%, 51%, 43%, 26% respectively. The **R-IPI** (rituximab era) gives 4-yr survival of 94/80/53%.
- **FLIPI** (follicular) — age >60, stage III/IV, **>4 nodal sites**, raised LDH, haemoglobin <12 g/dL.
- **MIPI** (mantle-cell) — age, performance status, LDH, WBC count, **Ki-67** index.
- Raised **serum LDH** and **β2-microglobulin** are independent adverse markers.

Major subtypes — features & treatment

- **Diffuse large B-cell lymphoma (DLBCL):** commonest NHL (~⅓ of cases), aggressive but curable. Standard first-line **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) × 6 cycles cures ~65–70%; **Pola-R-CHP** (polatuzumab vedotin replacing vincristine) benefits IPI ≥2 disease (POLARIX). **"Double-hit" lymphoma** (*MYC* + *BCL2* rearranged, a high-grade B-cell lymphoma) carries a poor prognosis and is often treated with **DA-EPOCH-R**. Relapsed/refractory disease → salvage chemo + **autologous stem-cell transplant**, or **CD19 CAR-T cells** (axi-cel, liso-cel, tisa-cel; ZUMA-7, TRANSFORM) which are now preferred for primary-refractory/early-relapsing disease.
- **Burkitt's lymphoma:** one of the fastest-growing human tumours (**doubling time <24 h**); *MYC* t(8;14) in >95%. Biopsy shows monomorphic medium B cells, ~100% proliferation and a classic **"starry-sky"** appearance from **tingible-body macrophages**; CD10+, BCL6+, BCL2-negative. Three forms — **endemic (African, jaw/EBV+)**, **sporadic (abdominal)**, **immunodeficiency-associated**. Needs *urgent* intensive cyclophosphamide-based therapy (**modified Magrath/CODOX-M-IVAC** or **DA-EPOCH-R**) with **mandatory CNS prophylaxis**; cure 80–90%. High tumour burden mandates **tumour-lysis-syndrome** prophylaxis.
- **Follicular lymphoma (FL):** commonest indolent NHL; **t(14;18)/BCL2** in >85%; CD10+, BCL6+, CD5/CD23-negative. Graded I–III by centroblast count. Asymptomatic patients are **observed ("watch and wait")**; symptomatic/bulky disease → **bendamustine-rituximab (BR)**, R-CHOP or R-CVP, ± maintenance rituximab; obinutuzumab and rituximab-lenalidomide are alternatives. Median survival 15–20 years; **histologic transformation to DLBCL ~3% per year**.

- **Marginal-zone lymphoma (MZL):** splenic (HCV-associated, villous lymphocytes), **MALT** (often localised stage I/II — *H. pylori* eradication or radiotherapy can be curative), and nodal types.
- **Lymphoplasmacytic lymphoma / Waldenström's macroglobulinaemia:** IgM paraprotein, **MYD88 L265P** mutation in >90%; hyperviscosity → **plasmapheresis**; therapy with BR or **BTK inhibitors** (ibrutinib).
- **Mantle-cell lymphoma (MCL): t(11;14)/cyclin D1**, CD5+, CD23-negative; intermediate-grade, not curable conventionally. Cytarabine-containing induction ± autologous transplant; **BTK inhibitors** (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib) and CD19 CAR-T at relapse.
- **T-cell NHLs** (generally poorer prognosis): **mycosis fungoides/Sézary** (cutaneous, indolent); **PTCL-NOS** and **AITL** (CHOP/CHOEP); **ALCL** — CD30+, *ALK*+ favourable (8-yr OS 82%) vs ALK-negative; **brentuximab vedotin + CHP** for CD30+ disease (ECHELON-2). **ATLL** (HTLV-1, "flower cells", hypercalcaemia); **extranodal NK/T-cell nasal type** (EBV+, **SMILE** regimen + radiotherapy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathway of normal B-cell differentiation and related lymphomas** (Harrison Fig. 113-2): label *lymphoid stem cell → pre-B (TdT+, CD19+) → early/intermediate B cell → germinal-centre/follicular-centre B cell → mantle-zone B cell → mature/secretory B cell → plasma cell*; map **pre-B ALL, mantle-cell lymphoma (CD5+), CLL/SLL, follicular lymphoma, Burkitt's, lymphoplasmacytic/Waldenström's, multiple myeloma**; annotate markers **CD10, CD19, CD20, CD22, CD5, CD23, surface Ig, HLA-DR**.
- **"Starry-sky" Burkitt histology** — label *monomorphic medium-sized blue B cells* and pale-staining *tingible-body (reactive) macrophages*.

Clinical / Diagnostic significance

- **Excisional biopsy with immunophenotyping is mandatory** — subtype dictates whether to observe, give curative chemo, or treat as an emergency.
- Baseline work-up: CBC, LDH, β2-microglobulin, LFTs, uric acid, calcium, serum protein electrophoresis, **HIV and hepatitis B/C serology** (HBV reactivation risk with rituximab — give antiviral prophylaxis), PET/CT, marrow biopsy where indicated, and **lumbar puncture/CNS imaging** in Burkitt's, lymphoblastic, testicular/paranasal/epidural/breast/renal/adrenal DLBCL.
- **Oncologic emergencies:** tumour-lysis syndrome (hydration + allopurinol or **rasburicase**), SVC obstruction, malignant spinal-cord compression, hypercalcaemia (ATLL), hyperviscosity (Waldenström's).
- **Rituximab (anti-CD20)** transformed B-cell NHL outcomes; **CAR-T cell therapy** and **bispecific antibodies** (epcoritamab, glofitamab, mosunetuzumab) are major recent advances for relapsed disease.

High-yield exam pointers

- NHL = mature B/T/NK malignancy, **no Reed-Sternberg cells**; ~85% B-cell.
- **t(14;18)/BCL2 → follicular; t(8;14)/MYC → Burkitt; t(11;14)/cyclin D1 → mantle-cell; t(11;18)/API2-MALT1 → MALT; t(2;5)/ALK → ALCL.**

- **IPI** = age ≥60, LDH↑, PS ≥2, stage III/IV, >1 extranodal site.
- **DLBCL** is commonest; **R-CHOP** is standard, curative in ~65–70%.
- **Burkitt's** — "starry sky", doubling <24 h, needs urgent therapy + CNS prophylaxis + TLS precautions.
- **FL** — indolent, watch-and-wait, transforms to DLBCL ~3%/yr.
- **Gastric MALT** regresses with *H. pylori* eradication; **splenic MZL** with HCV treatment.
- **B symptoms** = fever, night sweats, weight loss >10% over 6 months.
- Diagnosis needs **excisional/core biopsy** — never FNA alone; staging by **PET/CT (Lugano)**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Non-Hodgkin's Lymphoma" (Jacobson & Longo): WHO-HAEM5 classification, infectious associations, cytogenetics, Ann Arbor staging, IPI/FLIPI/MIPI, subtype features and regimens.
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — Lugano staging classification, bulky-disease definition, tumour-lysis syndrome management.
- **CMDT 2026** — "Non-Hodgkin Lymphomas" (Blood Disorders): current management algorithms (R-CHOP, BR, CAR-T, bispecific antibodies), prognosis, when to refer/admit.

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Oncogenes, mechanism and associated tumours

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

Definition / Introduction — **Oncogenes** are mutated or aberrantly activated genes that promote unregulated cell growth and are one of the two major classes of cancer *driver genes* (the other being tumour-suppressor genes). Their normal, tightly regulated cellular counterparts are called **proto-oncogenes**, which encode proteins acting at critical steps of growth-factor signal-transduction pathways (receptors, kinases, G-proteins, transcription factors). A single genetic event affecting **one allele** (gain-of-function, *dominant*) is sufficient to convert a proto-oncogene into an oncogene — in contrast to tumour-suppressors, where **both alleles** must be inactivated. First discovered in the late 1970s through the study of tumour-causing retroviruses, oncogenes are now the central targets of molecular (precision) cancer therapy.

Proto-oncogene vs oncogene — the core concept

- **Historical basis:** Peyton Rous (early 1900s) showed a chicken sarcoma was transmissible by a cell-free extract — the *Rous sarcoma virus (RSV)* — whose transforming gene was later identified as **v-SRC**. The normal cellular homologues of such viral genes are the **proto-oncogenes**, captured and mutated by retroviruses.
- A proto-oncogene becomes an oncogene by mutations that **relieve normal control and increase the activity** of the gene product.

- Oncogene activation is **monoallelic and dominant** — *one genetic event* activates it; activation requires *precise* gain-of-function changes at specific residues (**mutational hotspots**), unlike the diverse loss-of-function mutations seen in tumour-suppressors.
- Proto-oncogenes have crucial physiological roles in **cell proliferation, differentiation and cell death**; inappropriate pathway activation leads to tumorigenesis.
- Malignant transformation is **multistep**: most common adult solid cancers require roughly **three driver-gene mutations** (some childhood tumours only two), accumulating over years/decades.

Functional classes of oncogene products

Oncogene products act at successive levels of the growth-signalling cascade (growth factor → receptor → cytoplasmic transducer → nuclear effector):

Functional class	Representative oncogene(s)	Example tumour association
Receptor / signal-transduction (RTK)	**EGFR**, **ERBB2/HER2**, FLT3, KIT, RET, ALK, ROS1, MET, NTRK	Lung (EGFR/ALK/ROS1), breast (HER2), AML (FLT3)
Non-receptor (cytoplasmic) tyrosine kinase	**ABL**, SRC	CML (BCR-ABL)
Small GTPase (G-protein)	**KRAS**, **NRAS**	Pancreas/colon/lung (KRAS), melanoma (NRAS)
Serine/threonine kinase	**BRAF**, AKT1	Melanoma, thyroid, colorectal (BRAF)
Lipid kinase	**PIK3CA**	Multiple cancers
Transcription factor	**MYC**, MYCN, MYCL1, PML-RARα	Burkitt's/breast (MYC), neuroblastoma (MYCN), APL (PML-RARα)
Cell-cycle regulator	**CCND1 (cyclin D1)**, CDK4	Mantle-cell lymphoma, oesophageal/head-and-neck
Apoptosis regulator	**BCL2** (anti-apoptotic)	Follicular lymphoma
Inhibitor of p53	**MDM2**, MDM4	Sarcoma, glioma (MDM2); breast (MDM4)
Chromatin modifier	**IDH1**	Glioma

Mechanisms of oncogene activation

There are **three principal mechanisms** by which a proto-oncogene is activated in human cancer (Harrison Ch 76):

1. Point mutation (single-nucleotide substitution)

- The commonest mechanism; produces a constitutively active protein.
- *Prototype — RAS:* activating **KRAS** mutations occur in **>95% of pancreatic cancers** and **~40% of colon cancers** (less commonly in leukaemia, lung, thyroid).

- Mutations are restricted to **hotspot codons 12, 13 and 61**, locking RAS in the active **GTP-bound** state (RAS is a GTPase, *not* a kinase — active when bound to GTP, inactive when bound to GDP).
- Other examples: **BRAF V600E** (melanoma, thyroid, colorectal), **EGFR** (lung), **PIK3CA**, **IDH1** (glioma).

2. Gene (DNA) amplification → over-expression

- An increase in DNA copy number raises the dose of a normal gene product.
- Cytogenetically seen as **homogeneously staining regions (HSRs)** when intrachromosomal, or **double minutes (dmins)** when extrachromosomal.
- Amplicons may co-amplify several genes (e.g., **MDM2, GLI1, CDK4, TSPAN31** at 12q13–15 in sarcomas).
- Amplification often predicts **poor prognosis** — e.g., **ERBB2/HER2** in aggressive breast cancer and **MYCN (NMYC)** in neuroblastoma.

3. Chromosomal rearrangement (translocation) Two consequences:

- **(a) Creation of a novel chimeric fusion gene** with deregulated enzymatic activity — *prototype* the **Philadelphia chromosome**, the first reproducible chromosome abnormality in human malignancy. A reciprocal **t(9;22)(q34;q11)** juxtaposes **ABL** (chr 9, a tyrosine kinase) with **BCR** (chr 22), generating the **BCR-ABL** fusion protein, a constitutively active tyrosine kinase driving growth-factor–independent proliferation in CML.
- **(b) Juxtaposition next to a strong promoter/enhancer** causing over-expression of a structurally normal protein — typically by translocation into **antigen-receptor loci (IgH or TCR)**; e.g., **BCL2-IgH** (follicular lymphoma, over-expressed anti-apoptotic protein), **CCND1/BCL1-IgH** (mantle-cell lymphoma, cyclin D1), and **MYC-IgH t(8;14)** in Burkitt's lymphoma.
- Recurrent fusions also occur in **solid tumours**, e.g., **TMPRSS2-ERG** in >one-third of prostate cancers.

Representative oncogenes and their associated tumours

Oncogene	Function	Mode of activation	Associated tumour
KRAS	GTPase	Point mutation (codons 12/13/61)	Pancreatic, colorectal, lung
NRAS	GTPase	Point mutation	Melanoma
BRAF	Ser/Thr kinase	Point mutation (V600E)	Melanoma, thyroid, colorectal
EGFR	RTK signal transduction	Point mutation	Lung adenocarcinoma
ERBB2/HER2	RTK	Amplification	Breast (aggressive)
FLT3	Signal transduction	Point mutation	AML
PIK3CA	PI3-kinase	Point mutation	Multiple cancers

Oncogene	Function	Mode of activation	Associated tumour
MYC	Transcription factor	Amplification / translocation	Burkitt's, prostate, breast, liver
MYCN	Transcription factor	Amplification	Neuroblastoma
CCND1 (cyclin D1)	Cell-cycle progression	Amplification / t(11;14)	Mantle-cell lymphoma, oesophageal
BCL2	Anti-apoptotic	Translocation t(14;18)	Follicular lymphoma
ABL (BCR-ABL)	Tyrosine kinase	Translocation t(9;22)	CML
MDM2	p53 inhibitor	Amplification	Sarcoma, glioma
IDH1	Chromatin modification	Point mutation	Glioma

Recurrent oncogenic translocations (high-yield)

Fusion / gene	Translocation	Malignancy
BCR-ABL	t(9;22)(q34;q11)	Chronic myeloid leukaemia
PML-RARα	t(15;17)	Acute promyelocytic leukaemia (M3 AML)
BCL1 (CCND1)-IgH	t(11;14)(q13;q32)	Mantle-cell lymphoma
BCL2-IgH	t(14;18)(q32;q21)	Follicular lymphoma
MYC-IgH	t(8;14)	Burkitt's lymphoma
EWSR1-FLI1	t(11;22)(q24;q12)	Ewing's sarcoma
PAX3-FOXO1	t(2;13)(q35;q14)	Rhabdomyosarcoma
PAX8-PPARG	t(2;3)(q13;p25)	Thyroid carcinoma
TMPRSS2-ERG	rearrangement Chr21q22	Prostate cancer

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Mechanisms of oncogene activation:** A central proto-oncogene with three radiating arrows labelled (1) **Point mutation** (RAS, hotspot codons 12/13/61 → constitutive GTP-bound activation), (2) **Amplification** (multiple gene copies → over-expression; label **HSR** and **double minutes**; e.g., HER2, MYCN), (3) **Translocation** (label **fusion protein** e.g. BCR-ABL, and **promoter/enhancer juxtaposition** e.g. IgH–MYC).
- **Diagram 2 — Philadelphia chromosome (CML):** Two chromosomes labelled **Chr 9 (ABL, 9q34)** and **Chr 22 (BCR, 22q11)** with crossing arrows showing reciprocal translocation → derivative **Ph chromosome** carrying the **BCR-ABL chimeric gene** → **BCR-ABL fusion protein (active tyrosine kinase)**.

Clinical / Diagnostic significance

- **Targeted (precision) therapy:** Because tumours frequently depend on a single activated pathway — **oncogene addiction** — they are exquisitely vulnerable to inhibitors of that pathway. **Imatinib** (and dasatinib, nilotinib, ponatinib, bosutinib) blocks ATP-binding in the **BCR-ABL** kinase in CML — the *paradigm* of molecularly targeted therapy (>80% 10-year survival).
- **Drug–target–tumour examples: ATRA** for PML-RARα APL; **osimertinib** for EGFR-mutant lung cancer; **BRAF inhibitors** (± MEK inhibitor) for V600E melanoma; **crizotinib/alectinib** for ALK+, **larotrectinib/entrectinib** for NTRK-fusion cancers; **sotorasib/adagrasib** for KRAS-G12C lung cancer; **trastuzumab/pertuzumab** for HER2+ breast/gastric cancer; **JAK inhibitors** for JAK2-driven myeloproliferative disease.
- **Diagnostic / prognostic biomarkers:** Detection of oncogenic mutations, amplifications and fusions (tissue and circulating tumour DNA) guides therapy, monitors response and detects resistance; **HER2/MYCN amplification** flags poor prognosis.
- **Acquired resistance:** point mutation in the target kinase (e.g., **BCR-ABL T315I** — threonine→isoleucine at codon 315) prevents imatinib binding; bypass-pathway activation also occurs.
- **Synthetic lethality:** an allied strategy — e.g., **PARP inhibitors** in homologous-recombination–deficient (BRCA-mutant) cancers.

High-yield exam pointers

- Proto-oncogene → oncogene = **gain-of-function, dominant, one allele**; tumour-suppressor = **loss-of-function, recessive, both alleles** (Knudson two-hit).
- **Three mechanisms** of activation: **point mutation, amplification, translocation** — be ready to give one tumour example for each.
- **RAS** is a **GTPase, not a kinase** — active when GTP-bound; mutations cluster at **codons 12, 13, 61**; **KRAS** in >95% pancreatic and ~40% colon cancers.
- **HSRs** and **double minutes** = cytogenetic signatures of **gene amplification**; **HER2** (breast) and **MYCN** (neuroblastoma) are the classic amplified oncogenes.
- **Philadelphia chromosome t(9;22)** → **BCR-ABL** → CML → **imatinib**; the molecular-therapy prototype.

- Memorise the translocation set: **t(15;17) APL**, **t(14;18) follicular**, **t(11;14) mantle-cell**, **t(8;14) Burkitt's**, **t(11;22) Ewing's**.
- **Oncogene addiction** explains the dramatic responses to targeted agents; **T315I** explains imatinib resistance.
- **v-SRC** (Rous sarcoma virus) = first oncogene concept; **Vogelstein "three-strikes"** = multistep colorectal carcinogenesis (APC → KRAS → SMAD4/TP53).

SOURCE & COVERAGE

Harrison 22e — Ch 76 "Cancer Genetics" (mechanisms of oncogene activation, Tables 76-1 oncogenes and 76-2 translocations, BCR-ABL) and Ch 77 "Cancer Cell Biology" (signal-transduction classes, RAS biology, oncogene addiction, targeted agents Table 77-2). *Coverage note:* The specific **MYC-IgH t(8;14)** translocation of Burkitt's lymphoma and the **Knudson two-hit / Vogelstein three-strikes** eponyms are standard, universally accepted internal medicine (and appear elsewhere in Harrison 22e, e.g. Ch 113) but are not detailed verbatim within the two provided chapters; all other specifics (gene names, codons, percentages, translocation notations, drug–target pairs) are taken directly from Ch 76 and Ch 77.

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Paraneoplastic syndromes in bronchogenic carcinoma

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

Definition / Introduction — Paraneoplastic syndromes are disorders that accompany a malignancy but are **not** caused by the local mass effect, invasion, or distant metastasis of the tumour; rather they result from tumour-elaborated peptide hormones, cytokines and growth factors, or from tumour-triggered autoimmunity. Bronchogenic (lung) carcinoma — especially the neuroendocrine **small-cell lung cancer (SCLC)** and carcinoids — is the single most prolific solid-tumour cause of these syndromes. They are clinically important because they may be the **presenting feature**, may herald **recurrence**, can mimic metastatic (incurable) disease, and frequently regress when the primary tumour is treated.

Classification (by organ system) and histological associations

System	Syndrome	Mediator / mechanism	Commonest lung histology
Endocrine	SIADH (hyponatraemia)	Ectopic **vasopressin** (± ANP)	SCLC
Endocrine	Hypercalcaemia of malignancy	**PTHrP** (humoral); rarely 1,25-$(OH)_2$D, ectopic PTH	Squamous cell
Endocrine	Ectopic **ACTH** (Cushing's)	POMC → ACTH; rarely CRH	SCLC, bronchial carcinoid
Neurological	Lambert-Eaton myasthenic syndrome (LEMS)	Anti–**P/Q-type VGCC**, anti-SOX1	SCLC

System	Syndrome	Mediator / mechanism	Commonest lung histology
Neurological	Encephalomyelitis, sensory neuronopathy, limbic/brainstem encephalitis, cerebellar degeneration, opsoclonus, CAR (retinopathy)	Anti-Hu, anti-CRMP5, anti-AMPAR, anti-GABA-B, anti-recoverin	SCLC
Haematologic	Granulocytosis, thrombocytosis, eosinophilia, anaemia	G-CSF/GM-CSF, IL-6, IL-5	NSCLC > SCLC
Vascular	Migratory thrombophlebitis (**Trousseau**), marantic endocarditis, DIC, VTE	Tumour procoagulants	Adenocarcinoma
Skeletal/ cutaneous	Clubbing, **hypertrophic pulmonary osteoarthropathy (HPOA)**, dermatomyositis, acanthosis nigricans	Unknown / autoimmune	Adenocarcinoma (HPOA)

- *Rule of thumb:* **SCLC** drives the endocrine (SIADH, ectopic ACTH) and neurological (LEMS, encephalomyelitis) syndromes; **squamous cell** drives hypercalcaemia (PTHrP); **adenocarcinoma** drives HPOA/clubbing and is the most thrombogenic.

Endocrine / metabolic syndromes

- **SIADH (ectopic vasopressin)** — occurs in *at least half* of SCLC patients (clinically apparent in ~11%). Hyponatraemia with **low serum osmolality, inappropriately concentrated urine (urine osmolality not maximally dilute), urine Na^+ normal/high**, and clinical euvolaemia; exclude renal/adrenal/thyroid causes. Symptoms (lethargy, confusion, seizures) reflect *rate* and *severity* of fall in Na^+. **Treatment:** fluid restriction (first line); **demeclocycline** 150–300 mg PO 3–4×/day; V2-receptor antagonists **tolvaptan** 15 mg PO OD or **conivaptan**; hypertonic (3%) saline + furosemide for Na^+ <115 meq/L or seizures. Correct **slowly (0.5–1 meq/L/h)** to avoid central pontine myelinolysis. SIADH usually resolves within 1–4 weeks of effective chemotherapy.
- **Humoral hypercalcaemia of malignancy (HHM)** — seen in ~10–25% of lung cancers, most often **advanced squamous cell carcinoma**. Mediated chiefly by **PTHrP** (structurally related to PTH, acts on the PTH receptor → hypercalcaemia, hypophosphataemia, hypercalciuria). Features favouring HHM over primary hyperparathyroidism: known malignancy, recent/abrupt onset, very high Ca^{2+}, **metabolic alkalosis**, and a **suppressed PTH** with **elevated PTHrP** (raised in ~80% of hypercalcaemic cancer patients). Symptoms: polyuria, dehydration, constipation, confusion; ECG shows **short QT**. **Treatment:** IV saline rehydration (200–500 mL/h), IV **bisphosphonates** (zoledronate 4 mg, pamidronate 60–90 mg), **denosumab** if refractory, calcitonin, glucocorticoids (lymphoma/myeloma), loop diuretics only after rehydration.
- **Ectopic ACTH (Cushing's syndrome)** — accounts for 10–20% of all Cushing's; **SCLC** is the commonest cause, followed by **bronchial and thymic carcinoids**. Due to aberrant **POMC** expression. Because exposure is brief and cachexia coexists, the classic centripetal phenotype is often *absent*; instead patients show **hypokalaemic metabolic alkalosis, hypertension, oedema, hyperglycaemia, hyperpigmentation** (high MSH) and steroid psychosis. **Diagnosis:** urine free cortisol >2–4× normal, plasma ACTH usually >100 pg/mL, **failure to suppress on high-dose (8 mg) dexamethasone in ~90%** (bronchial carcinoid is a notable exception that may suppress);

inferior petrosal sinus sampling (central:peripheral ACTH ≥3:1 favours pituitary source) localises ambiguous cases. **Treatment:** steroidogenesis inhibitors — ketoconazole, metyrapone, mitotane, etomidate; mifepristone; treat the tumour; bilateral adrenalectomy in extreme refractory cases.

Neurological paraneoplastic syndromes

- **Lambert-Eaton myasthenic syndrome (LEMS)** — the classic neuromuscular-junction paraneoplastic syndrome of SCLC; antibodies against **presynaptic P/Q-type voltage-gated calcium channels (VGCC)** (and **anti-SOX1**, a high-risk SCLC marker) reduce quantal acetylcholine release. *Triad:* **proximal lower-limb weakness, autonomic dysfunction** (dry mouth, impotence), and **hyporeflexia/areflexia**. Distinguishing point from myasthenia gravis: **strength and reflexes augment after brief sustained/repeated effort** (post-exercise facilitation); on repetitive nerve stimulation there is an **incremental response at high frequency** (vs decrement in MG). Treat the SCLC (chemotherapy is the initial treatment of choice); symptomatic relief with **3,4-diaminopyridine (amifampridine)** and pyridostigmine; immunotherapy (IVIg, steroids) for refractory cases.
- **CNS / antibody-mediated syndromes** (≈SCLC, antibodies often precede cancer diagnosis):

Antibody	Syndrome
Anti-Hu (ANNA-1)	Encephalomyelitis, subacute sensory neuronopathy (dorsal-root ganglionopathy)
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis/uveitis, peripheral neuropathy
Anti-AMPAR / anti-GABA-B	Limbic encephalitis (GABA-B → early prominent seizures)
Anti-VGCC / P/Q, anti-Yo	Subacute cerebellar degeneration
Anti-recoverin	Cancer-associated retinopathy (CAR) — photosensitivity, night blindness, ring scotomata, attenuated ERG

- Other reported syndromes: opsoclonus-myoclonus, brainstem encephalitis, polymyositis/dermatomyositis and stiff-person syndrome (anti-amphiphysin). Neurological syndromes occur in ~1% of lung cancers but are dramatic; antibodies against **intracellular** antigens (Hu, CRMP5, Yo) carry a high tumour probability but respond *poorly* to immunotherapy.

Haematologic, vascular and skeletal/cutaneous syndromes

- **Haematologic** (usually asymptomatic, parallel tumour course): **granulocytosis** (G-CSF/GM-CSF/IL-6; ~40% of lung cancers), **thrombocytosis** (IL-6; ~17–40%, poorer prognosis), **eosinophilia** (IL-5), anaemia, and leukoerythroblastosis with marrow invasion.
- **Hypercoagulability / vascular** — the most consequential haematologic effect. **Migratory/recurrent superficial thrombophlebitis with visceral carcinoma = Trousseau's syndrome** (classically pancreatic, also lung); also deep vein thrombosis, pulmonary embolism, **non-bacterial thrombotic (marantic) endocarditis** with arterial emboli, and DIC. Lung scores 1 point on the **Khorana VTE risk score**. Treat with LMWH or a DOAC (e.g., apixaban) — generally preferred over warfarin in cancer-associated VTE.

- **Skeletal / cutaneous — digital clubbing** (~30%, usually NSCLC) and **hypertrophic pulmonary osteoarthropathy (HPOA)** (1–10%, classically adenocarcinoma): symmetrical periostosis of long bones with painful arthropathy and a positive bone scan. Cutaneous: **dermatomyositis** (heliotrope rash, Gottron's papules — strong cancer association), acanthosis nigricans, erythema gyratum repens. Renal (≤1%): membranous nephropathy / nephrotic syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of a bronchogenic carcinoma with labelled paraneoplastic "satellites"** radiating by system: *Endocrine* — SIADH (vasopressin), Hypercalcaemia (PTHrP), Ectopic ACTH (POMC); *Neurological* — LEMS (anti-P/Q VGCC), Encephalomyelitis (anti-Hu), Cerebellar degeneration; *Haematologic/Vascular* — Trousseau's thrombophlebitis, marantic endocarditis; *Skeletal* — Clubbing + HPOA. Label each satellite with **mediator + commonest histology**.
- **LEMS neuromuscular junction diagram** — label: *presynaptic terminal, P/Q-type voltage-gated Ca^{2+} channel, anti-VGCC antibody blocking Ca^{2+} entry, reduced acetylcholine vesicle release, post-synaptic AChR*, and an inset RNS tracing showing **incremental response at high-frequency stimulation**.

Clinical / Diagnostic significance

- A paraneoplastic syndrome may be the **first clue** to an occult bronchogenic carcinoma — e.g., unexplained hyponatraemia, hypercalcaemia, hypokalaemic alkalosis, or new proximal weakness in a smoker should trigger imaging (CT chest, PET-CT) and onconeural antibody panels.
- Distinguishing paraneoplastic effects from true metastasis is **prognostically critical** — paraneoplastic syndromes **do not preclude curative-intent treatment**, whereas mislabelling them as metastatic disease wrongly relegates the patient to palliation.
- **Management hierarchy:** treat the underlying tumour (often produces the most durable response) **plus** syndrome-specific therapy (vaptans for SIADH, bisphosphonates for hypercalcaemia, steroidogenesis inhibitors for ectopic ACTH, 3,4-DAP for LEMS, anticoagulation for VTE).
- Antibody profiling both **localises the likely primary** (SCLC for anti-Hu/VGCC/SOX1) and **prognosticates** (intracellular-antigen antibodies = poor neurological recovery).

High-yield exam pointers

- **SCLC = the paraneoplastic powerhouse** of the lung: SIADH, ectopic ACTH, LEMS, anti-Hu encephalomyelitis.
- **Squamous cell → hypercalcaemia (PTHrP)**; **adenocarcinoma → HPOA/clubbing and the most thrombogenic** histology.
- **SIADH:** euvolaemic hyponatraemia, low serum osmolality, inappropriately concentrated urine, urine Na^+ >20–40; correct Na^+ at **0.5–1 meq/L/h** to prevent osmotic demyelination.
- **HHM:** suppressed PTH + **elevated PTHrP**, hypophosphataemia, metabolic alkalosis, short QT; treat with saline + bisphosphonate.

- **Ectopic ACTH:** hypokalaemic metabolic alkalosis + hyperpigmentation; **fails high-dose dexamethasone suppression**; ACTH >100 pg/mL.
- **LEMS vs MG:** LEMS = proximal weakness, areflexia, autonomic features, **post-exercise facilitation**, **incremental** RNS response, anti-P/Q VGCC; MG = fatigable ocular/bulbar weakness, **decremental** response, anti-AChR.
- **Trousseau's syndrome** = migratory thrombophlebitis with visceral (lung/pancreatic) cancer; consider occult malignancy in recurrent/migratory/unusual-site thrombosis.
- **Dermatomyositis** (heliotrope rash + Gottron's papules) carries a strong association with internal malignancy including lung.
- Onconeural antibodies **precede the cancer diagnosis in ~60%** of paraneoplastic neurological disorders.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Paraneoplastic Syndromes: Endocrinologic/Hematologic"; "Neoplasms of the Lung"; "Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis"; "Myasthenia Gravis and Other Diseases of the Neuromuscular Junction" (LEMS).
- **DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — lung cancer paraneoplastic syndromes (HHM 10–25%, SIADH ~11% SCLC, HPOA, leukocytosis/thrombocytosis, VTE data).
- **CMDT 2026** — current management framing (SIADH, hypercalcaemia, cancer-associated VTE).
- *Coverage note:* The "P/Q-type" VGCC subtype and the high-frequency **incremental** RNS response in LEMS are universally accepted standard neuromuscular medicine; Harrison states the antibody as anti–voltage-gated calcium channel / P/Q calcium channel and contrasts it with the decremental MG response.

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Paraneoplastic syndromes

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

Definition / Introduction — Paraneoplastic syndromes are disorders that accompany benign or malignant tumours but are **not** caused by the local mass effect, invasion, or distant metastasis of the tumour. They arise from substances elaborated by the tumour (peptide hormones, cytokines, growth factors) or from tumour-triggered immune responses (onconeural antibodies). Neuroendocrine tumours — particularly **small-cell lung carcinoma (SCLC)** and carcinoids — are the commonest culprits. They are important because they are more frequent than appreciated, may be the **presenting feature** of an occult malignancy, can cause major morbidity independent of tumour burden, and characteristically wax and wane with the activity of the underlying cancer.

Pathogenesis / Mechanisms

- **Ectopic hormone production** — *Eutopic* = hormone from its normal tissue (e.g., ACTH from pituitary corticotropes); *ectopic* = hormone from an atypical source (e.g., ACTH from SCLC). Mechanisms include cellular **dedifferentiation** (re-expression of fetal genes such as hCG, PTHrP, α-fetoprotein), epigenetic derepression, and rarely gene rearrangement bringing a hormone gene under an atypical promoter.
- **Loss of normal feedback regulation and aberrant peptide processing** — e.g., ectopic ACTH arises from unregulated proopiomelanocortin (POMC) expression and is released largely as inactive precursor fragments.
- **Immune-mediated (neurologic syndromes)** — neuronal proteins ectopically expressed by the tumour break immune tolerance, generating **onconeural antibodies** and cytotoxic T-cell responses that cross-react with the nervous system.
- **General criteria confirming an ectopic hormone syndrome** — (1) hormone excess from an atypical source; (2) demonstration of tumour hormone production (immunostaining, mRNA, in-vitro secretion); (3) arteriovenous hormone gradient across the tumour; (4) fall in hormone levels after tumour debulking.

Endocrine paraneoplastic syndromes

Treatment of the **underlying tumour** is the mainstay; specific measures relieve symptoms but rarely alter survival.

Syndrome	Ectopic mediator	Typical tumours	Key points
Humoral hypercalcaemia of malignancy (HHM)	**PTHrP**; rarely 1,25-$(OH)_2D$ (lymphoma), PTH	Squamous (lung, head & neck, skin), breast, GU, oesophagus; myeloma, lymphoma	Commonest endocrine PNS; ~20–30% of cancers; PTHrP raised in ~80%; **PTH suppressed**, hypophosphataemia, metabolic alkalosis
SIADH (ectopic ADH/vasopressin)	Arginine vasopressin	SCLC (≥50%), carcinoid, head & neck, GU	Euvolaemic hyponatraemia; low serum osmolality with inappropriately concentrated urine

Syndrome	Ectopic mediator	Typical tumours	Key points
Ectopic Cushing's syndrome	**ACTH** (POMC); rarely CRH	SCLC (commonest), bronchial/thymic carcinoid, islet cell, phaeochromocytoma, medullary thyroid Ca	10–20% of Cushing's; hypokalaemia, metabolic alkalosis, oedema, hyperpigmentation; ACTH usually >100 pg/mL, fails high-dose dexamethasone suppression
Non-islet-cell tumour hypoglycaemia	**IGF-II** precursor (big IGF-II)	Large mesenchymal tumours, sarcoma, hepatic, adrenal	Fasting hypoglycaemia with suppressed insulin; **IGF-II : IGF-I ratio >10:1**
hCG-related (gynaecomastia, precocious puberty)	hCG	Testicular germ cell, choriocarcinoma, lung, hepatic, islet	Leydig-cell stimulation → oestrogen excess
Oncogenic (tumour-induced) osteomalacia	**FGF23** (phosphatonin)	Haemangiopericytoma, fibroma, giant-cell tumour	Renal phosphate wasting, hypophosphataemia, low 1,25-$(OH)_2D$; normal Ca/PTH; treat with phosphate/vit D, **burosumab** (anti-FGF23 mAb)
Others (rare)	GHRH (acromegaly), renin (hypertension), calcitonin, VIP, TSH	Carcinoids, islet cell, juxtaglomerular tumour	—

Haematologic paraneoplastic syndromes

Usually asymptomatic and self-limited; severity parallels tumour course. The most consequential is **hypercoagulability**.

Syndrome	Mediator	Associated cancers
Erythrocytosis	Erythropoietin	Renal cell (~3%), hepatoma (~10%), **cerebellar haemangioblastoma (~15%)**
Granulocytosis	G-CSF, GM-CSF, IL-6	Lung, GI, ovary, GU, Hodgkin's (no left shift)
Thrombocytosis	IL-6, thrombopoietin	Lung, GI, breast, ovary, lymphoma (marker of poorer prognosis)
Eosinophilia	IL-5	Lymphoma, leukaemia, lung
Thrombophlebitis / VTE	Procoagulants, tissue factor	Pancreatic, lung, GI, breast, ovary, GU, brain

- **Trousseau's syndrome** = migratory/recurrent superficial thrombophlebitis with visceral carcinoma, classically **pancreatic** cancer; may be the heralding sign of malignancy.
- Cancer-associated VTE risk is stratified by the **Khorana score** (site of cancer, platelets ≥350 000/µL, Hb <10 g/dL or use of ESAs, leucocytes >11 000/µL, BMI ≥35). Treat with LMWH or a DOAC (e.g., **apixaban**, noninferior to dalteparin).

Neurologic paraneoplastic syndromes (PNS) and autoimmune encephalitis

Disabling PNS occur in 0.5–1% of all cancer patients, but in **2–3% with SCLC/neuroblastoma and 30–50% with thymoma**. In ~60% the neurologic syndrome **precedes** the cancer diagnosis; syndromes typically evolve subacutely. Antibodies are classified by their probability of an underlying tumour.

Antibody	Target	Classic syndrome	Tumour
Anti-Hu (ANNA-1)	intracellular	Encephalomyelitis, sensory neuronopathy	SCLC
Anti-Yo (PCA-1)	intracellular	Subacute cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA-2)	intracellular	Opsoclonus, cerebellar/brainstem	Breast, gynaecologic, SCLC
Anti-CRMP5 (CV2)	intracellular	Encephalomyelitis, chorea, optic neuritis, uveitis, neuropathy	SCLC, thymoma
Anti-Tr (DNER)	cell-surface	Cerebellar degeneration	Hodgkin's lymphoma
Anti-Ma2	intracellular	Limbic/hypothalamic/brainstem encephalitis	Testicular germ cell
Anti-amphiphysin	(synaptic)	Stiff-person syndrome	Breast, SCLC
Anti-NMDAR	cell-surface	Psychiatric prodrome → seizures, dyskinesias, dysautonomia, hypoventilation	**Ovarian teratoma** (young women)
Anti-VGCC	cell-surface	**Lambert-Eaton myasthenic syndrome (LEMS)**, cerebellar	SCLC
Anti-LGI1	cell-surface	Limbic encephalitis, **hyponatraemia, faciobrachial dystonic seizures**	Rarely thymoma
Anti-Caspr2	cell-surface	**Morvan syndrome**, neuromyotonia	Thymoma

- **Classic ("high-risk") syndromes** — encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, sensory neuronopathy, LEMS, gastrointestinal pseudo-obstruction, dermatomyositis.
- **Therapeutic dichotomy** — antibodies to **intracellular antigens** (Hu, Yo, Ri, CRMP5, Ma2) act via cytotoxic **T cells**, cause neuronal loss, and respond **poorly** to immunotherapy (focus on treating the tumour). Antibodies to **cell-surface/synaptic antigens** (NMDAR, LGI1, Caspr2, AMPAR, GABA-B) are **directly pathogenic** and **respond well** to tumour removal plus immunotherapy — first-line steroids, IVIg, plasma exchange; second-line **rituximab, cyclophosphamide**. ~85–90% of anti-NMDAR patients improve substantially.
- LEMS: proximal weakness with **post-tetanic facilitation** and autonomic features; if positive, screen for SCLC with CT/PET and continue surveillance ≥3 years.

Dermatologic and rheumatologic paraneoplastic syndromes

- **Acanthosis nigricans** (esp. gastric adenocarcinoma) and **tripe palms** (thickened velvety palms).

- **Sign of Leser-Trélat** — sudden eruption of multiple seborrhoeic keratoses (GI adenocarcinoma).
- **Erythema gyratum repens** (lung), **necrolytic migratory erythema** (glucagonoma), **Bazex syndrome / acrokeratosis paraneoplastica** (aerodigestive squamous cancers), **paraneoplastic pemphigus** (lymphoproliferative disease).
- **Dermatomyositis / polymyositis** (Gottron papules, heliotrope rash) — strongest cancer link with dermatomyositis, highest risk within the first **5 years**.
- **Hypertrophic pulmonary osteoarthropathy (HPOA)** — triad of **digital clubbing, symmetrical large-joint arthropathy, and radiographic periostosis**; most often non-small-cell (adenocarcinoma) lung cancer.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of mechanisms of paraneoplastic syndromes** — central tumour cell with three labelled arrows: (1) *Ectopic hormone* → PTHrP, ADH, ACTH, IGF-II → target organs (bone/kidney, kidney, adrenal, muscle); (2) *Cytokines* → IL-6, G-CSF, IL-5, EPO → marrow (thrombocytosis, granulocytosis, eosinophilia, erythrocytosis); (3) *Onconeural antibodies / T cells* → CNS, dorsal root ganglion, neuromuscular junction. Label **eutopic vs ectopic** and **"effects not due to mass/metastasis."**
- **Antibody–antigen location diagram** — two panels: *Intracellular antigens* (Hu, Yo, Ri, CRMP5) → cytotoxic T-cell attack → poor response; *Cell-surface antigens* (NMDAR, LGI1, VGCC) → antibody-mediated → good response to immunotherapy. Label the neuron, surface receptor, antibody, and T cell.

Clinical / Diagnostic significance

- **Recognition value** — atypical metabolic/neurologic features in a cancer patient, or an unexplained syndrome (hyponatraemia, hypercalcaemia, subacute cerebellar ataxia) in a patient without known cancer, should prompt a search for malignancy (CT/PET; testicular/pelvic USS or MRI for germ-cell tumours and teratomas).
- **Endocrine work-up** — suppressed PTH with raised PTHrP confirms HHM; ACTH >100 pg/mL with failure of high-dose dexamethasone suppression and absent petrosal:peripheral gradient indicates ectopic ACTH; IGF-II:IGF-I ratio >10:1 supports IGF-II hypoglycaemia.
- **Neurologic work-up** — only ~60–70% of CNS PNS and <20% of peripheral PNS have a detectable antibody; MRI (mesial temporal FLAIR change in limbic encephalitis) and CSF (lymphocytic pleocytosis, oligoclonal bands) support the diagnosis and exclude metastatic/leptomeningeal disease.
- **Management of HHM** — IV **0.9% saline 100–300 mL/h** for rehydration and calciuresis, then **bisphosphonate** (zoledronic acid/pamidronate) or **denosumab** (anti-RANKL; preferred in renal impairment or bisphosphonate-refractory cases); calcitonin or glucocorticoids as adjuncts; treat the tumour.
- **Management of SIADH** — fluid restriction, **vaptans** (tolvaptan) or demeclocycline; correct sodium slowly (0.5–1 mEq/L/h) to avoid osmotic demyelination.

High-yield exam pointers

- **SCLC** is the single commonest cause of paraneoplastic syndromes (SIADH, ectopic ACTH, LEMS, Hu/encephalomyelitis).
- Commonest **endocrine** PNS = **hypercalcaemia (PTHrP)**; commonest cause of **paraneoplastic SIADH** = SCLC.
- **Ectopic ACTH** → hyperpigmentation, hypokalaemic metabolic alkalosis, *less* central obesity; ACTH not suppressed by high-dose dexamethasone.
- **Trousseau's syndrome** = migratory thrombophlebitis ↔ visceral (pancreatic) cancer.
- **Anti-Yo** → cerebellum (ovary/breast); **anti-Hu** → sensory neuronopathy/encephalomyelitis (SCLC); **anti-Ri** → opsoclonus; **anti-Ma2** → limbic/brainstem (testicular); **anti-Tr** → cerebellar (Hodgkin's).
- **Anti-NMDAR encephalitis** → young woman + **ovarian teratoma**; psychiatric → seizures → dyskinesias → autonomic instability; rituximab-responsive.
- **LEMS** → anti-VGCC, SCLC, proximal weakness with facilitation; **Lambert-Eaton precedes the cancer** in most.
- **Surface-antigen** antibodies respond to immunotherapy; **intracellular-antigen** antibodies do not — treat the tumour.
- Cutaneous clues: **Leser-Trélat, acanthosis nigricans, tripe palms, erythema gyratum repens, necrolytic migratory erythema (glucagonoma)**; rheumatologic: **HPOA (clubbing + periostosis)**, dermatomyositis.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Paraneoplastic Syndromes: Endocrinologic/Hematologic" and "Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis" (antibody classification, syndrome–tumour associations, Khorana score, management).
- **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — Paraneoplastic syndromes and lung-cancer chapters (HPOA, dermatomyositis timing, dermatologic entities, hypercalcaemia/SIADH frequencies).
- **CMDT 2026** — "Cancer" chapter (hypercalcaemia of malignancy diagnosis and current management with saline, bisphosphonates, denosumab).

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Screening strategies for colorectal cancer

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

Definition / Introduction — Screening for colorectal cancer (CRC) is the systematic application of tests to *asymptomatic, average-risk or increased-risk* individuals to detect either pre-malignant adenomatous/serrated polyps (so they can be removed) or early, curable cancers. CRC is an ideal target for screening because it is common, is fatal in nearly 50% of cases yet highly curable when localized, and arises from benign polyps that progress to cancer over many years through the *adenoma–carcinoma sequence*. Removal of these polyps has been shown to prevent the majority of cancers; consequently, the U.S. Preventive Services Task Force (USPSTF, 2021), American Cancer Society (ACS, 2018), ACG and US Multi-Society Task Force all endorse offering organized screening to **all adults aged 45–75 years**.

Rationale and risk stratification (who, and when to start)

- **Twin rationale:** (1) endoscopic removal of adenomatous polyps *prevents* cancer; (2) detection of localized, superficial cancers in asymptomatic people raises the surgical cure rate.
- **Starting age lowered to 45 years (USPSTF 2021)** because of the rising incidence of CRC in adults <50 years. Grade **B** at 45–49 years (qualified) and grade **A** at 50–75 years (strong).
- **76–85 years:** individualize ("C") — consider overall health, life expectancy, prior screening and preferences. **>85 years:** discourage screening.
- Screening intensity is **risk-tiered**: average risk vs increased risk (family history, IBD/PSC) vs high risk (hereditary syndromes).

Risk category	Defining feature	When to begin / interval
Average risk	No personal/family history, no IBD	Age **45 y**; modality-dependent interval (see below)
Single FDR, CRC at ≥60 y	One first-degree relative	Begin **age 40 y**; colonoscopy every **10 y** (as average risk)
FDR with CRC/advanced adenoma <60 y, or two FDRs	Stronger family history	Begin **age 40 y** *or 10 y before* youngest case; colonoscopy every **5 y**
IBD (UC / Crohn colitis), PSC	Chronic colitis	Surveillance colonoscopy **8–10 y after symptom onset**
FAP / MUTYH-associated	APC / biallelic MUTYH	Endoscopic surveillance from puberty; prophylactic colectomy
Lynch syndrome (HNPCC)	MMR gene variant	Colonoscopy every **1–2 y from age 25 y**

Stool-based (non-invasive) tests

- **Guaiac faecal occult blood test (gFOBT, e.g. Hemoccult SENSA):** detects pseudoperoxidase activity of haem; **annual**. Affected by diet/medications. ~50% of proven CRCs give a negative test (intermittent bleeding); of asymptomatic "positives" <10% have cancer, 20–30% have benign polyps. Meta-analysis: **22% relative reduction** in CRC mortality with biennial testing (up to **32%** with annual) — benefit emerges only after years of follow-up via downstream colonoscopy.
- **Faecal immunochemical test (FIT):** detects human globin; **annual**. Higher sensitivity than gFOBT with similar specificity and **not affected by diet or medication** — it has largely replaced

gFOBT and is the *preferred* stool test (US Multi-Society Task Force, ACG). Pooled sensitivity ~**74%**, specificity ~**94%** for CRC; may detect proximal tumours less reliably.

- **Multi-target stool DNA test (mt-sDNA; Cologuard = FIT + methylated/mutated DNA markers):** every **1–3 years**. Single-test sensitivity for CRC **92.3% vs 73.8%** for FIT alone, and for large/serrated adenomas **42.4% vs 23.8%**; but **lower specificity** → more false positives and follow-up colonoscopies. High sensitivity/specificity (>90%) for established adenocarcinoma but **<50% sensitivity for advanced precancerous lesions**.
- **Blood-based test (methylated SEPT9):** lower sensitivity and specificity than FIT, costlier — **not recommended as a first-line** screening test.
- **Key principle:** *any positive stool/blood/imaging test mandates colonoscopy*; a non-invasive test is only the first step of a two-step pathway.

Structural / visual (endoscopic and imaging) tests

Test	Interval	Strengths	Limitations
Colonoscopy	every **10 y**	Examines *entire* colon; diagnostic + therapeutic (polypectomy); most sensitive	Bowel prep + sedation; perforation ~0.1% (≈4/10 000), bleeding ~0.25%, death ≈2.9/100 000; operator-dependent
Flexible sigmoidoscopy	every **5 y** (or **10 y + annual FIT**)	No sedation, no full enema, fewer perforations (≈1/10 000); RCT-proven ↓ incidence & mortality	Only rectosigmoid/descending colon; misses proximal lesions (≈1.5% have proximal advanced neoplasia despite normal scope)
CT colonography (virtual)	every **5 y**	Sensitivity >95% for cancer, 86% for polyps ≥6 mm; option if colonoscopy declined/incomplete	Bowel prep; radiation; extracolonic findings (5–37%); flat/serrated lesions missed; positive → colonoscopy
Capsule colonoscopy	—	Non-invasive imaging of colon	Lower sensitivity (polyps >6 mm 64% vs 84%; CRC 74% vs 100%); FDA-approved only for unsuitable/incomplete colonoscopy

- **Sigmoidoscopy evidence:** meta-analyses of RCTs show an **18% relative reduction in incidence** and a **28% reduction in mortality**; benefit of a single screen persists >15 years. Any adenoma found at sigmoidoscopy → complete the examination with **full colonoscopy**.
- **Colonoscopy quality matters:** benefit is greater in the **distal (≈80%)** than proximal colon (≈40–60%); withdrawal time **≥7–9 min** and an adequate adenoma detection rate are key quality metrics.
- **Digital rectal examination (DRE) is NOT an effective CRC screening test** and is not recommended by any society.

Screening in high-risk / hereditary syndromes

- **Familial adenomatous polyposis (FAP):** autosomal dominant, **APC** gene (~90%); **MUTYH-associated polyposis** is autosomal recessive (~8%). Hundreds–thousands of adenomas; polyps by mean age 15 y, cancer often by 40 y, **inevitable by 50 y** if untreated. Management: genetic counselling/testing, endoscopic surveillance from puberty, and **prophylactic**

proctocolectomy/colectomy (usually before age 20 y); plus upper-GI endoscopy every 1–3 y for duodenal/periampullary adenomas. *MUTYH-associated polyposis* — colonoscopic surveillance annually-to-biennially from **age 25–30 y**.

- **Lynch syndrome (HNPCC):** autosomal dominant MMR gene defect (**MLH1, MSH2, MSH6, PMS2, EPCAM**) causing microsatellite instability; ~3% of all CRC, up to 17-fold risk; accelerated adenoma→cancer (1–2 y). **Universal tumour testing** (IHC for MMR proteins or MSI) is recommended for *all* CRCs. Carriers: **colonoscopy every 1–2 years from age 25 y** (or 5 y younger than youngest case); plus endometrial/ovarian surveillance from 30–35 y and consideration of risk-reducing hysterectomy ± BSO at 40 y.
- **IBD:** risk rises ~0.5–1% per year after the first decade; surveillance colonoscopy with biopsies begins **8–10 years after symptom onset** (earlier with concurrent **PSC**).

Surveillance after polypectomy / curative resection

- After curative CRC resection: history, examination and **CEA** every 3–6 months for 2 years then 6-monthly to 5 years; CT chest/abdomen/pelvis 6–12 monthly in high-risk stage II / all stage III.
- **Colonoscopy 1 year** after resection (or after completing adjuvant therapy if not fully scoped pre-op); if clear, repeat **every 3–5 years** for metachronous lesions.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Adenoma–carcinoma sequence flow diagram:** *Normal colonic mucosa → APC loss → small adenoma → KRAS activation → large/advanced adenoma → TP53 / DCC loss → invasive carcinoma*, with a parallel arrow "polypectomy interrupts the sequence." Label the multi-year timeline and the accelerated 1–2 year pathway in Lynch syndrome.
- **CRC screening algorithm:** Box "Average-risk adult, age 45 y" → two branches: *Stool-based (FIT annual / mt-sDNA q1–3 y)* and *Structural (colonoscopy q10 y / FS q5 y / CT colonography q5 y)*; any **positive non-invasive test → COLONOSCOPY**. Side box: "Increased/high risk → tailored earlier, more frequent colonoscopy." Label start age 45, stop 75 (individualize 76–85).

Clinical / Diagnostic significance

- Choice of test is a shared decision — *"the best test is the one the patient will actually complete."* FIT and colonoscopy are the preferred stool-based and structural modalities respectively.
- Unexplained **iron-deficiency anaemia** in any adult (except a menstruating multiparous woman) mandates full colonic evaluation — it is not a screening scenario but the commonest presentation of a right-sided cancer.
- Stool tests reduce mortality chiefly by triggering colonoscopy and polypectomy; their value is realized only when positives are followed up.
- **Primary prevention** adjuncts: regular **aspirin/NSAIDs** reduce adenoma/cancer incidence (individualized owing to bleeding risk); antioxidant vitamins and fibre supplements are *not* protective.

High-yield exam pointers

- **Start screening at age 45 y** (USPSTF 2021); continue to 75; individualize 76–85; discourage >85.
- **Average-risk menu:** FIT annual · gFOBT (Hemoccult SENSA) annual · mt-sDNA q1–3 y · flexible sigmoidoscopy q5 y · **colonoscopy q10 y** · CT colonography q5 y.
- **Colonoscopy = gold standard** (most sensitive, therapeutic); **FIT = preferred non-invasive test** (replaced gFOBT, diet-independent).
- **DRE is not a screening test.** Any positive non-invasive test → **colonoscopy**.
- **FAP:** APC, AD, colectomy before age 20 y; **MUTYH** is AR. **Lynch:** MMR genes, colonoscopy q1–2 y from age 25 y; universal MSI/IHC testing of all CRCs.
- **IBD/PSC:** surveillance colonoscopy 8–10 y after onset.
- Family history of CRC → begin at **age 40 y** or 10 y before youngest affected relative.
- Sigmoidoscopy misses the proximal colon; complete with colonoscopy if any adenoma found.
- Post-resection: colonoscopy at **1 year**, then q3–5 y.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Lower Gastrointestinal Cancers / Colorectal Cancer" (Table 86-3 screening strategies; stool, endoscopic and imaging modalities; hereditary syndromes) and "Prevention and Early Detection of Cancer" (Table 75-3 USPSTF/ACS recommendations; modality evidence — FOBT/FIT, sigmoidoscopy and colonoscopy mortality data, SEPT9, CT colonography).
- **CMDT 2026** — "Cancer" chapter, *Colorectal Cancer — Screening for Colorectal Neoplasms* (Table 44-12 average- and family-history-risk recommendations; FIT/gFOBT, mt-sDNA Cologuard/Cologuard Plus, colonoscopy, flexible sigmoidoscopy, CT and capsule colonography; post-resection surveillance) and "Gastrointestinal Disorders" chapter (FAP and Lynch syndrome surveillance and management).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — corroborative oncologic background on hereditary CRC syndromes and the adenoma–carcinoma sequence.
- *Coverage note:* The corpus covers this topic well. Society guideline numbers cited are US-based (USPSTF/ACS/ACG); the corpus does not give India-specific (ICMR) CRC screening recommendations, so none are quoted.

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Sickle cell anaemia

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

Definition / Introduction — Sickle cell anemia (SCA) is the **autosomal-recessive** hemoglobinopathy caused by *homozygosity* for the sickle β-globin gene (HbSS, α2βS2). A single point mutation produces an abnormal hemoglobin (**HbS**) that **polymerizes when deoxygenated**, deforming the red cell into the classic sickle shape. The result is a **chronic hemolytic anemia** punctuated by **vaso-occlusive** events and progressive multi-organ damage. It is the most prevalent of the "sickle cell disease" (SCD) phenotypes and one of the commonest Mendelian disorders worldwide.

Molecular genetics, epidemiology & inheritance

- **Mutation:** point mutation in the β-globin gene (**HBB, chromosome 11p15**) — **GAG→GTG in codon 6**, substituting **valine for glutamic acid** (**β6 Glu→Val**; Harrison numbers it residue 7 by counting the initiator methionine), generating **βS**. The mutant tetramer is **α2βS2 (HbS)**.
- **Inheritance:** autosomal recessive — homozygote (βS/βS) = sickle cell anemia; heterozygote (βA/βS) = **sickle cell trait**; compound heterozygotes (HbS-β-thal, HbSC, HbSE) give the broader **sickle cell disease** spectrum.
- **Heterozygote advantage:** HbS arose in Africa ~7,000–22,000 years ago and reached high frequency because carriers are relatively protected against *Plasmodium falciparum* malaria (balanced polymorphism).
- **HbS haplotypes** (Senegal, Benin, Bantu, Cameroon, **Arab-Indian**) modulate severity via their average **HbF level** — *Senegal* and *Arab-Indian* haplotypes have higher HbF and a milder, often Indian-relevant course.
- **Burden:** sickle cell trait affects 2–15% of emigrant populations and up to ~half the population in parts of Africa, India and the Middle East; carriers outnumber patients ~25:1. Median age of death in SCA is now in the **5th–6th decade** (CMDT: ~40–50 years).

Pathophysiology (the two interlinked sub-phenotypes)

- **Polymerization:** HbS behaves like HbA when oxygenated but on **deoxygenation polymerizes** into fibres; the process is exquisitely concentration-dependent — proportional to roughly the **30th power of intracellular Hb concentration**, so small rises in MCHC or cell dehydration markedly accelerate sickling.
- **Promoters of sickling:** hypoxia, acidosis, dehydration, hyperosmolarity, cold, infection and stasis. **HbF cannot enter the polymer** and therefore powerfully retards sickling (basis of HbF-inducing therapy).
- **Membrane injury:** repeated sickling causes K^+/Cl^- co-transport and Gardos-channel activation with cellular dehydration, phosphatidylserine externalization and oxidative damage → **irreversibly sickled cells (ISCs)** permanently deformed regardless of oxygenation.
- **Vaso-occlusion (viscosity arm):** rigid, adhesive sickle cells, leukocytes and platelets occlude the microvasculature → tissue ischemia/infarction and the acute painful episode.
- **Hemolysis (endothelial arm):** sickle red cells survive **<20 days** (normal ~120). **Intravascular hemolysis** depletes haptoglobin/hemopexin and releases free hemoglobin, heme and arginase, which **scavenge nitric oxide (NO)**, activate platelets/endothelium and drive vasoconstriction, a

pro-inflammatory/pro-thrombotic state and **pulmonary hypertension, priapism, leg ulcers, stroke and nephropathy**.

Genotypes (classification of sickle hemoglobinopathies)

Genotype	Hb fractions (typical)	Clinical severity
Sickle cell trait (HbAS)	HbA 60–70%, **HbS 30–40%**	Benign; usually normal life expectancy
Sickle cell anemia (HbSS)	**HbS >75%**, HbF 2–15%, HbA2 ~3–4%, **no HbA**	Most severe; reference phenotype
HbS-β^0 thalassemia	HbS >75%, HbF 2–15%, HbA2 5–6%, no HbA; **low MCV**	Clinically like HbSS
HbS-β^+ thalassemia	HbS 60–90%, HbA 5–40%, low MCV	~half the complication rate; spleen often palpable
HbSC disease	HbS ~50%, HbC ~50%	Milder; ↑ **proliferative retinopathy**, target cells
HbSE	HbS ~65%, HbE ~35%	Mild; often Asian/Indian ancestry
HbSS-α thalassemia	high HbA2, low MCV	~30% of HbSS; fewer strokes/leg ulcers, less PHT/renal disease

Clinical features & complications

- **Onset:** in the **first year of life** as protective HbF declines and the γ→β switch completes.
- **Constitutional:** chronic hemolytic anemia with **jaundice, pigment (calcium-bilirubinate) gallstones (~40%)**, early splenomegaly then **autosplenectomy**, and **delayed puberty/growth**.
- **Acute painful (vaso-occlusive) episode:** commonest acute event — severe, often symmetrical/stereotyped pain in back, chest and long bones; lasts days–weeks; provoked by infection, dehydration, hypoxia, cold. **Dactylitis (hand-foot syndrome)** is the typical first presentation in infants.
- **Acute chest syndrome (ACS):** 2nd commonest acute event, occurs in **>50%** — fever, chest pain, cough, hypoxia and a **new pulmonary infiltrate**; causes include in-situ thrombosis, infection, **fat embolism from necrotic marrow** and hypoventilation; a leading cause of death.
- **Neurological: stroke/silent infarction in 10–15%** (ischemic in childhood, may be hemorrhagic in adults); neurocognitive decline.
- **Bone/joint: osteonecrosis** (avascular necrosis, esp. bilateral femoral heads, ~half of patients) and **Salmonella > Staphylococcus osteomyelitis**.
- **Genitourinary: priapism (~30% of males)**; nephropathy in ~30% of adults (hyperfiltration → albuminuria → CKD); papillary infarction → hematuria and **hyposthenuria**.
- **Other: leg ulcers** (over the malleoli), proliferative **retinopathy**, **pulmonary hypertension (5–10%, poor prognosis)**, hepatopathy/intrahepatic cholestasis.
- **Acute anemic crises: aplastic crisis** (parvovirus **B19**), **splenic sequestration** (children), hyperhemolytic and delayed hemolytic transfusion reactions, folate deficiency.
- **Infection:** functional **hyposplenism** → overwhelming infection with **encapsulated organisms** (pneumococcus, *Haemophilus*, *Salmonella*); a major cause of childhood death.

Diagnosis / investigations

- **CBC & film:** normocytic anemia (Hct usually 20–30%), **ISCs**, target cells, **nucleated RBCs**, **Howell-Jolly bodies** (hyposplenism), reticulocytosis (10–25%), leukocytosis (12–15 $\times 10^9$/L), reactive thrombocytosis; raised indirect bilirubin and LDH, low/absent haptoglobin.
- **Sickle solubility test:** rapid screen — positive in both trait and disease (cannot distinguish them).
- **Confirmatory: Hb electrophoresis / HPLC** — in HbSS, **HbS 85–98% with no HbA**; HbF often raised (**HbF 15–20% confers a milder course**). Differentiates HbSS from trait, HbSC and HbS-β-thal (see table).
- **DNA-based testing:** for definitive genotype, genetic counseling and antenatal diagnosis.
- **Screening:** newborn/cord-blood screening; **antenatal diagnosis** by chorionic villus sampling or cell-free fetal DNA; partner testing when either carries HbS/β-thal trait.

Management

Modality	Mechanism / indication	Key detail
Hydroxyurea	**Induces HbF** (anti-polymerization); disease-modifying	**Standard of care** for all HbSS & HbS-β^0; start infants from ~9 months at ~20 mg/kg, titrate to max tolerated (CMDT 15–35 mg/kg/day); halves pain & ACS; **mortality reduced ~49%** at 17.5 yr
Voxelotor	Increases Hb–O_2 affinity, **inhibits HbS polymerization**	1500 mg/day; raises Hb ~1 g/dL; reduces hemolysis (≥12 yr)
Crizanlizumab	**Anti-P-selectin** mAb; blocks cell-endothelial adhesion	IV monthly; reduces painful episodes ~45%
L-glutamine	Reduces RBC oxidative stress	~25% fewer painful episodes, ~33% fewer hospitalizations
Transfusion / exchange	Severe anemia, **stroke** prevention/treatment, **severe ACS**, multiorgan failure, **pre-op to Hb ~10 g/dL**	Prefer **automated red-cell exchange**; antigen-match **Rh (C, E/c, e) and K**; avoid in routine pain
Allogeneic HSCT	Potentially curative	HLA-identical sibling event-free survival **>95%**; only ~15% have a matched donor; haploidentical improving
Gene therapy (ex vivo)	Two FDA-approved curative options	Lentiviral **βA-T87Q** (anti-sickling Hb) and **CRISPR/Cas9 BCL11A** disruption to de-repress HbF → 30–50% HbF/HbAT87Q, near-total VOC prevention

- **Acute painful episode:** identify/treat precipitant; **IV opioids** by PCA or fixed schedule (not "as-needed") with breakthrough dosing; hydration with **half-normal saline (avoid over-hydration)**; **VTE prophylaxis**, incentive spirometry, laxatives/antihistamines; **O_2 only if hypoxic**; monitor first 48–72 h for evolving ACS.
- **Preventive package: prophylactic penicillin** (125 mg <3 yr, 250 mg ≥3 yr, twice daily until age 5), **pneumococcal/Hib/meningococcal vaccination**, **folic acid 1 mg/day**, **transcranial Doppler screening annually ages 2–16** with transfusion for high-risk velocities, **microalbuminuria screen**

by age 10 (ACE inhibitor/ARB for albuminuria, avoid NSAIDs), **annual retinal screen from age 10**.

- **Referral:** to a Comprehensive Sickle Cell Centre with multidisciplinary follow-up.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Pathophysiology of sickle cell disease" (Harrison Fig. 103-3):** *Oxygenated HbS (solution)* → **Deoxygenation** → *HbS polymer / sickled RBC* → branch into **(1) Vaso-occlusion** (endothelial + leukocyte/platelet adhesion → ischemia/pain/ACS) and **(2) Hemolysis** (RBC survival <20 days → free Hb + **arginase** → **NO depletion** → vasoconstriction, pulmonary HTN, platelet activation). Label: *βS codon-6 GAG→GTG (Glu→Val)*, *ISC (irreversibly sickled cell)*, *Arginine→NO via NO synthase*.
- **Inheritance (Punnett) square:** two carrier parents (**AS × AS**) → 25% AA (normal), 50% AS (trait), **25% SS (disease)**. Label genotypes and 1-in-4 affected ratio.

Clinical / Diagnostic significance

- Distinguish **trait vs disease**: solubility test positive in both; **electrophoresis/HPLC** is decisive (trait HbA>HbS and asymptomatic; disease HbS>>HbA or no HbA).
- **HbF level** is the single best modifier of severity — the rationale for hydroxyurea and HbF-reactivating gene therapy.
- A febrile sickle patient is a **medical emergency** (hyposplenic sepsis); ACS and acute stroke mandate **exchange transfusion**.
- **Sickle cell trait** is largely benign but linked to exertional rhabdomyolysis/sudden death, hematuria, hyposthenuria, VTE and the rare aggressive **renal medullary carcinoma**.

High-yield exam pointers

- **β6 Glu→Val (GAG→GTG)**, βS, tetramer **α2βS2**; autosomal recessive; chromosome 11.
- HbS polymerizes only when **deoxygenated**; polymerization ∝ ~**30th power** of Hb concentration; **HbF cannot polymerize** (protective).
- Heterozygote advantage against **falciparum malaria**.
- **Dactylitis (hand-foot syndrome)** = often the earliest manifestation in infants.
- **Acute chest syndrome** = leading cause of death; new infiltrate + hypoxia ± fat embolism from marrow.
- **Aplastic crisis = parvovirus B19**; **osteomyelitis = Salmonella**; smear shows **Howell-Jolly bodies** (autosplenectomy).
- **Hydroxyurea** is disease-modifying for all HbSS/HbS-β^0 (works by raising HbF; ~49% mortality reduction).
- Curative options: **HLA-matched sibling HSCT** (EFS >95%) and **FDA-approved gene therapy** (lentiviral βA-T87Q and CRISPR-edited BCL11A).
- **Penicillin prophylaxis + pneumococcal vaccine + TCD screening + folic acid** form the pediatric preventive bundle.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Disorders of Hemoglobin"** (HbS mutation, polymerization, pathophysiology Fig. 103-3, genotype/Hb-fraction tables, complications, hydroxyurea/voxelotor/crizanlizumab/L-glutamine, transfusion, HSCT and gene therapy, preventive screening).
- **CMDT 2026 — "Blood Disorders" (Sickle Cell Anemia & Related Syndromes)** (clinical findings, laboratory criteria, Hb-distribution Table 15-9, supportive care and current drug management).
- **DeVita's Cancer: Principles & Practice of Oncology, 12e** (hydroxyurea/ESCORT-HU and the sickle-cell-trait association of **renal medullary carcinoma**).

Coverage note: The corpus covers this topic richly; the cited HbF-percentage cut-off for a benign course (15–20%) and exact drug doses are taken verbatim from CMDT/Harrison. Harrison labels the substituted residue "7" (counting the initiator methionine); the universally taught designation **β6** is used here, both being the same valine substitution.

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Spleen structure and function

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

Definition / Introduction — The **spleen** is the largest secondary lymphoid organ of the body and the major **reticuloendothelial (mononuclear phagocyte) organ**, lying in the left upper quadrant (LUQ) entirely within the rib cage. It is uniquely positioned in the **portal (low-pressure) circulation** and is functionally divided into **red pulp** (a blood-filtering compartment) and **white pulp** (lymphoid, immune compartment) — terms coined by *Malpighi*. It serves dual roles as a fastidious blood filter (quality control of red cells) and an immune organ (antibody synthesis and clearance of opsonised pathogens). The normal adult spleen weighs **<250 g** and is not normally palpable.

Development, gross anatomy and accessory spleens

- **Embryology:** arises from the **dorsal mesogastrium at ~5 weeks' gestation** as a series of *hillocks* (mesenchymal condensations) that coalesce and migrate to the LUQ. It is mesodermal in origin yet remains a lymphoid/RE organ.
- **Failure of the hillocks to fuse** leaves rests of splenic tissue → **accessory spleens (splenunculi)** in **~20%** of persons; important to recognise, as they cause relapse after splenectomy for haematologic disease and must be sought (often hilar or pancreatic-tail).
- **Peritoneal attachments (ligaments):** *gastrolienal (gastrosplenic) ligament* anchors spleen to the stomach (carries short gastric vessels), and the *lienorenal (splenorenal) ligament* anchors it to the left kidney (carries the splenic artery/vein and pancreatic tail).
- **Vascular supply:** the **splenic artery** (a branch of the coeliac trunk) carries ~**150 mL/min** of blood and ramifies into **central arterioles**; venous drainage is via the splenic vein into the portal system.
- **Normal dimensions:** weight <250 g (decreases with age); maximum **cephalocaudad diameter 13 cm by ultrasonography**, or maximum length 12 cm / width 7 cm by radionuclide scan.

Microscopic architecture — red pulp and white pulp

Compartment	Components	Principal function
White pulp	**Periarteriolar lymphoid sheath (PALS)** = T-cell zone sheathing central arteriole; **primary follicles** and **secondary follicles with germinal centres** = B-cell zones; surrounding **marginal zone**	Immune surveillance, antigen presentation, antibody synthesis, marginal-zone B-cell response to encapsulated organisms
Marginal zone	Lymphoid zone at the white-pulp/red-pulp interface, rich in specialised B cells and macrophages	First contact with blood-borne antigens; T-independent responses to **polysaccharide capsular antigens**
Red pulp	**Pulp cords (cords of Billroth)** lined by RE/macrophages — anatomical "dead ends"; **venous sinuses** with slit-like inter-endothelial pores	Mechanical and immunologic filtration of erythrocytes; **culling** and **pitting**

- **The "open" circulation / filtration mechanism:** most blood leaving the central arterioles empties into the **macrophage-lined cords**. To re-enter the circulation, red cells must **squeeze through narrow slits in the cord lining into the sinuses** → venules. **Old, rigid, damaged or antibody-coated red cells are too poorly deformable to pass and are retained and destroyed** — this is the structural basis of red-cell quality control.
- The low portal pressure and slow transit minimise damage to normal erythrocytes while exposing abnormal cells to prolonged macrophage scrutiny.

Physiologic functions of the spleen

- **1. Quality control of erythrocytes (red pulp):**
  - **Culling** — removal of senescent and defective red cells.
  - **Pitting** — removal of intra-erythrocytic inclusions without destroying the cell: **Howell-Jolly bodies (nuclear remnants)**, **Heinz bodies (denatured haemoglobin)**, **Pappenheimer/basophilic-stippling (siderotic) granules**, and intracellular **parasites** (e.g., malaria) are "pinched off" as the cell traverses the slits.
- **2. Immune function (white pulp):** synthesis of **antibodies** (notably IgM by germinal-centre and marginal-zone B cells) and generation of immune responses to blood-borne pathogens; antigen presentation in PALS and follicles.
- **3. Clearance of opsonised material:** removal of **antibody-coated bacteria and antibody-coated blood cells**, and of poorly opsonised **encapsulated organisms** and particulates from the circulation.
- **4. Reservoir/sequestration:** the normal human spleen holds about **one-third of the total body platelet mass** plus a pool of **marginated neutrophils**, available to mobilise during bleeding or infection. (Unlike some animals, the *normal human spleen does not store or contract to autotransfuse red cells.*)
- **5. Extramedullary haematopoiesis (EMH):** a latent fetal function reactivated when marrow cannot meet demand (e.g., myelofibrosis) — a cause of splenomegaly.

Splenomegaly — mechanisms and the concept of hypersplenism

- **Pathogenic mechanisms of enlargement** (a useful exam framework):
  - **Work hypertrophy / RE hyperplasia** — for removal of defective red cells (*hereditary spherocytosis, thalassemia, early sickle cell, haemoglobinopathies*).
  - **Immune hyperplasia** — response to infection (*infectious mononucleosis, subacute bacterial endocarditis, malaria*) or immune disease (*ITP, SLE, Felty's syndrome*).
  - **Congestive (passive congestion)** — portal hypertension (*cirrhosis, Budd-Chiari, splenic/portal vein obstruction, CHF*); chronic congestion = *"Banti's disease."*
  - **Infiltration** — lymphomas, leukaemias, metastases (melanoma commonest), amyloidosis, and **storage disorders (Gaucher's, Niemann-Pick)**.
  - **Extramedullary haematopoiesis** — myelofibrosis with myeloid metaplasia.
- **Hypersplenism** is a clinico-pathologic syndrome defined by: (1) **splenomegaly**, (2) **cytopenia(s) of one or more lineages**, (3) **normal or hyperplastic bone marrow**, and (4) **correction (or improvement) of cytopenias after splenectomy**. Cytopenias arise from increased pooling/destruction in congested cords or by immune mechanisms; red cells may become **spherocytic** from membrane loss during prolonged transit.
- **Massive splenomegaly** (spleen >8 cm below the costal margin or drained weight ≥1000 g) markedly narrows the differential: *chronic myeloid leukaemia, myelofibrosis with myeloid metaplasia, lymphomas, chronic lymphocytic leukaemia, hairy cell leukaemia, polycythaemia vera, Gaucher's disease, sarcoidosis, autoimmune haemolytic anaemia, diffuse splenic hemangiomatosis.*

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Schematic spleen unit (Fig. 70-1):** draw a **central artery/arteriole** with concentric zones — label **periarteriolar lymphoid sheath (T-cell area)**, **primary follicle (B-cell)**, **secondary follicle with germinal centre (B-cell)**, **marginal lymphoid zone**, then the **red pulp** showing **pulp cords (cords of Billroth, RE cells)** as dead-ends and **pulp sinuses with sinusoidal pores** draining to the **splenic venous system**. Annotate the arrow: "stiff/old/damaged red cells cannot enter the sinuses — culled."
- **Diagram 2 — Surface markings / palpation:** outline the LUQ spleen behind ribs 9–11; mark **Traube's space** (borders: *6th rib superiorly, left midaxillary line laterally, left costal margin inferiorly*) and show the line of bimanual palpation from the right lower quadrant towards the left costal margin.

Clinical / Diagnostic significance

- **Examination:** percussion (**Castell's sign**, **Nixon's method**, **Traube's space dullness**) is best done first, then **bimanual palpation** / ballottement / **Middleton manoeuvre** (palpation from above). Palpation sensitivity 56–71%, percussion 59–82%; both are unreliable in obesity or post-prandially. **Ultrasonography is the imaging investigation of choice** (normal craniocaudal diameter ≤13 cm); CT/MRI better define focal lesions and infarcts; radionuclide scans demonstrate **accessory splenic tissue**.
- **Peripheral-smear clues to hyposplenism/post-splenectomy state: Howell-Jolly bodies**, **Heinz bodies**, **basophilic stippling**, **target cells**, **acanthocytes**, **nucleated RBCs**, anisocytosis and

poikilocytosis; **thrombocytosis (up to 1 × 10^6/µL)** and **leukocytosis (up to 25,000/µL)** transiently after splenectomy. Such changes appearing in a patient with an *intact* spleen suggest **splenic infiltration by tumour** interfering with culling/pitting.

- **Splenectomy — indications:** therapeutic control of symptomatic massive splenomegaly, **traumatic/iatrogenic rupture**, correction of cytopenias in hypersplenism or immune destruction (e.g., refractory **ITP**, **hereditary spherocytosis**, autoimmune haemolytic anaemia), and as effective secondary/tertiary therapy for **hairy cell leukaemia, prolymphocytic leukaemia and splenic marginal-zone / mantle-cell lymphoma**. **Splenic marginal-zone lymphoma** characteristically presents with massive splenomegaly and responds to splenectomy or rituximab (DeVita). The only real contraindication is **marrow failure where the spleen is the sole haematopoietic site**.
- **Overwhelming post-splenectomy infection (OPSI):** the gravest sequela. Susceptibility to **encapsulated organisms** — *Streptococcus pneumoniae* (most important), *Haemophilus influenzae* type b, *Neisseria meningitidis* — and to **Babesia** (avoid endemic areas) and *Capnocytophaga*. Overall sepsis risk ~**7% over 10 years**; **case-fatality of pneumococcal sepsis 50–80%**; risk highest in the **first 3 years** and in those aged <20. Mechanism: failure to clear opsonised bacteria + impaired antibody response to **T-independent polysaccharide antigens**.
- **Prevention: pneumococcal (PCV13/conjugate ± PPSV23), Hib and meningococcal vaccines**, given ideally **≥2 weeks before elective splenectomy** (repeat pneumococcal at ~5 years); patient education that **any unexplained fever is a medical emergency**; antibiotic standby. **Autosplenectomy** occurs in sickle cell disease from repeated infarction — a palpable spleen after age 5 in SCD suggests a coexisting haemoglobinopathy.

High-yield exam pointers

- Spleen = largest **secondary lymphoid organ**; embryology = **dorsal mesogastrium, 5 weeks**; **accessory spleens in ~20%**.
- **Red pulp = filter** (cords of Billroth + sinuses → *culling & pitting*); **white pulp = immunity** (PALS = T cells, follicles + marginal zone = B cells).
- **Pitting** removes inclusions → their reappearance (**Howell-Jolly bodies**) is the cardinal smear sign of **hyposplenism**.
- Normal weight **<250 g**; **US craniocaudad ≤13 cm**; spleen holds **~⅓ of body platelets**.
- **Hypersplenism tetrad:** splenomegaly + cytopenia + hypercellular marrow + response to splenectomy.
- **Massive splenomegaly (>1000 g / >8 cm):** think **CML, myelofibrosis, CLL, hairy cell leukaemia, lymphoma, PV, Gaucher's, kala-azar**.
- **OPSI** by encapsulated organisms — vaccinate **2 weeks pre-elective splenectomy**; **case-fatality 50–80%**.
- **Traube's space** dullness and **Castell's sign** = bedside tests for splenomegaly; **ultrasound** is confirmatory.
- **Banti's syndrome** = congestive splenomegaly of portal hypertension; **autosplenectomy** = sickle cell disease.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Enlargement of Lymph Nodes and Spleen"** (structure/function of the spleen, red/white pulp, culling and pitting, hypersplenism, massive splenomegaly, splenectomy and OPSI, vaccination); cross-referenced with Harrison's chapters on **non-Hodgkin's lymphoma / immune system** for white-pulp lymphoid architecture and marginal-zone B-cell biology.
- **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — splenic marginal-zone lymphoma and the role of splenectomy in indolent B-cell neoplasms.
- *Coverage note:* This topic is **flagged thin** in the corpus — Harrison covers splenic **function, hypersplenism and splenectomy** in depth but gives only a **brief account of detailed histological/anatomical structure**; the white-pulp microanatomy (PALS, marginal zone, cords of Billroth) and surgical/peritoneal anatomy above are standard, universally-accepted textbook internal medicine/anatomy added for completeness and are faithful to the source where present (e.g., Fig. 70-1 labels). CMDT was not used (spec flag cmdt = false).

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Neutrophil development

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

Definition / Introduction — *Granulopoiesis* is the bone-marrow production of neutrophils from the pluripotent haematopoietic stem cell (HSC) through a series of committed progenitors and morphologically recognisable precursors. In the normal adult, neutrophils are produced **only in the marrow**, where roughly three-fourths of nucleated cells are committed to leukocyte production. The system generates about **1.3×10^{11} neutrophils per 80-kg person per day** and maintains a large marrow reserve that can be mobilised during inflammation. The entire journey from the first recognisable precursor to a mature segmented neutrophil takes **about 2 weeks**.

1. Progenitor hierarchy and lineage commitment

- Neutrophils and monocytes arise from a **common stem cell** under the control of **colony-stimulating factors (CSFs)** and **interleukins**; the minimum number of HSCs needed to sustain haematopoiesis is estimated at **400–500** at any time.
- Differentiation pathway (Harrison Fig. 101-2): **HSC → multipotent progenitor → common myeloid progenitor (CMP) → granulocyte-monocyte progenitor (GMP) → granulocyte progenitor → myeloblast**.
- **Soluble growth-factor regulation:** stem-cell factor (SCF) and IL-3 act early; **GM-CSF** and **G-CSF** drive granulocytic commitment and terminal maturation. **G-CSF** and **GM-CSF** are described as critical to the whole developmental process.

- **Transcription-factor control:** *C/EBPα* governs the granulocyte-monocyte branch point; *C/EBPε* (gene **CEBPE**) directs the granulocyte progenitor and specifically controls packaging of secondary-granule contents.

2. Morphologic maturation stages (the answer's core)

The morphologic sequence is **myeloblast → promyelocyte → myelocyte → metamyelocyte → band (stab) form → segmented (mature) neutrophil** (Harrison Fig. 67-2). The **myeloblast is the first recognisable precursor**.

Stage	Division	Key morphology	Granule event	Surface markers (cumulative)
Myeloblast	Yes (mitotic)	Large cell, **prominent nucleoli**, fine chromatin, agranular cytoplasm	No specific granules yet	CD33, CD13, CD15
Promyelocyte	Yes (mitotic)	**Largest** of the series; nucleolus still present	**Primary (azurophil) granules appear**	CD33, CD13, CD15
Myelocyte	Yes (last dividing cell)	Round/oval nucleus, no nucleolus; "dawn of neutrophilia"	**Secondary (specific) granules appear**	CD33, CD13, CD15, **CD14, CD11b**
Metamyelocyte	No (post-mitotic)	**Kidney-bean / indented** nucleus	Granule synthesis complete	CD33, CD13, CD15, CD14, CD11b
Band (stab) form	No	**Sausage / band-shaped** non-segmented nucleus	—	+ **CD10, CD16**
Segmented neutrophil	No	Condensed **multilobed nucleus (up to 4 lobes)**, clumped chromatin	—	CD33, CD13, CD15, CD14, CD11b, CD10, CD16

- **Two functional compartments:** the **proliferative (mitotic) pool** comprises the myeloblast, promyelocyte and myelocyte; the **myelocyte is the last cell capable of mitosis**. From the **metamyelocyte onward no cell division occurs** — these constitute the **post-mitotic maturation / storage pool**.
- As the band matures, the nucleus assumes a lobulated configuration; the physiologic role of the multilobed nucleus is uncertain but may permit the marked deformation needed for tissue migration and neutrophil extracellular trap (NET) formation.

3. Granule formation during maturation

Granule genesis is **stage-specific** and is the morphologic hallmark used to distinguish precursors:

- **Primary / azurophil granules** — synthesised at the **promyelocyte** stage; true lysosomes containing **myeloperoxidase, neutrophil elastase, cathepsin G, hydrolases, cationic proteins, bactericidal/permeability-increasing protein (BPI)** (kills gram-negative bacteria) and **defensins** (broad antimicrobial cysteine-rich peptides).
- **Secondary / specific granules** — synthesised at the **myelocyte** stage; contain **lactoferrin, vitamin B_{12}-binding protein, membrane components of the NADPH oxidase (NOX2), histaminase, the**

laminin receptor and receptors for chemoattractants and adherence factors (e.g., CR3/CD11b). They lack acid hydrolases, so are **not classic lysosomes**, and their contents are readily released extracellularly to modulate inflammation.

- *(Standard hematology adds a third, late tertiary/gelatinase granule pool; Harrison Ch. 67 itself describes only the primary and secondary granules.)*

4. Kinetics, marrow release and circulating pools

- **Transit time:** the proliferation phase **through the metamyelocyte takes ~1 week**, and the maturation phase **from metamyelocyte to mature neutrophil takes another ~1 week**.
- **Marrow release** is triggered by **IL-1, TNF-α, CSFs, complement fragments (C3a/C5a) and chemokines**, delivering cells to blood in an unstimulated state.
- **Anatomic distribution:** under normal conditions **~90% of the neutrophil pool is in the bone marrow**, **2–3% in the circulation**, and the remainder in tissues.
- **Circulating pool has two dynamic compartments:** a **freely flowing pool** (~half the cells) and a **marginated pool** in contact with endothelium; *epinephrine* (exercise, stress) demarginates cells and can double the count in minutes, whereas *glucocorticoids* increase marrow release.
- **Lifespan:** circulating half-life is only **6–7 hours**; after entering tissues neutrophils survive **1–4 days** before apoptosis (prolonged by G-CSF and IFN-γ). Most are lost across the gut mucosa; senescent cells are cleared by lung and splenic macrophages.
- **Functional acquisition mirrors morphology:** adhesion and chemotactic machinery appears late — selectin ligand **sialyl-Lewis^x (CD15s)**, **L-selectin (CD62L)** and the **β_2-integrins (CD11a/b/c with common CD18)** become functional in the band/segmented stages, enabling rolling, tight adhesion and diapedesis only in the mature cell.

5. Disordered development — quick correlations

- **Neutropenia** can arise from *depressed production* (cytotoxic drugs, B_{12}/folate deficiency, congenital marrow failure), *peripheral destruction* (autoimmune, Felty syndrome) or *excess pooling*.
- **Neutrophilia** reflects increased production, increased marrow release, or **demargination** — the basis for the rapid rises seen with infection, glucocorticoids, epinephrine and exercise.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Maturation ladder (label each stage left-to-right):** *Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band form → Segmented neutrophil.* Annotate: "prominent nucleoli" (myeloblast); "primary/azurophil granules appear" (promyelocyte); "secondary/specific granules appear + last mitotic division" (myelocyte); "kidney-bean nucleus" (metamyelocyte); "band-shaped nucleus" (band); "multilobed (≤4 lobes)" (neutrophil). Bracket *Myeloblast–Myelocyte* as **"mitotic / proliferative pool"** and *Metamyelocyte–segmented* as **"post-mitotic maturation–storage pool."**
- **Pool distribution pie/box:** three compartments labelled **Marrow ~90%**, **Circulating 2–3% (freely flowing + marginated)**, **Tissue (remainder)**, with arrows for *G-CSF / steroids / endotoxin* (marrow release) and *epinephrine* (demargination).

Clinical / Diagnostic significance

- **Left shift:** appearance of immature forms (bands, metamyelocytes) in blood signals accelerated marrow release in infection/inflammation; a **leukemoid reaction** is persistent neutrophilia ≥30,000–50,000/μL with **mature, non-clonal** cells (distinguishes from CML).
- **Maturation arrest** underlies several neutropenias: **severe congenital neutropenia** (*ELANE*-encoded neutrophil elastase, *HAX-1*/Kostmann), and **WHIM syndrome** (CXCR4 mutation) shows marrow **myeloid arrest with hypersegmentation and myelokathexis**.
- **Acute promyelocytic leukaemia (APL)** is a clonal arrest at the **promyelocyte** stage; **CML** expands the entire granulocytic series across all maturation stages.
- **Nuclear clues: hypersegmentation (>5 lobes)** suggests **vitamin B_{12}/folate deficiency** (or WHIM); the **Pelger-Hüet anomaly** (LBR mutation) gives benign **bilobed "pince-nez"** nuclei that mimic bands; acquired *pseudo-Pelger-Hüet* occurs in MDS.
- **Cytoplasmic clues of toxicity: toxic granulation** (prominent azurophil granules), **Döhle bodies** (rough-ER aggregates) and cytoplasmic vacuoles indicate severe infection/sepsis (and COVID-19).
- **Absolute neutrophil count (ANC = bands + mature neutrophils):** infection risk rises sharply <1000/μL; endogenous-flora control is lost <500/μL; the local inflammatory response is **absent <200/μL**.

High-yield exam pointers

- Sequence to memorise: **Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band → Segmented neutrophil**.
- **Promyelocyte = primary (azurophil/MPO-containing) granules; Myelocyte = secondary (specific/lactoferrin) granules**; myelocyte is the **last dividing cell**.
- Total marrow transit **~2 weeks** (≈1 week proliferative + ≈1 week maturation); blood half-life **6–7 h**; tissue survival **1–4 days**.
- Distribution: **~90% marrow, 2–3% blood, rest tissues**; circulating = **freely flowing + marginated** halves.

- Marker progression: CD33/CD13/CD15 throughout; **CD14/CD11b from myelocyte**; **CD10/CD16 from band stage**.
- Daily output ~**1.3×10^{11}**; **G-CSF/GM-CSF** are the master cytokines; **C/EBPα and C/EBPε** the key transcription factors.
- Production ~**1.3×10^{11}/day**, regulated reserve mobilised by endotoxin/steroids; epinephrine causes demargination (pseudo-neutrophilia).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of Granulocytes and Monocytes" (neutrophil maturation sequence, Fig. 67-2 stage/marker table, granule contents, marrow pools and kinetics, ANC thresholds, morphologic anomalies); "Hematopoietic Stem Cells" (progenitor hierarchy HSC→CMP→GMP and growth-factor/transcription-factor regulation, Fig. 101-2).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — consulted for myeloid-malignancy correlation (maturation-arrest leukaemias).

Coverage note (spec gap = true): Harrison 22e covers granulopoiesis and the full morphologic staging well within Ch. 67 and Ch. 101; DeVita (an oncology text) does **not** carry dedicated normal granulopoietic morphology, so the developmental detail here is drawn from Harrison. Classic "mitotic vs maturation-storage pool" terminology and the **tertiary/gelatinase granule** are universally accepted standard haematology but are only partially explicit in the corpus, so they are flagged rather than over-attributed.

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Acute promyelocytic leukaemia

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

Definition / Introduction — Acute promyelocytic leukemia (**APL**) is the distinct subtype of acute myeloid leukemia (AML) defined by the balanced translocation **t(15;17)(q22;q12)** generating the **PML::RARA** fusion gene, whose chimeric protein blocks myeloid differentiation at the promyelocyte stage. It is both the most curable AML (≈85–90%+ long-term survival) *and* the most dangerous at presentation because of a life-threatening **disseminated intravascular coagulation (DIC)/hyperfibrinolysis** that causes early haemorrhagic death. The therapeutic revolution lies in two **differentiating/targeting** agents — **all-*trans* retinoic acid (ATRA, tretinoin)** and **arsenic trioxide (ATO)** — which have converted APL into a largely chemotherapy-free, curable disease. APL is therefore managed as a **medical emergency**: treat first on morphological suspicion, do not wait for genetic confirmation.

Why APL is managed differently — biology and diagnosis

- **PML::RARA** is both the diagnostic marker and the drug target. **ATRA** binds RARα and forces terminal differentiation of leukaemic promyelocytes; **ATO** degrades the PML::RARA oncoprotein, induces apoptosis, causes G1–S/G2–M arrest and has anti-angiogenic activity (per the DeVita drug data).

- **Hallmark morphology:** hypergranular promyelocytes with bundles of **Auer rods** ("faggot cells"); the microgranular (hypogranular) variant has a bilobed nucleus and high WBC.
- **Diagnostic confirmation:** rapid **PML::RARA RT-PCR** and/or **FISH** for t(15;17); immunophenotype typically **HLA-DR–negative, CD34–negative, CD33/CD13/myeloperoxidase strongly positive**.
- **Coagulopathy is the killer:** release of granule procoagulants/annexin-II–driven hyperfibrinolysis produces DIC; early death from intracranial or pulmonary haemorrhage is the main cause of treatment failure. Rare ATRA-resistant variants (e.g. **ZBTB16(PLZF)::RARA**, lacking classic t(15;17)) must be recognised because they respond poorly to ATRA/ATO.

Risk stratification (Sanz) — drives the regimen choice

The corpus splits APL for treatment into **low-risk** (presenting WBC $\leq 10 \times 10^9$/L) and **high-risk** (WBC $>10 \times 10^9$/L), the latter requiring immediate cytoreduction. The widely used three-tier **Sanz score** refines this:

Risk group	Presenting WBC	Platelet count
Low	$\leq 10 \times 10^9$/L	$>40 \times 10^9$/L
Intermediate	$\leq 10 \times 10^9$/L	$\leq 40 \times 10^9$/L
High	$>10 \times 10^9$/L	any

- Low- and intermediate-risk are managed together as "**low/standard-risk**" and treated with chemotherapy-free **ATRA + ATO**.
- High-risk disease carries the greatest early-death risk (differentiation syndrome + haemorrhage) and warrants added cytoreductive chemotherapy.

Emergency supportive care (start immediately, before genetics)

- **Begin ATRA on clinical suspicion** of APL — it reduces the frequency of DIC and buys time while PCR/FISH is pending; the persistently high early-death rate is the rationale for not delaying.
- **Aggressive correction of coagulopathy:** transfuse to keep **platelets >30–50 × 10^9/L** and **fibrinogen >100–150 mg/dL** using platelets, **cryoprecipitate** and **fresh frozen plasma**; monitor PT/aPTT, fibrinogen and D-dimer at least twice daily until the coagulopathy resolves.
- **Avoid leukapheresis** in APL (worsens coagulopathy/precipitates fatal haemorrhage); avoid central lines/invasive procedures while coagulopathy persists.
- **Tumour-lysis prophylaxis:** hydration and allopurinol (rasburicase if marked hyperuricaemia/renal injury, avoiding G6PD deficiency).

Induction therapy — by risk group

Risk	Standard induction regimen	Key points
Low/standard-risk (WBC ≤10)	**ATRA 45 mg/m²/day** PO + **ATO 0.15 mg/kg/day** IV until complete remission (chemotherapy-free)	ATRA + ATO proved **superior** to ATRA + idarubicin in EFS and OS (*APL0406*); CR approaches ~**100%** with excellent long-term survival
High-risk (WBC >10)	ATRA + ATO **plus cytoreductive chemotherapy** — an **anthracycline (idarubicin)** or **gemtuzumab ozogamicin**	Immediate cytoreduction needed because of the rapidly rising WBC and severe differentiation-syndrome/haemorrhage risk after starting ATRA (*APML4*, *AML17* support ATO across all risk groups)

- The historical **AIDA**-type backbone (ATRA + idarubicin) remains an alternative where ATO is unavailable, but **ATRA + ATO is now standard of care** for low-risk disease and reduces cumulative chemotherapy toxicity.
- **Oral ATO** formulations (validated in China) are non-inferior to IV ATO in non-high-risk APL and improve convenience.

Differentiation (APL) syndrome — recognise and treat early

- **Onset:** typically within the **first 1–3 weeks** of ATRA (or ATO) therapy; caused by adhesion of differentiating neoplastic cells to pulmonary vascular endothelium and cytokine release.
- **Features:** unexplained **fever, fluid retention/weight gain, dyspnoea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, hypoxaemia**, and rising leukocyte count; renal impairment in severe cases. **Mortality ≈10% if unrecognised.**
- **Management: dexamethasone 10 mg IV twice daily** at first suspicion, plus diuresis/supportive care and cytoreductive chemotherapy if hyperleukocytosis; **temporarily discontinue ATRA (and/or ATO)** only in severe cases (renal failure or ICU admission for respiratory distress) and resume once resolved.
- **Prophylaxis:** consider prednisone/dexamethasone prophylaxis especially in high-risk patients to blunt the syndrome.

Consolidation, maintenance and monitoring

- **Consolidation:** continue **ATRA + ATO** in repeating cycles after CR — e.g. ATO **0.15 mg/kg/day, 5 days/week for weeks 1–4 of an 8-week cycle × 4 cycles**, with intermittent ATRA — to achieve **molecular (PCR-negative) remission**.
- **Maintenance:** with the chemotherapy-free ATRA + ATO regimen, prolonged maintenance is generally **not required**; in chemotherapy-containing (AIDA-type) protocols, maintenance uses **ATRA ± 6-mercaptopurine + methotrexate**, particularly for high-risk patients.
- **Measurable residual disease (MRD):** serial **RT-PCR for PML::RARA** is the standard tool — disappearance of the transcript predicts durable remission, while persistence or re-emergence reliably predicts **molecular relapse**, allowing pre-emptive re-treatment before overt relapse, especially in high-risk patients.

- **Drug monitoring:** ATO prolongs the **QT interval** — baseline and serial **ECG**, and aggressive repletion of **potassium and magnesium**; ATRA can cause headache/**pseudotumour cerebri**, dryness and hypertriglyceridaemia.

Relapsed/refractory disease

- ATO is highly active in **relapse**; for patients not previously exposed, **ATO ± ATR-A (± gemtuzumab ozogamicin)** can re-induce remission.
- Achieve a **second molecular remission**, then consolidate with **autologous HSCT** if PCR-negative, or **allogeneic HSCT** if PCR-positive/poor reserve. (In contrast to other AML subtypes, transplant is reserved for relapse, not first remission.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Box 1 — Risk-adapted treatment algorithm (flow diagram):** "Suspected APL (faggot cells / coagulopathy)" → "Start ATRA + correct DIC immediately" → "Confirm PML::RARA (PCR/FISH)" → branch to **Low-risk (WBC ≤10): ATRA + ATO** and **High-risk (WBC >10): ATRA + ATO + anthracycline/gemtuzumab** → "Consolidation (ATRA+ATO cycles)" → "PML::RARA RT-PCR MRD monitoring" → "Molecular CR = cure / PCR re-emergence = pre-emptive salvage". Side-arrow label: "Differentiation syndrome → dexamethasone 10 mg BD, hold ATRA if severe."
- **Box 2 — Molecular target:** label **chromosome 15 (PML)** and **chromosome 17 (RARα)** → **t(15;17)** → **PML::RARA fusion protein** → blocked promyelocyte differentiation; arrows showing **ATRA → differentiation** and **ATO → degradation of PML::RARA + apoptosis**.

Clinical / Diagnostic significance

- APL is an **oncological emergency**: the leading preventable cause of death is **early haemorrhage from DIC**, so empirical ATRA and blood-product support precede genetic confirmation.
- **PML::RARA RT-PCR** is uniquely valuable both diagnostically and for MRD-directed therapy — APL is the paradigm of molecular monitoring in leukaemia.
- The cure of APL with **non-cytotoxic targeted differentiation therapy** is a landmark proof of concept in precision oncology; recognition of **ATRA-resistant RARA variants** prevents mismanagement.
- Vigilance for **differentiation syndrome** and **ATO-induced QT prolongation** is essential during induction.

High-yield exam pointers

- APL = AML with **t(15;17) / PML::RARA**; morphology = hypergranular promyelocytes with **faggot (multiple Auer-rod) cells**; immunophenotype **HLA-DR–/CD34– negative**.
- **Treat on suspicion** — start **ATRA immediately**; do not await cytogenetics; **avoid leukapheresis**.
- **Low-risk = WBC ≤10 × 10^9/L → chemo-free ATRA (45 mg/m^2/d) + ATO (0.15 mg/kg/d)**; CR ~100% (APL0406 trial, superior to ATRA + idarubicin).
- **High-risk = WBC >10 × 10^9/L → add anthracycline (idarubicin) or gemtuzumab ozogamicin** for immediate cytoreduction.

- **Differentiation syndrome:** first 1–3 weeks, fever/dyspnoea/effusions/infiltrates/hypoxaemia → **dexamethasone 10 mg IV BD**, hold ATRA if severe; ~10% mortality if missed.
- **DIC management:** keep **fibrinogen >100–150 mg/dL** and **platelets >30–50 × 10^9/L** with cryoprecipitate/FFP/platelets.
- **ATO toxicity = QT prolongation** → monitor ECG, K^+ and Mg^{2+}; **ATRA toxicity = pseudotumour cerebri/headache, hypertriglyceridaemia, differentiation syndrome**.
- **MRD by PML::RARA PCR** directs cure (negativity) and pre-emptive salvage (re-emergence); relapse salvage uses **ATO-based re-induction → autologous HSCT (PCR-neg) or allogeneic HSCT (PCR-pos)**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Acute Myeloid Leukemia" (Treatment of Acute Promyelocytic Leukemia section; t(15;17)/PML::RARA, ATRA + arsenic trioxide, APL/differentiation syndrome, DIC, PML-RARA PCR monitoring; content spans the ch109–ch110 page-bleed).
- **DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — "Management of Acute Leukemias" (Acute Promyelocytic Leukemia: ATRA/ATO, standard- vs high-risk, ATRA + ATO vs ATRA + idarubicin, oral ATO; APML4/AML17 trials) and the arsenic-trioxide drug profile (mechanism, induction/consolidation dosing, QT-prolongation/differentiation-syndrome toxicity).
- **CMDT 2026** — "Blood Disorders" (Acute Promyelocytic Leukemia: t(15;17)/PML-RARα, >90% curable with ATRA + ATO across induction/consolidation/maintenance; DIC; supportive care).

Coverage note: The corpus stratifies APL by a **low-risk (WBC ≤10 × 10^9/L) vs high-risk (>10 × 10^9/L)** dichotomy; the three-tier **Sanz** classification (adding a platelet >40 × 10^9/L cut-off to define the intermediate group), the precise DIC transfusion thresholds (fibrinogen >100–150 mg/dL; platelets >30–50 × 10^9/L), the dexamethasone 10 mg BID dose for differentiation syndrome, and the AIDA maintenance schedule (ATRA + 6-mercaptopurine + methotrexate) are universally accepted standard haematology included to satisfy the "summarize management" ask, consistent with the corpus framework.

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Thrombocytopenia

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

Definition / Introduction — Thrombocytopenia is a **platelet count <150,000/µL** (normal 150,000–450,000/µL). It results from one or more of three processes: **(1) decreased bone-marrow production, (2) sequestration (usually in an enlarged spleen), and (3) increased platelet destruction.** It is the commonest cause of abnormal bleeding, ranging from incidental laboratory finding to life-threatening mucocutaneous and intracranial haemorrhage. The single most important first step in any thrombocytopenic patient is to **review the peripheral blood smear** and exclude *pseudothrombocytopenia*.

Pathophysiologic classification (three mechanisms)

Mechanism	Representative causes	Smear / marrow clue
Decreased production	Marrow aplasia, myelodysplasia, leukaemia/infiltration, chemotherapy, B12/folate deficiency, inherited disorders	Usually accompanied by ↓ RBC/WBC; marrow shows ↓ megakaryocytes
Sequestration	Splenomegaly (portal hypertension, infiltration)	Count rarely falls <40,000/µL from spleen alone; ~⅓ of platelets normally pooled in spleen
Increased destruction	Immune (ITP, drug-induced, HIT), consumptive (DIC, TTP/HUS)	Large/young platelets; marrow shows ↑ megakaryocytes

- **Thrombopoietin (TPO)**, made in the liver (↑ by interleukin-6), is the major regulator; falling platelet/megakaryocyte mass raises TPO and drives production. Platelet life-span is **7–10 days**.
- **Pseudothrombocytopenia** is an *in vitro* artefact — EDTA-dependent platelet agglutination by antibodies (IgG > IgM/IgA) producing clumps on the smear. **Redraw in sodium citrate (blue top) or heparin (green top)**, or examine a finger-stick smear before diagnosing true thrombocytopenia.

Approach to the patient

- **History:** drug ingestion (prescription, over-the-counter, herbal — drugs are the commonest cause), prior platelet counts, family history, systemic illness, infection/HIV risk, pregnancy.
- **Examination:** spleen size (confirm with ultrasound — mild splenomegaly is easily missed), signs of chronic liver disease, and the bleeding pattern.
- **Bleeding–count correlation:** a count of **~5000–10,000/µL** is needed to maintain microvascular integrity. **Petechiae** (pinpoint, non-blanching haemorrhages) first appear at sites of high venous pressure (ankles/feet) and signify *low platelet number, not dysfunction*. **Wet purpura** (haemorrhagic blood blisters on oral mucosa) and **retinal haemorrhage** herald risk of life-threatening bleeding.
- **Investigations:** CBC + smear first; if other cell lines are abnormal or the smear shows fragments, proceed to **bone marrow examination**. Marrow is indicated in isolated thrombocytopenia in patients **>60 years** or those failing initial therapy (myelodysplasia can present as isolated thrombocytopenia).

- The evaluation algorithm branches on whether Hb/WBC are normal or abnormal, and whether the smear shows normal morphology, platelet clumping (pseudothrombocytopenia), or **fragmented RBCs (microangiopathy — DIC, TTP/HUS)**.

Common acquired causes

- **Infection-induced** — the commonest *non-iatrogenic* cause. Many viral/bacterial infections lower the count via both reduced production and reduced survival; may accompany **DIC** (especially gram-negative sepsis and severe COVID-19). HIV (early), infectious mononucleosis act through immune mechanisms; late HIV causes pancytopenia/dysplastic production.
- **Drug-induced** — the commonest cause overall. Two patterns: a **predictable dose-related marrow suppression** (chemotherapeutics), and **classic drug-dependent antibodies** that react with platelet antigens only when the drug is present (notably **quinine** and **sulfonamides**). Onset typically after ~21 days (median) of exposure or on re-exposure, resolving 7–10 days after withdrawal. *GpIIb/IIIa inhibitors* (abciximab, eptifibatide, tirofiban) can cause an abrupt drop **within 24 h** via naturally occurring cross-reacting antibodies. Drugs in Table 120-1 include amiodarone, carbamazepine, phenytoin, vancomycin, trimethoprim-sulfamethoxazole, ranitidine, ibuprofen, naproxen, ceftriaxone, ciprofloxacin and gold. *All drugs should be suspect and stopped/substituted where possible.*
- **Inherited thrombocytopenia** (uncommon) — autosomal dominant **macrothrombocytopenia** linked to the non-muscle myosin heavy chain **MYH9 gene** (*May-Hegglin anomaly, Sebastian, Epstein's and Fechtner syndromes*); characteristic **large platelets**. Always take a family history in unexplained thrombocytopenia.

Heparin-induced thrombocytopenia (HIT)

- An immune, prothrombotic reaction to **antibody against the platelet factor 4 (PF4)–heparin complex**, which activates platelets via the **FcγRIIa** receptor (also activates monocytes/endothelium). Distinct from other drug causes: thrombocytopenia is **rarely severe (nadir rarely <20,000/μL)** and, far from bleeding, it **markedly increases thrombosis (HITT, in up to 50%)**.
- **Timing:** typically **5–14 days** after starting heparin; *<5 days* if exposed within the prior few weeks/months (pre-formed antibody). Occurs with both unfractionated (more common) and LMW heparin.
- **Diagnosis — "4Ts" score: Th**rombocytopenia, **T**iming of count fall, **Th**rombosis/sequelae, and o**Th**er causes absent. Confirm with **PF4/polyanion immunoassay (ELISA)** — sensitive but low specificity (≈50% positive after cardiopulmonary bypass) — and the more specific **serotonin-release assay**. HIT remains a clinical diagnosis.
- **Treatment:** *stop all heparin immediately*; anticoagulate with a **non-heparin agent** — IV direct thrombin inhibitor **argatroban** (or bivalirudin), **fondaparinux**, or a **DOAC** (most experience with rivaroxaban). **Avoid LMWH (cross-reacts)** and **avoid starting warfarin alone** (risk of venous limb gangrene from protein C/S depletion — overlap with a DTI/fondaparinux/DOAC after platelet recovery). Image for thrombosis (≥ lower-limb duplex); anticoagulate **3–6 months** if thrombosis present.

- **VITT** (vaccine-induced immune thrombotic thrombocytopenia) — a rare spontaneous-HIT-like syndrome after the **adenoviral ChAdOx1-S/nCoV-19** vaccine, with very **high D-dimer** and thrombosis at unusual sites (cerebral venous sinuses); ~20% fatal; treat with **IVIgG + non-heparin anticoagulant**.

Immune thrombocytopenic purpura (ITP)

- Acquired immune-mediated platelet destruction (and impaired megakaryocyte release). **Children:** acute, post-infectious, self-limited. **Adults:** chronic. **Secondary ITP** is associated with SLE, HIV, hepatitis C and (variably) *H. pylori*.
- **Clinical:** mucocutaneous bleeding (ecchymoses, petechiae, oral/GI/menorrhagia) with a very low count but otherwise **normal smear (often large platelets)**; wet purpura/retinal haemorrhage warn of severe bleeding.
- **Diagnosis of exclusion:** antiplatelet antibody testing is *not* useful (poor sensitivity/specificity). Test for HIV, HCV, SLE, immunoglobulins; **Coombs' test if anaemic** — ITP + autoimmune haemolytic anaemia = ***Evans syndrome***.
- **Treatment** (counts >30,000/µL without bleeding need none — no excess mortality):
  - First line: **prednisone 1 mg/kg** or **dexamethasone 40 mg/day × 4 days**; **anti-Rh0(D) immune globulin 50–75 µg/kg** (*Rh-positive, non-splenectomised patients only*); **IVIgG 1–2 g/kg over 1–5 days** for rapid rise / severe bleeding.
  - Second line: **rituximab** (anti-CD20; durable remission ~30%), **TPO-receptor agonists** — romiplostim (SC), eltrombopag / avatrombopag (oral), and **splenectomy** (now used less than TPO-RAs). Vaccinate against **encapsulated organisms** (pneumococcus, meningococcus, *H. influenzae*) before splenectomy.

Thrombotic microangiopathies — TTP & HUS

Both show **microangiopathic haemolytic anaemia (MAHA)** — thrombocytopenia + **schistocytes**, ↑ LDH, ↑ unconjugated bilirubin, ↓ haptoglobin, with microvascular thrombi. **PT and aPTT are characteristically normal** (this distinguishes them from DIC, where coagulopathy with prolonged PT/aPTT predominates).

Feature	TTP	HUS
Defect	Deficiency of / antibody to **ADAMTS13** (cleaves VWF ultra-large multimers); **activity <10% diagnostic**	Mostly **Shiga-toxin** (*E. coli* O157:H7) post-diarrhoeal; atypical HUS = **complement** dysregulation
Classic features	Moschcowitz **pentad** (1924): MAHA, thrombocytopenia, **renal failure, neurologic signs, fever**	Acute **renal failure**, MAHA, thrombocytopenia; preceded by (bloody) diarrhoea, mainly children
Inherited form	**Upshaw-Schulman syndrome**	Atypical HUS (complement gene variants/anti-factor H)
Treatment	**Plasma exchange (TPE)** mainstay (mortality 85–100% → 10–30%); glucocorticoids (adjunct); **rituximab** ↓ relapse; **caplacizumab** (anti-VWF nanobody)	Mainly **supportive** ± dialysis (diarrhoeal mortality <5%); **anticomplement therapy** for aHUS; plasma exchange does not alter typical HUS

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Algorithm for evaluating the thrombocytopenic patient (Fig. 120-2):** Box "Platelet count <150,000/μL" → check "Haemoglobin and WBC" → branches *Normal* (→ "Peripheral blood smear") and *Abnormal* (→ "Bone marrow examination"). Smear branches: "Platelets clumped → redraw in sodium citrate/heparin" (pseudothrombocytopenia); "Normal RBC morphology, platelets normal/large" → *Consider: drug-induced, infection-induced, idiopathic immune (ITP), congenital*; "Fragmented RBCs" → *Microangiopathic haemolytic anaemia (DIC, TTP)*.
- **Pathogenesis of TTP (Fig. 120-4):** label *Endothelial cell → ultra-large VWF multimers*; *ADAMTS13 protease* cleaving multimers in the normal state; in TTP — *"No protease/inhibited ADAMTS13" → persistent ultra-large VWF multimers → platelet aggregation and microvascular thrombosis*.

Clinical / Diagnostic significance

- Always **inspect the smear first** — it separates pseudothrombocytopenia, immune destruction (large platelets) and microangiopathy (schistocytes) at a glance and directs the entire work-up.
- **PT/aPTT** discriminate consumptive states: prolonged in **DIC**, normal in **TTP/HUS/ITP**.
- New thrombocytopenia + neurologic or renal signs + MAHA is **TTP until proven otherwise** — start plasma exchange empirically before ADAMTS13 confirmation, as it is rapidly fatal untreated.
- In a heparin-exposed patient with a falling count and new thrombosis, apply the **4Ts**, stop heparin and switch to a non-heparin anticoagulant — do **not** transfuse platelets or start warfarin alone.
- **Platelet transfusion** is generally avoided/contraindicated in HIT and TTP (fuels thrombosis); reserve for marrow-failure bleeding and severe ITP haemorrhage.

High-yield exam pointers

- Threshold **<150,000/μL**; three mechanisms — **production, sequestration, destruction**.
- **Drugs = commonest cause overall; infection = commonest non-iatrogenic cause.** Quinine & sulfonamides classically cause drug-dependent antibodies.
- **Pseudothrombocytopenia** = EDTA artefact → redraw in citrate/heparin.
- **HIT:** PF4–heparin antibody, nadir rarely <20,000/μL, day **5–14**, **causes thrombosis not bleeding**; avoid LMWH & warfarin-alone; use argatroban/fondaparinux/DOAC.
- **ITP:** diagnosis of exclusion; treat if bleeding or count <30,000; steroids/IVIgG/anti-D first line, TPO-RA/rituximab/splenectomy later; **Evans = ITP + AIHA**.
- **TTP:** ADAMTS13 <10%, **Moschcowitz pentad**, *Upshaw-Schulman* = inherited; treat with **plasma exchange + caplacizumab/rituximab**.
- **HUS:** *E. coli* O157:H7, post-diarrhoeal, children, renal-predominant; aHUS = complement → anticomplement therapy.
- **PT/aPTT normal** in TTP/HUS/ITP but **prolonged in DIC** — a frequent discriminator question.

- MAHA labs: **schistocytes, ↑LDH, ↑indirect bilirubin, ↓haptoglobin**.

> **SOURCE & COVERAGE**
>
> Harrison's Principles of Internal Medicine, 22e — **Ch 120 "Disorders of Platelets and Vessel Wall"** (B.A. Konkle), covering definition, mechanisms, approach, drug/infection-induced thrombocytopenia, HIT/VITT, ITP, and TTP/HUS. The chapter's cross-referenced topics (general hemostasis approach, Ch 69; chemotherapy-induced cytopenia, Ch 78) were not separately provided but are summarised only at the level stated in Ch 120. Specific eculizumab naming for aHUS is given in the text only as "anticomplement therapy." No coverage gap for the asked topic.

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Tumour lysis syndrome

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

Definition / Introduction — Tumour lysis syndrome (TLS) is a life-threatening oncologic metabolic emergency characterised by the tetrad of **hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia**, caused by the rapid destruction of a large number of swiftly proliferating neoplastic cells with massive release of intracellular contents into the circulation. **Acidosis** may also develop and **acute renal failure occurs frequently**. It is the commonest disease-related metabolic emergency in haemato-oncology and is largely **preventable** — recognition of risk and prophylaxis are the most important steps in management.

Pathophysiology — the four metabolic derangements

- **Core mechanism**: Effective cytotoxic therapy (or rarely spontaneous necrosis) lyses tumour cells, dumping intracellular **potassium, phosphate and nucleic acids** into the blood faster than the kidney can clear them; the nucleic-acid purines are catabolised to **uric acid**.
- **Hyperuricaemia → uric acid nephropathy**: Turnover of nucleic acids raises serum uric acid. In the **acidic local environment** of the distal nephron, uric acid precipitates in the **tubules, medulla and collecting ducts**, causing obstructive uropathy and renal failure. **Lactic acidosis and dehydration** promote precipitation. **Uric acid crystals in urine** are strong evidence of uric acid nephropathy; the **urinary uric acid : creatinine ratio is >1** in acute hyperuricaemic nephropathy and **<1** in renal failure from other causes.
- **Hyperphosphataemia → hypocalcaemia**: Release of intracellular phosphate pools causes a **reciprocal fall in serum calcium**, producing **severe neuromuscular irritability and tetany**. **Calcium phosphate** precipitates in the renal interstitium and microvasculature (**nephrocalcinosis**), further impairing renal function.
- **Hyperkalaemia**: Potassium is the principal intracellular cation; massive cell destruction releases it abruptly. In the setting of renal failure, hyperkalaemia can rapidly become **life-threatening, causing ventricular arrhythmias and sudden death** — the most immediately lethal feature of TLS.

- **Renal injury is multifactorial**: both uric-acid and calcium-phosphate crystals are **directly toxic to tubular epithelium**, inducing local inflammatory and pro-oxidative responses; in addition, **soluble uric acid** causes a **crystal-independent** fall in renal blood flow through vasoconstriction and impaired autoregulation.

Aetiology and precipitating factors

Domain	Examples (Harrison 22e)
Classic high-risk tumours	**Burkitt's lymphoma**, **acute lymphoblastic leukaemia** (ALL), **AML**, other rapidly proliferating lymphomas
Lower-risk / occasional	Chronic leukaemias; **rarely solid tumours**; rarely **spontaneous** tumour necrosis
Drug triggers	**Venetoclax** (bcl-2 antagonist — notably increases TLS frequency in lymphoid neoplasms); **glucocorticoids**; hormonal agents (**letrozole, tamoxifen**); monoclonal antibodies (**rituximab, obinutuzumab, ofatumumab, gemtuzumab**)
Timing	Usually **during or 1–5 days after** chemotherapy; hyperuricaemia may already be present before treatment

Risk stratification and classification

- **Tumour-burden markers predict risk**: TLS likelihood (e.g. in Burkitt's lymphoma) relates to **tumour burden and baseline renal function**. **Hyperuricaemia and high serum LDH (>1500 U/L)**, both correlating with total tumour burden, also correlate with the risk of TLS.
- **Pretreatment evaluation in at-risk patients**: complete blood count, **serum chemistry** (electrolytes, creatinine, calcium, phosphate, uric acid) and **urinalysis**. With abnormal baseline renal function, image the **kidneys and retroperitoneum by sonography/CT to exclude obstructive uropathy**, and watch urine output closely.
- **Pseudohyperkalaemia caveat**: very high leukocyte and platelet counts can **artefactually raise serum potassium** through cell lysis *after* the blood is drawn — follow **plasma** (not serum) potassium; in pseudohyperkalaemia there are **no ECG changes**.
- **Cairo–Bishop framework** (standard textbook classification — see Coverage note): **Laboratory TLS** = ≥2 of the metabolic abnormalities (raised uric acid, K^+, phosphate; low calcium) within ~3 days before to 7 days after therapy; **Clinical TLS** = laboratory TLS plus an end-organ consequence — **acute kidney injury (rising creatinine), cardiac arrhythmia/sudden death, or seizure**.

Clinical features and investigations

- **Metabolic/renal**: oliguric or anuric **acute renal failure**, flank pain, haematuria (uric-acid stones/sludge).
- **Hyperkalaemia**: muscle weakness, paraesthesiae, **peaked T waves**, widened QRS, ventricular arrhythmias, cardiac arrest.
- **Hypocalcaemia (from hyperphosphataemia)**: tetany, carpopedal spasm, paraesthesiae, **neuromuscular irritability**, seizures, prolonged QT.

- **Investigations**: serial **uric acid, K^+, phosphate, calcium, creatinine**, urea, LDH; **urinalysis** for uric-acid crystals and uric acid : creatinine ratio; **ECG** for hyperkalaemic changes; renal/retroperitoneal **imaging** if obstruction suspected.

Prevention and management

Recognition of risk and prevention are the most important steps. The standard preventive approach is **allopurinol plus aggressive hydration**. **Urinary alkalinisation with sodium bicarbonate is no longer recommended** — though it increases uric-acid solubility, a high urinary pH **decreases the solubility of xanthine, hypoxanthine and calcium phosphate**, potentially increasing intratubular crystallisation.

Intervention	Mechanism / detail (Harrison 22e)	Notes
Aggressive IV hydration	Normal or ½-normal saline at **3000 mL/m²/day**	Cornerstone; maintains high urine output and dilutes solutes
Allopurinol	Xanthine oxidase inhibitor — blocks *new* uric acid formation	**300 mg/m²/day**; IV form if oral not tolerated; does **not** remove pre-formed uric acid
Febuxostat	Potent **non-purine selective xanthine oxidase inhibitor**	Fewer hypersensitivity reactions than allopurinol; **no dose adjustment** in mild–moderate renal impairment; superior uric-acid control vs allopurinol in intermediate-to-high-risk haematologic malignancy; preferred in **allopurinol allergy and/or renal failure**
Rasburicase (recombinant urate oxidase)	Converts poorly soluble **uric acid → readily soluble allantoin** (urate oxidase is absent in primates)	Acts within **hours**; **0.2 mg/kg IV daily**; for high-risk **prophylaxis** and established hyperuricaemia, especially with renal failure
Renal replacement therapy	Removes K^+, phosphate, uric acid and fluid	**Haemodialysis preferred**; consider **early**; haemofiltration gives gradual continuous removal

- **Rasburicase cautions**: **contraindicated in G6PD deficiency** (cannot detoxify the hydrogen peroxide end-product of the urate-oxidase reaction → haemolysis); causes **ex vivo degradation of uric acid** in the test tube at room temperature, giving **spuriously low uric acid** values — **blood samples must be cooled immediately** to deactivate the enzyme.
- **Escalation (Fig. 80-4 algorithm)**: After 24–48 h, if **uric acid >8.0 mg/dL or creatinine >1.6 mg/dL**, correct treatable (obstructive) renal failure and **start recombinant urate oxidase 0.2 mg/kg IV daily**; if no improvement, **delay chemotherapy or start dialysis**. If **uric acid <8.0 mg/dL and creatinine <1.6 mg/dL**, proceed with chemotherapy and monitor chemistry every 6–12 h.
- **Indications for urgent haemodialysis**: K^+ **>6.0 meq/L**; uric acid **>10 mg/dL**; creatinine **>10 mg/dL**; phosphate **>10 mg/dL or rising**; **symptomatic hypocalcaemia**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow diagram** — Labels: *Cytotoxic chemotherapy / rapid tumour cell lysis* → release of **K^+**, **phosphate**, **nucleic acids (purines)**; purines → *xanthine oxidase* → **uric acid**; arms to **Hyperkalaemia** (ventricular arrhythmia, sudden death), **Hyperphosphataemia** → **reciprocal Hypocalcaemia** (tetany; calcium-phosphate nephrocalcinosis), **Hyperuricaemia** (uric-acid crystal precipitation in tubules → uric-acid nephropathy) → converging on **Acute Kidney Injury**. Mark drug blockade points: **Allopurinol/Febuxostat** at xanthine oxidase; **Rasburicase** converting uric acid → **allantoin**.
- **Management algorithm box** (after Fig. 80-4) — Labels: *Hydrate (saline 3000 mL/m^2/day)* → *Allopurinol 300 mg/m^2/day* → *Monitor chemistry* → decision node at 24–48 h (**uric acid 8.0 / creatinine 1.6 mg/dL**) → *Rasburicase* → *Dialysis*, with the dialysis-threshold list (**K^+ >6, uric acid >10, creatinine >10, phosphate >10, symptomatic hypocalcaemia**).

Clinical / Diagnostic significance

- TLS is **largely preventable**; identifying the high-risk patient (bulky, chemo-sensitive haematologic malignancy; high LDH; pre-existing renal impairment) and instituting hydration plus a hypouricaemic agent before therapy is the key intervention.
- **Hyperkalaemia is the most immediately fatal** disturbance — continuous cardiac monitoring and prompt treatment are mandatory.
- The **urinary uric acid : creatinine ratio (>1)** helps distinguish acute hyperuricaemic nephropathy from other causes of renal failure.
- Choice of hypouricaemic agent is risk-adapted: **allopurinol** for prevention in lower risk, **rasburicase** for high-risk prophylaxis and established hyperuricaemia (especially with renal failure), **febuxostat** where allopurinol is contraindicated or renal function is impaired.
- **Early dialysis** rather than delayed dialysis improves outcome once defined biochemical thresholds are crossed.

High-yield exam pointers

- TLS tetrad: **hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia** ± acidosis ± acute renal failure.
- Classic culprits: **Burkitt's lymphoma, ALL, AML**; drug trigger to remember — **venetoclax (bcl-2 antagonist)**.
- Onset **during or 1–5 days after** chemotherapy; high **LDH >1500 U/L** flags high tumour burden/risk.
- Standard prophylaxis = **aggressive hydration (3000 mL/m^2/day) + allopurinol (300 mg/m^2/day)**; **bicarbonate urinary alkalinisation is no longer recommended**.
- **Rasburicase** converts uric acid → **allantoin**; **contraindicated in G6PD deficiency**; **cool the sample** to avoid spuriously low uric acid.
- **Febuxostat** = non-purine selective xanthine oxidase inhibitor; useful in **allopurinol allergy / renal impairment**.
- **Pseudohyperkalaemia** with high WBC/platelets — follow **plasma** K^+; no ECG changes.

- **Dialysis thresholds**: K^+ >6 meq/L, uric acid >10, creatinine >10, phosphate >10 (or rising), symptomatic hypocalcaemia — **haemodialysis preferred**.

> **SOURCE & COVERAGE**
>
> Harrison 22e — Ch 80 "Oncologic Emergencies" (Tumor Lysis Syndrome section and Fig. 80-4 management algorithm). **Coverage note**: All metabolic mechanisms, at-risk tumours/drugs, LDH/risk markers, drug doses and dialysis thresholds are grounded in Ch 80. The **Cairo–Bishop laboratory-vs-clinical TLS classification** (and its specific cut-offs/timing window) is universally accepted standard internal medicine but is **not** stated in the provided Harrison chapter text; it has been included for completeness and flagged here.

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Unstable haemoglobin

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

Definition / Introduction — Unstable hemoglobins are rare inherited hemoglobin variants in which a globin mutation makes the hemoglobin tetramer structurally unstable, so it denatures and precipitates within the red cell. They are also called **congenital Heinz body hemolytic anemias**. The usual clinical expression is **nonspherocytic hemolytic anemia** with jaundice, reticulocytosis, pigmenturia, and often splenomegaly, but severity ranges from almost silent hemolysis to recurrent crises.

Classification and examples

- **Place in hemoglobin disorders:** Harrison classifies them under **hemoglobinopathies** with abnormal physical, chemical, or functional properties, specifically among hemoglobins that oxidize readily; the phenotype is **hemolytic anemia and jaundice**.
- **Genetic basis:** mutations affect alpha- or beta-globin and disturb the **tertiary or quaternary structure** of the hemoglobin molecule. Many cases arise from a **new mutation**, so absence of a family history does not exclude the diagnosis.
- **Common structural mechanisms:**
  - Introduction of **proline into an alpha helix**, disrupting normal globin folding.
  - Replacement by a **polar amino acid in the hydrophobic interior** of the globin molecule, destabilizing the heme pocket or globin contacts.
  - Interface mutations that weaken tetramer stability and promote denaturation.
- **Number of variants:** Harrison notes **156 unstable hemoglobin variants** have been described; most are rare and family-specific.
- **Important examples from Harrison:**
  - **Hemoglobin Köln**: beta 99 Val -> Met; found in multiple families and a classic unstable beta-chain variant.
  - **Hemoglobin Hasharon**: alpha 47 Asp -> His; described particularly in Ashkenazi Jews.
  - **Hemoglobin Zurich**: beta 63 His -> Arg; notable because it may show **oxidant drug-induced hemolysis**.

- **Laboratory expression of the variant:** in many heterozygotes the abnormal hemoglobin forms about **20-35%** of total hemoglobin, but **hyperunstable variants may be undetectable** on routine fractionation and may mimic a thalassemic phenotype.

Pathogenesis of Heinz-body hemolysis

- Normal hemoglobin keeps heme protected within a stable globin pocket; unstable variants unfold more easily, especially under oxidative stress.
- The unstable hemoglobin **precipitates intracellularly** as **Heinz bodies**, which are intraerythrocytic aggregates of denatured hemoglobin.
- Heinz bodies damage the red-cell membrane and reduce deformability. When such cells traverse splenic cords and sinusoids, macrophages remove the inclusions by **pitting**.
- Pitting produces characteristic **bite cells** and **blister cells**. Repeated pitting and membrane injury shorten red-cell survival, causing mainly **extravascular hemolysis** in the spleen.
- During more severe episodes, there may also be intravascular hemolysis with **pigmenturia**, low haptoglobin, hemoglobinemia, hemoglobinuria, or later urinary hemosiderin.
- Oxidant stress, infection, fever, and selected oxidant drugs can increase denaturation, explaining episodic worsening on a background of chronic compensated hemolysis.

Clinical features

- **Presentation:** lifelong or incidentally detected **Coombs-negative nonspherocytic hemolytic anemia**; some patients present in childhood, while mild variants are detected only during family studies or after a hemolytic episode.
- **Symptoms:** fatigue, exertional dyspnea, pallor, intermittent jaundice, dark urine after hemolytic stress, or abdominal discomfort from splenomegaly or gallstones.
- **Signs:** pallor, icterus, **splenomegaly**, and occasionally hepatomegaly. Growth and development are usually normal in mild disease.
- **Baseline severity:** Harrison describes the associated disease as **usually mild** and often not requiring transfusion; adult hemoglobin may be only mildly reduced, roughly in the **9-14 g/dL** range in typical tabulated cases.
- **Crises:** acute worsening may follow oxidant drugs, intercurrent infection, or any stress increasing oxidative injury. Hb Zurich is the exam example for drug-triggered hemolysis.
- **Complications of chronic hemolysis:** unconjugated hyperbilirubinemia, pigment gallstones, folate demand from chronic reticulocytosis, episodic hemoglobinuria, and rarely transfusion-related iron burden if severe disease is repeatedly transfused.

Laboratory diagnosis

- **CBC and reticulocytes:** normocytic or mildly macrocytic anemia because of reticulocytosis; leukocyte and platelet counts are usually normal unless hypersplenism coexists.
- **Hemolysis profile:** increased reticulocyte count, indirect bilirubin, and LDH; reduced haptoglobin; urine hemoglobin or hemosiderin if intravascular hemolysis has occurred.
- **Peripheral smear:** polychromasia with **bite cells/blister cells**. Spherocytes are not the defining abnormality, helping separate it from hereditary spherocytosis or autoimmune hemolysis.

- **Heinz body demonstration:** Heinz bodies are **not seen on ordinary Wright-Giemsa smears**. Use a **supravital stain** such as brilliant cresyl blue, cresyl violet, crystal violet, or methyl violet to show dark globular inclusions of denatured hemoglobin.
- **Stability testing:** heat-stability testing by heating blood to **50°C** or incubation with **isopropanol** precipitates unstable hemoglobins; Harrison emphasizes that these tests need careful controls.
- **Hemoglobin analysis:** HPLC or capillary electrophoresis may detect a variant peak; however, a negative HPLC does not exclude a **hyperunstable** variant because the abnormal hemoglobin may be rapidly degraded.
- **Molecular confirmation:** DNA sequencing of alpha- and beta-globin genes is definitive and is important for family studies and genetic counseling.
- **Family study:** evaluate parents, siblings, and children with CBC, reticulocyte count, smear, hemoglobin fractionation, and targeted mutation testing once the proband mutation is known.

Differential diagnosis

Disorder	Key overlap	Differentiating points
G6PD deficiency	Oxidant-triggered hemolysis, Heinz bodies, bite cells	X-linked; normal blood between attacks in many patients; enzyme assay low between episodes but may be falsely normal soon after hemolysis because of reticulocytosis
Hereditary spherocytosis	Jaundice, splenomegaly, gallstones	Spherocytes and raised MCHC; membrane disorder rather than hemoglobin instability; Heinz bodies are not the key lesion
Autoimmune hemolytic anemia	Hemolysis, jaundice, splenomegaly	Direct antiglobulin test positive; spherocytes common; acquired and immune-mediated
Thalassemia syndromes	Chronic inherited anemia; abnormal hemoglobin studies	Microcytosis and target cells dominate; defect is reduced globin synthesis, not unstable tetramer precipitation; hyperunstable Hb may mimic thalassemia and needs DNA testing
Sickle cell disease	Hemolysis and pigment gallstones	HbS polymerization with vaso-occlusion; sickled cells and characteristic HbS fraction on HPLC
M hemoglobins / methemoglobinemia	Abnormal hemoglobin with cyanosis	Main feature is slate-gray cyanosis/methemoglobin, not Heinz-body hemolysis; treatment usually unnecessary for inherited M hemoglobins
PNH	Coombs-negative hemolysis, hemoglobinuria	Acquired clonal disorder; thrombosis and cytopenias may occur; flow cytometry shows CD55/CD59 deficiency

Management and counseling

- **General principle:** most unstable hemoglobins need **supportive care**, not disease-specific drug therapy.
- **Avoid triggers:** avoid known oxidant drugs whenever possible, especially in patients with previous drug-triggered hemolysis or Hb Zurich-like variants. Practical avoid-list includes

dapsone, primaquine-type antimalarials, nitrofurantoin, phenazopyridine, rasburicase, methylene blue, sulfonamides, pegloticase, and quinolones when safer alternatives exist.

- **During acute hemolysis:** stop the trigger, treat infection, maintain hydration and urine output, monitor hemoglobin, bilirubin, LDH, renal function, and urine pigment, and transfuse packed red cells only for symptomatic or severe anemia.
- **Chronic care:** folate replacement is reasonable when chronic reticulocytosis is present; monitor for gallstone symptoms and splenic enlargement.
- **Transfusion:** Harrison notes disease is usually mild and **does not require transfusion**. Repeated transfusion should be avoided unless clearly indicated because it adds alloimmunization and iron-overload risk.
- **Splenectomy:** not routine. Consider only in selected severe, transfusion-dependent or hypersplenic cases after hematology review; if performed, give appropriate pneumococcal, meningococcal, and Haemophilus influenzae type b vaccination and fever education.
- **Genetic counseling:** explain autosomal codominant/inherited hemoglobin-variant behavior, possible de novo mutation, variable expression, and the value of DNA-confirmed diagnosis before reproductive counseling.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis flow diagram:** globin mutation -> unstable Hb tetramer -> intracellular denaturation -> Heinz bodies -> splenic pitting -> bite/blister cells -> extravascular hemolysis -> jaundice, splenomegaly, reticulocytosis, pigmenturia.
- **Peripheral smear diagram:** label normal RBC, Heinz body on supravital stain, bite cell after splenic pitting, blister cell, reticulocyte/polychromasia.

Clinical / Diagnostic significance

- Think of unstable hemoglobin in **Coombs-negative nonspherocytic hemolytic anemia** with Heinz bodies, especially when G6PD assay is normal or attacks are familial/recurrent.
- A routine smear can miss the diagnosis because Heinz bodies require **vital/supravital staining**.
- HPLC can be misleading: some variants appear as 20-35% abnormal hemoglobin, while **hyperunstable variants may be absent** because they precipitate or degrade rapidly.
- Drug history is essential; oxidant drugs may convert compensated hemolysis into a crisis.
- Do not label all bite-cell hemolysis as G6PD deficiency. A normal G6PD level away from crisis plus positive heat/isopropanol instability testing should redirect work-up toward unstable Hb.
- DNA sequencing is the most reliable final test and prevents unnecessary immune, marrow, liver, and cardiopulmonary work-ups.

High-yield exam pointers

- Write the synonym: **congenital Heinz body hemolytic anemia**.
- Core lesion: structurally unstable Hb -> **precipitated denatured Hb** -> Heinz bodies.
- Heinz bodies need **brilliant cresyl blue/cresyl violet/crystal violet/methyl violet** supravital staining.

- Smear clue after splenic pitting: **bite cells and blister cells**.
- Harrison examples: **Hb Köln, Hb Hasharon, Hb Zurich**.
- Hb Zurich is the classic unstable Hb susceptible to **oxidant drug-induced hemolysis**.
- Diagnosis: hemolysis labs + supravital stain + **heat 50°C/isopropanol instability test** + HPLC/capillary electrophoresis + globin gene sequencing.
- Routine HPLC may miss **hyperunstable** variants.
- Most cases are mild: avoid oxidants, folate if chronic hemolysis, transfuse only when clinically necessary.

SOURCE & COVERAGE

Harrison 22e — "Disorders of Hemoglobin"; Harrison 22e — "Interpreting Peripheral Blood Smears" and "Hemolytic Anemias"; CMDT 2026 — "Blood Disorders". Coverage note: the specified DeVita's Cancer 12e heme-malignancy text was grepped but has no substantive benign unstable-hemoglobin coverage, so this thin topic is grounded mainly in Harrison and CMDT.

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Vitamin B12 deficiency

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

Definition / Introduction — Vitamin B12 (cobalamin) deficiency is a state of inadequate tissue cobalamin resulting in **megaloblastic anaemia** (ineffective erythropoiesis with defective DNA synthesis) and a characteristic **neuropsychiatric syndrome**, most importantly *subacute combined degeneration* of the cord. Cobalamin is a cobalt-containing corrin-ring vitamin synthesised solely by micro-organisms; humans depend entirely on **food of animal origin**. Because body stores (2–3 mg) last 3–4 years, deficiency develops insidiously and is usually due to **malabsorption** (chiefly pernicious anaemia) rather than dietary lack — except in vegans. The hallmark is that *neurological damage may be irreversible and can occur even with a normal blood count*, making early recognition critical.

Biochemistry, sources and physiology of absorption

- **Structure/forms** — cobalt atom at the centre of a corrin ring. Active coenzyme forms: **adenosylcobalamin (ado-B12)**, mitochondrial cofactor for *L-methylmalonyl-CoA mutase*; **methylcobalamin**, cytoplasmic/plasma cofactor for *methionine synthase*. Hydroxocobalamin is the therapeutic precursor form.
- **Dietary sources & requirement** — meat, fish, eggs and dairy; plant foods are devoid of B12. Western diet supplies 5–30 µg/day; **daily requirement ~1–3 µg**; body stores 2–3 mg (mainly liver), sufficient for **3–4 years**.
- **Two cobalamin-dependent reactions** — (1) methylmalonyl-CoA → succinyl-CoA (ado-B12); a block raises **methylmalonic acid (MMA)**. (2) homocysteine + 5-methyl-THF → methionine (methylcobalamin); a block raises **homocysteine** and regenerates THF.
- **The "methylfolate trap"** — in B12 deficiency, methionine synthase fails, so 5-methyl-THF accumulates in plasma while intracellular folate polyglutamates fall (THF starvation). This impairs thymidylate synthesis (dUMP→dTMP), producing the *common final pathway of*

megaloblastosis shared by folate and B12 deficiency, and explains why large doses of folic acid partially correct the anaemia (but **not** the neuropathy) of B12 deficiency.

Step	Mechanism
Release from food	Gastric acid + pepsin free B12; it binds **haptocorrin (HC / TC I)** from saliva
Pancreatic phase	Trypsin digests HC; B12 transferred to **intrinsic factor (IF)**
Intrinsic factor	Glycoprotein from gastric **parietal cells** (fundus/body); gene at 11q13
Ileal uptake	IF–B12 binds **cubilin** receptor on ileal enterocyte; trafficked via **amnionless (AMN)**
Transport	After ~6 h, B12 enters portal blood on **transcobalamin II (TC II)**; delivered to tissues via TC II receptor + megalin
Enterohepatic cycle	0.5–5 µg enters bile/day and is reabsorbed (intact in vegans → slow deficiency; lost in malabsorption → faster)

Causes of B12 deficiency

- **Inadequate intake (dietary) — vegans/strict vegetarians**; large at-risk group are Indian Hindus (subnormal levels in up to 50% of young Indian vegans, though frank megaloblastic anaemia is uncommon as the enterohepatic cycle is intact).
- **Malabsorption — the commonest mechanism:**

Site	Causes
Gastric	**Pernicious anaemia** (autoimmune, commonest severe cause); total/partial gastrectomy; congenital IF deficiency; food-cobalamin malabsorption (atrophic gastritis, **PPIs**, bariatric surgery)
Intestinal	**Stagnant-loop syndrome** (bacterial overgrowth — jejunal diverticulosis, blind loop, stricture, fistula); **ileal resection (≥1.2 m terminal ileum)**/Crohn disease; **Imerslund-Gräsbeck syndrome** (cubilin/AMN mutation, selective malabsorption + proteinuria); tropical sprue; **fish tapeworm** (*Diphyllobothrium latum*); gluten-induced enteropathy
Other	Zollinger-Ellison syndrome; chronic pancreatitis; HIV; **TC II deficiency** (congenital)

- **Drugs / toxic — metformin** (lowers TC I); prolonged PPI use; colchicine, neomycin; **nitrous oxide (N_2O)** irreversibly oxidises methylcobalamin and inactivates methionine synthase (megaloblastosis after prolonged anaesthesia; myeloneuropathy in those exposed/abusing N_2O).

Pernicious anaemia (the key autoimmune cause)

- **Definition** — severe lack of IF due to **autoimmune atrophic gastritis** of the gastric body/fundus.
- **Epidemiology** — incidence ~120/100,000 (UK); M:F ≈ 1:1.6; **median onset 70–80 years**; commoner in those of African ancestry and blood group A.
- **Associations** — other organ-specific autoimmune disease: **autoimmune thyroid disease, vitiligo, type 1 diabetes, Addison disease, hypoparathyroidism**; increased risk of **gastric carcinoma** and gastric carcinoid.

- **Serology — IF antibodies**: "blocking" (type I, ~55%, prevents B12–IF binding) and "binding" (type II, ~35%); **parietal-cell antibody** (~90%, directed at gastric H^+/K^+-ATPase, but non-specific). **Raised serum gastrin**, **low pepsinogen I**.
- **Histology** — atrophy of all layers of body/fundus, loss of parietal and chief cells, intestinal metaplasia; antrum spared.

Clinical features

- **Anaemia** — insidious; symptoms often mild relative to severe anaemia (good adaptation). Pallor, mild **icterus/lemon-yellow tint** (haemolysis + ineffective erythropoiesis), fatigue.
- **Epithelial/GI — glossitis** (beefy, smooth red tongue), angular cheilosis, anorexia, weight loss, diarrhoea; reversible **melanin hyperpigmentation**.
- **Neuropsychiatric — subacute combined degeneration (SACD):** symmetrical demyelination of the **posterior columns and lateral (pyramidal) tracts** of the cervico-thoracic cord.
  - Earliest: distal **paraesthesiae** and peripheral neuropathy.
  - Posterior column: loss of **vibration and proprioception**, sensory ataxia, **positive Romberg sign**, **Lhermitte sign**.
  - Pyramidal: spastic weakness, **hyperreflexia**, extensor plantars (the combination of absent ankle jerks with extensor plantars is classic).
  - Higher centres: dementia, depression, psychosis ("megaloblastic madness"), optic atrophy, anosmia.
  - Autonomic: postural hypotension, impotence, bladder/bowel incontinence.
  - *Crucial point:* neurological disease may occur with a **normal CBC and normal MCV** and is potentially reversible only if treated within ~6 months.
- **Other** — infertility, recurrent fetal loss; raised homocysteine is a (weak) vascular/thrombotic risk factor.

Investigations and diagnosis

- **Peripheral smear — oval macrocytes**, marked anisopoikilocytosis, **MCV usually >100 fL** (110–140 fL), **hypersegmented neutrophils (>5 lobes)**; leucopenia and thrombocytopenia in severe cases; **reticulocytopenia**.
- **Bone marrow** — hypercellular, **megaloblastic** erythroid hyperplasia with **nuclear–cytoplasmic asynchrony** (open "sieve-like" chromatin with mature haemoglobinised cytoplasm), **giant metamyelocytes/giant bands**, hyperpolyploid megakaryocytes.
- **Ineffective erythropoiesis ("intramedullary haemolysis")** — raised **unconjugated bilirubin**, very high **LDH**, low haptoglobin, raised urine urobilinogen.
- **Confirmatory biochemistry:**

Test	Comment
Serum cobalamin	Normal ~118–148 to 738 pmol/L; deficiency usually <74 pmol/L (<100 ng/L); borderline 74–148 pmol/L. *False-normal in up to 50% of PA sera due to IF antibodies interfering with assay*

Test	Comment
Serum MMA	Raised — relatively **specific for B12** deficiency (normal in folate deficiency); also raised in renal failure
Serum homocysteine	Raised in **both** B12 and folate deficiency (less specific; also up in renal disease, B6 deficiency, hypothyroidism)
Tests for cause	IF + parietal-cell antibodies, serum gastrin (↑) and pepsinogen I (↓) for PA; gastric endoscopy; coeliac serology; check **iron status** (coexistent iron + B12 deficiency in 15–20% of elderly may mask macrocytosis)

- The Schilling test is **obsolete** (radioactive B12 unavailable).

Treatment

- **Parenteral (standard for severe deficiency / PA / neuropathy) — hydroxocobalamin** preferred (better retention): six **1000 µg IM** doses at 3–7-day intervals to replenish stores, then **1000 µg IM every 3 months** for maintenance. (Cyanocobalamin, used in the US, needs higher/more frequent dosing — e.g. 1000 µg IM monthly.) CMDT regimen: 100–1000 µg IM/SC, daily for 1 week → weekly for 1 month → monthly.
- **Oral/sublingual** — high-dose **1000–2000 µg/day** cyanocobalamin or methylcobalamin is effective even in PA, as ~1% is absorbed passively independent of IF; requires good compliance and monitoring; preferred for food-cobalamin malabsorption.
- **Lifelong therapy** for PA, total gastrectomy and ileal resection. Treat/screen patients on long-term PPIs or after bariatric surgery.
- **Critical caveats:**
  - **Always exclude/correct B12 deficiency before giving folic acid** — folate monotherapy may correct the anaemia but **precipitate or worsen SACD**.
  - **Hypokalaemia** and a transient rise in platelets may occur in the first days of treatment (brisk haematopoiesis); monitor in severe anaemia.
  - Expect **reticulocytosis at 5–7 days**; blood picture normalises by ~2 months. Transfusion is rarely needed (give packed cells slowly if essential).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Subacute combined degeneration — spinal cord cross-section:** draw a cord transverse section and shade/label the **posterior (dorsal) columns — fasciculus gracilis & cuneatus** and the **lateral corticospinal (pyramidal) tracts** as the demyelinated regions; label *"posterior + lateral column demyelination; anterior columns spared."*
- **Cobalamin absorption pathway:** stomach (parietal cell → **intrinsic factor**; haptocorrin from saliva) → duodenum (**pancreatic trypsin** frees B12 from HC → binds IF) → **terminal ileum (cubilin/AMN receptor)** → portal blood on **transcobalamin II** → tissues/liver store. Label each box.

Clinical / Diagnostic significance

- A raised MCV with **hypersegmented neutrophils** on a routine count is often the first clue — pursue B12/folate before labelling "anaemia of chronic disease."
- **MMA + homocysteine** distinguish true tissue deficiency from a borderline serum B12 and detect deficiency despite normal levels; **MMA is the more specific marker**.
- In any patient with **unexplained myelopathy, sensory ataxia, dementia or psychosis**, check B12 — neurology can present without anaemia.
- Diagnosing **pernicious anaemia** mandates one-time gastroscopy (gastric atrophy, carcinoma/carcinoid surveillance) and screening for associated autoimmune endocrinopathy.
- The therapeutic trap to avoid in exams: **never treat megaloblastic anaemia with folic acid alone** until B12 is replete.

High-yield exam pointers

- Body stores last **3–4 years**; only source is **animal food**; commonest cause of severe deficiency is **pernicious anaemia (autoimmune)**.
- **MMA raised in B12 deficiency, NOT in folate deficiency**; homocysteine raised in both.
- PA antibodies: **IF antibody = specific but ~50% sensitive**; **parietal-cell antibody = sensitive (90%) but non-specific**.
- Neurology = **subacute combined degeneration** → posterior + lateral columns; absent ankle jerks + extensor plantars + positive Romberg/Lhermitte.
- Smear: **oval macrocytes + hypersegmented neutrophils**; marrow: megaloblasts with **nuclear–cytoplasmic asynchrony**, giant metamyelocytes.
- Treat with **hydroxocobalamin IM**; give **folate only after B12 corrected**; watch for **hypokalaemia** and reticulocytosis on day 5–7.
- **Nitrous oxide** inactivates methionine synthase → can precipitate acute B12 myeloneuropathy.
- **Metformin** and long-term **PPIs** are recognised drug causes; screen at-risk patients.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Megaloblastic Anemias" (Hoffbrand) and "Vitamin and Trace Mineral Deficiency and Excess."
- **CMDT 2026** — "Blood Disorders: Vitamin B12 Deficiency" (current diagnostic thresholds and treatment regimens).
- *Coverage note:* The spec-listed specialty text (DeVita's *Cancer: Principles & Practice of Oncology*) addresses haematologic **malignancies**, not benign nutritional/megaloblastic anaemia, so it does not cover this topic; Harrison's dedicated haematology chapter by A.V. Hoffbrand is the authoritative subspecialty source used here, supplemented by CMDT for management.

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Occupational carcinogens

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Occupational cancers* are malignancies whose development is causally attributable to exposure to physical, chemical or biological **carcinogens encountered in the workplace**. They are the prototype of *preventable* cancer because the causative agent is identifiable, often a "complete carcinogen" (acting as both initiator and promoter), and the route of exposure is amenable to engineering and regulatory control. Occupational and environmental exposures are estimated to contribute up to ~10% of all lung cancers, and a substantial fraction of bladder cancer and virtually all mesothelioma. They characteristically show a **long latency (often decades)** between first exposure and tumour, and risk that rises with intensity and duration of exposure.

Principal occupational carcinogens — cancer caused and industrial source

Carcinogen	Type of cancer caused	Industrial use / setting of exposure
Asbestos	Bronchogenic carcinoma; pleural & **peritoneal mesothelioma**; laryngeal	Mining, milling, insulation, construction, shipbuilding/ship repair, pipe-fitting, brake linings
Aromatic amines (benzidine, 2-naphthylamine — "dyes")	**Bladder (urothelial) carcinoma**	Dye, rubber, paint, textile and aluminium industries
Benzene	**Acute myeloid (myelocytic) leukaemia**	Petrochemical, rubber, shoe/leather, solvent, petrol industries
Vinyl chloride monomer	**Hepatic angiosarcoma**	PVC plastic polymerisation
Arsenic (inorganic)	Skin, **lung**, liver (angiosarcoma), bladder, kidney	Smelting, microelectronics, wood preservatives, pesticides/herbicides; contaminated deep-well water

Carcinogen	Type of cancer caused	Industrial use / setting of exposure
Chromium (hexavalent)	Lung, nasal sinus	Chrome plating, pigment/dye manufacture, stainless-steel welding, tanning
Nickel dust	Lung, nasal sinus	Nickel refining, electroplating, alloy and battery manufacture
Polycyclic aromatic hydrocarbons (coal tar, soot, pitch)	Skin — **scrotal SCC** (chimney sweeps); lung	Coke ovens, coal-tar/pitch, roofing, soot (chimney sweeping), aluminium production
Crystalline silica	Lung carcinoma (on a background of silicosis)	Sandblasting, quarrying, stone-cutting, foundry, ceramics, artificial-stone benchtops
Radon gas / radon daughters	Lung carcinoma	Underground uranium and hard-rock mining; indoor accumulation
Beryllium	Lung carcinoma (highly suspect)	Alloy processing for nuclear power/weapons, aerospace, electronics
Ionising radiation	Leukaemia, thyroid, breast, bone, lung, soft tissue (many)	Radiology/radiography, nuclear industry, radium-dial painting
Diesel exhaust	Lung carcinoma (miners)	Mining, transport, professional drivers
Wood dust / formaldehyde	Sinonasal adenocarcinoma; nasopharyngeal	Furniture and cabinet making, joinery
Nitrogen / sulphur mustard gas	Lung, head & neck, nasal sinus	Chemical-weapon and munitions manufacture
Ultraviolet (sunlight)	Non-melanoma skin cancer; melanoma	Outdoor work (farming, fishing, construction)

Key carcinogen groups — clinical detail

- **Asbestos** — the single most important occupational carcinogen. All fibre types cause disease; it produces **asbestosis** (diffuse interstitial fibrosis, usually after ≥10 years of exposure, presenting ≥15 years later), **pleural plaques** (a radiographic marker of exposure, not impairment), bronchogenic carcinoma and **mesothelioma**. **>80% of mesotheliomas are attributable to asbestos**, so documented mesothelioma in an exposed worker is *compensable*. Smoking and asbestos act **multiplicatively** for lung (not mesothelioma) risk.
- **Aromatic amines** — *benzidine* and *2-naphthylamine* are excreted in urine and concentrated in the bladder, producing urothelial carcinoma in dye, rubber and paint workers; **schistosomiasis** (***S. haematobium***) is the parallel infective cause of (squamous) bladder cancer in endemic regions such as Egypt.
- **Benzene** — a myelotoxin causing aplastic anaemia and **acute myeloid leukaemia**; also implicated in myelodysplasia.
- **Vinyl chloride** — the classic cause of **hepatic angiosarcoma**, a rare sentinel tumour highly specific for occupational exposure (arsenic and thorotrast are the other causes).

- **Crystalline silica** — silicosis carries an increased risk of lung cancer and of **tuberculosis** ("silicotuberculosis"); *eggshell* calcification of hilar nodes is a clue. Resurgent in **artificial-stone (engineered quartz) benchtop** workers.
- **Arsenic** — chronic exposure produces **palmar/plantar hyperkeratosis, hyperpigmentation and Mees' lines**, with skin, lung, liver (angiosarcoma), bladder and kidney cancers.
- **Polycyclic aromatic hydrocarbons** — the historical *Percival Pott* observation of scrotal squamous-cell carcinoma in chimney sweeps (soot) is the first described occupational cancer.
- **Beryllium** — causes chronic granulomatous lung disease (diagnosed by the **beryllium lymphocyte proliferation test, BeLPT**) and is a suspect lung carcinogen.

Prevention — primary, secondary and tertiary

Primary prevention (most important — "hierarchy of controls"):

- **Elimination / substitution** of the carcinogen — e.g., asbestos replaced by synthetic mineral fibres (fibreglass, refractory ceramic fibres); ban/restrict known agents.
- **Engineering controls** — enclosure of process, **local exhaust ventilation**, closed systems (vinyl chloride polymerisation), **wet methods** and dust suppression for silica.
- **Administrative controls** — limiting exposure duration, job rotation, restricted-area zoning, worker education and a documented **occupational history**.
- **Personal protective equipment (PPE)** — respirators, protective clothing (least effective; last line).
- **Regulation** — enforce permissible exposure limits / threshold limit values, and *ALARA* ("as low as reasonably achievable") for ionising radiation.
- **Smoking cessation** — essential because tobacco is **multiplicative** with asbestos and additive/multiplicative with radon; importantly, β-carotene supplementation **increased** lung cancer in asbestos-exposed smokers (CARET trial), so antioxidant chemoprevention is *not* advised.

Secondary prevention (early detection / surveillance):

- Periodic **chest radiograph, HRCT and pulmonary function tests** in dust-exposed workers; **low-dose CT** screening in eligible high-risk smokers.
- **Urine cytology / haematuria surveillance** in aromatic-amine-exposed workers; **biological monitoring** (e.g., urinary arsenic, BeLPT for beryllium).
- Recognition of pleural plaques and pre-employment/periodic medical examination.

Tertiary prevention: early definitive treatment, rehabilitation, and **workers' compensation / medico-legal certification** (mesothelioma, asbestosis, silicosis are notifiable, compensable diseases). Population-level measures include vaccination against oncogenic infections (HBV, HPV) and IARC carcinogen classification with national registries.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Carcinogen → target organ" body map:** a human silhouette with labelled arrows — *Asbestos → lung & pleura (mesothelioma)*; *Aromatic amines → urinary bladder*; *Benzene → bone marrow (AML)*; *Vinyl chloride → liver (angiosarcoma)*; *Arsenic → skin*; *PAH/soot → scrotal skin (SCC)*; *Wood dust/Ni/Cr → nasal sinuses*; *Radon/silica/diesel → lung*.
- **Hierarchy of controls (inverted pyramid):** top-to-bottom labels — *Elimination → Substitution → Engineering controls → Administrative controls → PPE* (annotate "most effective" at top, "least effective" at bottom).

Clinical / Diagnostic significance

- A meticulous **occupational and environmental history** is essential in any patient with lung fibrosis, an unexplained malignancy, haematuria or cytopenia — exposure may be remote and bystander (e.g., shipyard painters/electricians, household contacts of asbestos workers).
- **Sentinel tumours** point directly to specific exposures: hepatic angiosarcoma → vinyl chloride/arsenic; pleural mesothelioma → asbestos; scrotal SCC → soot/PAH; sinonasal adenocarcinoma → wood dust/nickel.
- Investigations: HRCT and PFT (pneumoconioses), pleural biopsy/thoracoscopy with calretinin/WT-1 for mesothelioma, cystoscopy + urine cytology (bladder), bone-marrow study (benzene/AML), BeLPT (beryllium).
- Recognising an occupational cause carries **public-health duty** — notification, workplace inspection, screening of co-workers and statutory compensation.

High-yield exam pointers

- **Asbestos** → lung cancer + **pleural/peritoneal mesothelioma**; >80% mesotheliomas are asbestos-related; smoking multiplies lung (not mesothelioma) risk.
- **Aromatic amines (benzidine, 2-naphthylamine)** → **bladder cancer** (dye/rubber/paint industry).
- **Benzene** → **AML**; **Vinyl chloride** → **hepatic angiosarcoma**; **Arsenic** → **skin/lung/bladder + Mees' lines**.
- **PAH/soot** → **scrotal SCC** (Pott, chimney sweeps) — the first recognised occupational cancer.
- **Chromium & Nickel** → **lung and nasal-sinus cancer**; **Radon & diesel exhaust** → **lung cancer (miners)**.
- **Silica** → lung cancer + **increased TB risk** (silicotuberculosis); artificial-stone workers are a re-emerging group.
- Prevention pyramid: **Elimination > Substitution > Engineering > Administrative > PPE**; plus smoking cessation, exposure limits and surveillance.
- β-carotene **harms** asbestos-exposed smokers (CARET) — do not use as chemoprevention.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Prevention and Early Detection of Cancer" (Table of Suspected Carcinogens), "Occupational and Environmental Lung Disease" (categories of occupational exposure and respiratory responses), "Heavy Metal Poisoning" (arsenic), and "Cancer Genetics" (chimney-sweep/soot historical note).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — bladder-cancer epidemiology (aromatic amines in painting/rubber/aluminium industries; arsenic; *S. haematobium*) and sinonasal/formaldehyde occupational associations.
- **CMDT 2026** — "Occupational Pulmonary Diseases" (pneumoconioses table; list of industrial pulmonary carcinogens; asbestos as cocarcinogen with tobacco; mesothelioma).

Coverage note: The corpus covers occupational carcinogens richly but in a *scattered* fashion (carcinogen→cancer table in the cancer-prevention chapter; industrial sources in the occupational-lung and heavy-metals chapters; bladder/aromatic-amine and formaldehyde detail in DeVita). The structured **hierarchy-of-controls** prevention framework and the **Percival Pott** eponym are standard, universally accepted occupational-medicine teaching (Harrison confirms the chimney-sweep observation and asbestos-fibre substitution; the formal control hierarchy is not given verbatim).

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Pancreatic carcinoma

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

Definition / Introduction — Pancreatic carcinoma denotes malignant neoplasia of the pancreas, of which **ductal adenocarcinoma (PDAC)** of the exocrine pancreas is by far the commonest and most lethal subtype (overall 5-year survival ≈13%). About **75% arise in the head** and 25% in the body/tail. Its posterior retroperitoneal location and absence of early symptoms mean most patients present late — only 10–20% have resectable disease, >30% present locally advanced and >50% metastatic. This answer covers the presenting clinical features, the serum/tumour markers used in diagnosis and monitoring, and the current surveillance recommendations for high-risk individuals.

Presenting clinical features (history)

- **Painless obstructive jaundice** — the classic presentation of a **head-of-gland** tumour obstructing the distal common bile duct; clinically visible once bilirubin >2 mg/dL, accompanied by dark urine, **pale/clay-coloured stools** and **pruritus** (bile-salt deposition). Jaundice is present in ~75% of periampullary tumours.
- **Abdominal pain** (~40–70%) — typically dull **mid-epigastric "boring" pain radiating to the back** from retroperitoneal invasion of the splanchnic (coeliac) nerve plexus; exacerbated by eating or lying flat and relieved by sitting forward (the latter often signifies extrapancreatic, inoperable spread).
- **Weight loss and cachexia** (~50%) with loss of muscle mass; **≥5% weight loss** in the year preceding diagnosis occurs in ~75% of patients.

- **New-onset or unexpectedly worsening diabetes mellitus** (type 3c), often with concomitant weight loss, or an unexplained rise in HbA1c in the preceding 1–2 years — may herald the cancer (new diabetes after age 45 is a recognised clue).
- **Steatorrhoea / malabsorption** (~15%) from exocrine insufficiency and pancreatic-duct obstruction — bulky, malodorous, greasy stools.
- **Fatigue (~30%), pruritus (~30%), anorexia,** and **new-onset depression (~40%)** — the depression association, though reported, remains debated.
- **Acute pancreatitis** without an alternative cause, especially in patients ≥40 years, may occasionally be the first presentation.

Eponymous and examination signs

Sign	Finding	Significance
Courvoisier's sign	Palpable, non-tender, distended gallbladder with painless jaundice	Suggests malignant distal biliary obstruction (vs stone disease); accurate ~50% of the time
Trousseau's syndrome/sign	Migratory superficial thrombophlebitis ± DVT/PE and arterial thrombi	Reflects the cancer-associated **hypercoagulable state**
Virchow's node	Palpable **left supraclavicular** lymph node (thoracic duct drainage)	Sign of advanced/metastatic disease
Sister Mary Joseph's nodule	Subcutaneous **periumbilical** metastatic nodule	Indicates peritoneal metastasis
Blumer's shelf / ascites / hepatomegaly	Peritoneal & hepatic spread	Late, incurable disease

- Other late signs: a hard fixed epigastric mass, splenomegaly or gastric varices (splenic vein occlusion), and silvery stools (combined biliary obstruction + ampullary bleeding) in **ampulla of Vater** tumours.

Serum and tumour markers

- **CA19-9 (carbohydrate antigen 19-9)** — the principal and only FDA-approved serum marker, though **for monitoring, not screening/early detection**.
  - **Biology:** a high-molecular-weight glycolipid that is a **sialylated derivative of the Lewis (a) blood-group antigen**, shed by tumour mucins. **~8–15% of people are Lewis-antigen "non-secretors"** and cannot express CA19-9 → falsely normal levels.
  - **Performance:** sensitivity ~70%, specificity ~87%; **false elevations** occur in biliary obstruction/cholestasis, cholangitis, and acute/chronic pancreatitis — so CA19-9 should ideally be measured **after the bilirubin has normalised**.
  - **Prognostic/monitoring role:** higher pre-operative levels correlate with higher stage and unresectability; a **CA19-9 ≥500 U/mL** (IAP) or ≥1000 U/mL (MD Anderson) defines *biologically borderline* disease; **failure of an elevated level to fall after resection** predicts poor

survival (post-operative CA19-9 ≥180 U/mL: HR ≈3.58 in RTOG 97-04). Falling levels on neoadjuvant therapy indicate response.

- **CEA (carcinoembryonic antigen)** and **CA125** — drawn as baseline adjuncts; **CA125 is especially useful in the Lewis-negative non-secretors** with undetectable CA19-9. Serial trends of all three guide therapeutic decisions.
- **Routine bloods:** mild anaemia, cholestatic liver enzyme pattern (raised conjugated bilirubin, ALP), occasionally raised lipase/amylase, raised HbA1c/glucose. **Plasma chromogranin A** is elevated in pancreatic neuroendocrine tumours (a differential), but is falsely raised by PPIs.
- Emerging "liquid biopsy" markers (ctDNA, cell-free DNA methylation, circulating tumour cells) are investigational and not yet standard.

Diagnostic workup (for completeness)

- **Multiphase (pancreatic-protocol) contrast-enhanced CT** is the first-line imaging — defines the tumour, vascular (SMA/SMV/portal/coeliac/hepatic) relationships, resectability and metastases; **EUS** is more sensitive for small tumours and guides biopsy.
- **MRI/MRCP** is an alternative; **PET-CT** detects occult metastases but is not routine staging.
- **Tissue diagnosis** by **EUS-guided FNA/core biopsy** (sensitivity ~90%) — also enables molecular profiling (KRAS, microsatellite/MMR status, BRCA/PALB2).
- **Staging** uses the AJCC 8th-edition **TNM** system; disease is grouped as resectable, borderline resectable, locally advanced (unresectable) and metastatic.

Surveillance / screening recommendations

- **Average-risk (general) population: do NOT screen** — low prevalence makes CA19-9/imaging screening inefficient (unacceptable false-positive rate); the **USPSTF recommends against** population screening.
- **High-risk individuals warrant surveillance** (per the International **Cancer of the Pancreas Screening — CAPS — Consortium**). Eligible groups:
  - **Hereditary syndromes regardless of family history:** *Peutz-Jeghers syndrome* (STK11/LKB1), *familial atypical multiple-mole melanoma* (p16/CDKN2A), and *hereditary pancreatitis* (PRSS1).
  - **Germline pathogenic-variant carriers** in **ATM, BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6 or TP53** *plus* at least one affected first- or second-degree relative.
  - **Familial pancreatic cancer** — kindreds with ≥1 first-degree and ≥1 additional relative with PDAC.
- **Modality: annual surveillance** alternating/combining **endoscopic ultrasound (EUS) and MRI/MRCP** (low radiation, detect cystic precursors and small solid lesions). Enrolment on a prospective registry with genetic counselling is advised.
- **Age to start:** generally **age 50**, *or* **10 years before** the youngest affected relative's age at diagnosis; earlier in selected syndromes — **age 40** for *CDKN2A* or *PRSS1* carriers, **age 35** for *Peutz-Jeghers syndrome*, and **within ~20 years of onset** of hereditary pancreatitis.

- **Risk magnitude (justifies surveillance):** one first-degree relative ↑ risk ~4.6-fold, two ~6.4-fold, ≥3 ~32-fold; syndromic fold-risks — Peutz-Jeghers 76–140×, hereditary pancreatitis ~53×, FAMMM/p16 15–22×, Lynch 9–36×, ATM ~6×, BRCA2 3.5–10×.
- **Cystic-lesion surveillance:** incidental cysts ≤2 cm are low-risk — MRI at 1 year then every 2 years; **EUS-FNA** if a cyst reaches ≥2 cm or develops high-risk features. **Main-duct IPMNs** and **mucinous cystic neoplasms** are resected; branch-duct IPMNs with "worrisome features" (cyst ≥3 cm, mural nodule, main-duct dilatation, raised CA19-9) need closer EUS evaluation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Pancreas anatomy and tumour spread:** Draw the pancreas (head with uncinate process, neck, body, tail) crossing the L2 vertebra, labelling **common bile duct, ampulla of Vater, duodenal C-loop, superior mesenteric artery (SMA), superior mesenteric vein (SMV)–portal vein confluence, coeliac axis, splenic vessels**; show a head tumour obstructing the CBD (jaundice) and arrows to **Virchow's (left supraclavicular) node** and **Sister Mary Joseph's (periumbilical) nodule**.
- **Diagram 2 — CA19-9 biology/utility box:** Label "**sialylated Lewis(a) antigen**," "Lewis-negative non-secretors (8–15%) → false-normal," "false-high in cholestasis/pancreatitis," and the monitoring cut-offs (≥500/≥1000 U/mL = biologically borderline; rising post-op = poor prognosis).

Clinical / Diagnostic significance

- **Painless jaundice + Courvoisier-positive gallbladder** in an older patient should prompt urgent imaging for periampullary/pancreatic-head cancer.
- **CA19-9 is a monitoring and prognostic tool, not a screening test** — always interpret against bilirubin and Lewis status; use **CEA/CA125** when CA19-9 is uninformative.
- **New-onset diabetes with weight loss after age 45–50** is a recognised early clue — consider occult PDAC.
- **Trousseau's syndrome** mandates anticoagulation (LMWH or a DOAC) and should trigger an occult-malignancy search.
- Identifying a **BRCA1/2 or PALB2** germline variant changes management (PARP inhibitor + platinum sensitivity) and triggers family cascade testing and surveillance.

High-yield exam pointers

- **PDAC = commonest, most lethal pancreatic cancer; 75% in head; KRAS mutated in 90–95%** (also CDKN2A >90%, TP53 ~75%, SMAD4 ~50%).
- **Classic triad to write:** painless obstructive jaundice + Courvoisier-positive gallbladder + epigastric pain radiating to back.
- **Four eponyms:** Courvoisier (gallbladder), Trousseau (migratory thrombophlebitis), Virchow (L supraclavicular node), Sister Mary Joseph (umbilical nodule).
- **CA19-9 = sialylated Lewis(a) antigen;** ~8–15% Lewis-negative non-secretors give false-normal values; raised by cholestasis/pancreatitis; sensitivity ~70%, specificity ~87%.
- **No screening in average-risk population (USPSTF against).**

- **High-risk surveillance = annual EUS + MRI** from age 50 (or 10 years before youngest affected relative); earlier in CDKN2A/PRSS1 (40), Peutz-Jeghers (35).
- **Diagnosis:** pancreatic-protocol CT + EUS-FNA; **stage by AJCC 8th-edition TNM.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Pancreatic Cancer" (clinical features, eponymous signs, CA19-9/CEA/CA125 serum markers, germline syndromes and fold-risks, high-risk MRI/EUS screening).
- **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — "Cancer of the Pancreas" (presenting-symptom frequencies, CA19-9 biology and prognostic cut-offs, CAPS Consortium screening eligibility, gene panel and start ages, biological/conditional staging).
- **CMDT 2026** — "Carcinoma of the Pancreas & Ampulla of Vater" (CA19-9 sensitivity/specificity, current high-risk surveillance schedule and start ages, cystic-lesion surveillance).

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Vitamin K-dependent clotting factors and anticoagulants

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — The **vitamin K-dependent factors** are a group of plasma proteins whose biological activity requires post-translational **γ-carboxylation** of glutamic acid residues, a reaction for which **vitamin K** is an obligatory cofactor. They comprise the procoagulant zymogens **factors II (prothrombin), VII, IX and X** and the natural anticoagulants **protein C and protein S** (plus protein Z and the non-haemostatic Gla proteins of bone, kidney, lung and placenta). γ-Carboxylation confers the ability to bind **calcium** and assemble on **anionic phospholipid membranes** — without it these proteins are inert. This single biochemical step is the pharmacological target of **vitamin K antagonists (warfarin)**, and it explains the wider impact of all anticoagulant classes on haemostasis.

The vitamin K-dependent factors and the carboxylation reaction

- **Procoagulant factors: II (prothrombin), VII, IX, X** — easily recalled by the mnemonic *"1972"* (factors **IX, VII, X, II**).
- **Anticoagulant (regulatory) proteins: Protein C** and its cofactor **Protein S**; also **Protein Z**.
- **Non-coagulation Gla proteins:** osteocalcin (bone) and matrix Gla protein — Harrison notes vitamin K–dependent proteins also occur in bone, lung, kidney and placenta.
- **Mechanism:** Vitamin K is the cofactor for **γ-glutamyl carboxylase (GGCX)**, which converts **glutamate (Glu) → γ-carboxyglutamic acid (Gla)** on these proteins. The Gla residues chelate **Ca^{2+}**, allowing the factor to dock onto phospholipid surfaces (e.g. activated platelets) and participate in cascade complexes.
- **The vitamin K cycle:** carboxylation oxidises reduced vitamin K (hydroquinone) to **vitamin K epoxide**; **vitamin K epoxide reductase (VKORC1)** regenerates the reduced form so the cofactor can be reused. Dietary vitamin K is often limiting, making this recycling essential.

- **Plasma half-lives** (clinically pivotal): **factor VII shortest (~6 h) → PT prolongs first**; factor X ≈ 24 h; **prothrombin ≈ 72 h** (longest); protein C and protein S are also short-lived.
- **Genetic disease:** inherited mutations of **GGCX** or **VKORC1** cause combined deficiency of *all* vitamin K–dependent factors (activity 1–30%), a congenital bleeding disorder responsive to vitamin K_1 (5–20 mg) or PCC.

Why this matters: PT/INR, deficiency and the newborn

- Because PT is sensitive to **II, VII and X**, vitamin K deficiency or warfarin **prolongs the PT/INR before the aPTT**.
- **Acquired vitamin K deficiency** — causes: poor intake, **broad-spectrum antibiotics** (suppress gut flora), malabsorption/cholestasis (fat-soluble vitamin), chronic liver disease.
- **Distinguishing from liver failure: Factor V is NOT vitamin K–dependent** and is made only in hepatocytes — *low FVII with normal FV = vitamin K deficiency*; *low FV = hepatocellular failure*.
- **Haemorrhagic disease of the newborn** (vitamin K deficiency bleeding) — prevented by routine neonatal vitamin K; neonates also have physiologically low protein C (relevant to warfarin necrosis).
- **Treatment of deficiency:** vitamin K_1 (phytonadione) **10 mg parenteral** restores factors in 8–24 h; the **SC route is avoided** (erratic absorption); for urgent correction give **FFP or 4-factor PCC**.

Impact of anticoagulant medications — overview

Class	Example(s)	Molecular target	Effect on vit-K factors / monitoring
Vitamin K antagonist	**Warfarin**	Inhibits **VKORC1** → ↓ functional II, VII, IX, X, protein C/S	Directly lowers vit-K factors; monitor **PT/INR**
Unfractionated heparin	Heparin	Activates **antithrombin** → inhibits **IIa & Xa (1:1)**	No effect on synthesis; monitor **aPTT** / anti-Xa
LMWH	Enoxaparin, dalteparin	Antithrombin-mediated, **predominantly anti-Xa**	Usually no monitoring; anti-Xa if needed
Pentasaccharide	Fondaparinux	Antithrombin-mediated, **pure anti-Xa**	No routine monitoring
Direct oral – IIa	**Dabigatran**	Reversible **direct thrombin (IIa)** inhibitor	Fixed dose; aPTT/dTT qualitative
Direct oral – Xa	**Rivaroxaban, apixaban, edoxaban**	Reversible **direct factor Xa** inhibitor	Fixed dose; anti-Xa if needed

Warfarin — the vitamin-K-antagonist in depth

- **Mechanism:** a racemic R/S mixture; the **S-enantiomer** is more potent and is metabolised by **CYP2C9**. By blocking **VKOR** it prevents regeneration of reduced vitamin K, so the liver secretes **under-carboxylated, inactive factors (PIVKA)**.
- **Pharmacology:** rapidly/almost completely absorbed, peak ~90 min, **half-life 36–42 h**, **>97% albumin-bound**.

- **Delayed onset:** the antithrombotic effect awaits clearance of pre-formed factors and depends on fall in **factor X and prothrombin** (t½ 24 and 72 h) — hence **overlap with a parenteral anticoagulant (heparin/LMWH/fondaparinux) for ≥5 days** and until INR is therapeutic for ≥2 days.
- **Pharmacogenomics: CYP2C92/3** and **VKORC1** variants increase sensitivity and bleeding risk; FDA labelling advises lower initiation doses in carriers. Starting dose **5–10 mg**.
- **Monitoring: PT standardised as INR** = (patient PT / mean normal PT)^ISI; target **INR 2.0–3.0** for most indications, **2.5–3.5** for mechanical (especially mitral) valves. Diet, drugs and disease alter response → frequent monitoring.
- **Adverse effects:**
  - **Bleeding** (commonest; rises sharply when INR exceeds range).
  - **Warfarin-induced skin necrosis** — 2–5 days after starting, well-demarcated necrotic lesions on thigh/buttock/breast; due to a transient **procoagulant state from rapid fall of short-lived protein C** → microvascular thrombi. **Protein C/S–deficient patients** must be bridged with a parenteral anticoagulant and started low.
  - **Teratogenicity** — crosses the placenta causing **warfarin embryopathy**; contraindicated in pregnancy (but safe in breastfeeding).
- **Reversal:** asymptomatic high INR → **vitamin K 1 mg PO/IV**; serious bleeding → **vitamin K 5–10 mg slow IV plus 4-factor prothrombin complex concentrate** (contains all four vitamin K–dependent procoagulants; normalises INR faster than FFP).

Impact of the other anticoagulant classes

- **Heparin (UFH):** binds **antithrombin** (a serpin), accelerating inhibition of **thrombin and factor Xa equally (anti-Xa:anti-IIa 1:1)**; also releases **TFPI**. Parenteral, monitored by **aPTT/anti-Xa**. Complications: bleeding, **heparin-induced thrombocytopenia (HIT)** — an IgG/PF4 immune prothrombotic syndrome 5–14 days in, more common than with LMWH — and **osteoporosis**. **Reversed fully by protamine sulfate (≈1 mg per 100 U heparin)**.
- **LMWH (enoxaparin):** mean MW ~5000; chains mostly too short to bridge thrombin → **predominant anti-Xa** activity; better bioavailability, less HIT/osteoporosis, renally cleared (caution if CrCl <30). **Protamine gives only partial (~60%) reversal.**
- **Fondaparinux:** synthetic pentasaccharide, **pure antithrombin-mediated anti-Xa**, t½ 17 h, once-daily SC; does **not cause HIT** and is **not reversed by protamine** (contraindicated if CrCl <30).
- **DOACs: dabigatran** (direct **IIa**) and **rivaroxaban/apixaban/edoxaban** (direct **Xa**). Predictable fixed dosing, no routine monitoring, fewer interactions/intracranial bleeds than warfarin (but more GI bleeding at higher doses); cleared partly renally (dabigatran 80%). **Contraindicated in pregnancy.**
- **DOAC reversal: vitamin K and FFP are ineffective**. Specific antidotes — **idarucizumab** (antibody fragment, **5 g IV**) for dabigatran; **andexanet alfa** (decoy Xa) for rivaroxaban/apixaban. If unavailable, **4-factor PCC 25–50 U/kg**. Activated charcoal if ingestion <4 h.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **The vitamin K cycle (Warfarin's site of action):** draw the closed cycle with labels — *Glutamate (Glu)* → (via **γ-glutamyl carboxylase** + O_2 + CO_2) → *γ-Carboxyglutamate (Gla)* on **factors II, VII, IX, X, protein C, protein S**; *Reduced vitamin K (hydroquinone)* → oxidised to *Vitamin K epoxide* → regenerated by **VKORC1 (vitamin K epoxide reductase)**; mark **Warfarin ⊥ blocking VKORC1**.
- **Coagulation cascade with anticoagulant targets:** Tissue factor/VIIa → IXa → **Xa** → **prothrombin (II)** → **thrombin (IIa)** → fibrinogen → fibrin; arrows showing **warfarin ↓ synthesis of II/VII/IX/X**, **heparin–antithrombin on IIa & Xa**, **LMWH/fondaparinux on Xa**, **rivaroxaban/apixaban/edoxaban on Xa**, **dabigatran on IIa**.

Clinical / Diagnostic significance

- **PT/INR** is the bedside readout of vitamin K–dependent procoagulant function — used to diagnose vitamin K deficiency, monitor warfarin and assess hepatic synthetic capacity.
- **Mixing study corrects** in vitamin K deficiency (factor deficiency) but not when an inhibitor is present.
- **FV vs FVII discrimination** separates vitamin K deficiency from liver failure.
- **Bridging principle:** never start warfarin alone in active/high-risk thrombosis (delayed onset + transient hypercoagulability) — overlap with a parenteral agent.
- **Procedure planning:** hold DOACs 1–2 days (longer if renal impairment); reverse warfarin with vitamin K + 4F-PCC for emergency surgery.

High-yield exam pointers

- Vitamin K–dependent factors = **II, VII, IX, X** (procoagulant) + **protein C, protein S** (anticoagulant) — mnemonic "**1972**".
- Vitamin K is cofactor for **γ-glutamyl carboxylase**; recycled by **VKORC1 — warfarin blocks VKORC1**.
- **Factor VII (shortest t½) → PT/INR rises first**; prothrombin (t½ 72 h) longest.
- **Warfarin skin necrosis** = early fall of short-lived **protein C** (worse in protein C/S deficiency).
- **Warfarin is teratogenic; DOACs and warfarin both contraindicated in pregnancy** — LMWH/UFH are the pregnancy anticoagulants.
- Reversal map: **warfarin → vitamin K + 4F-PCC; UFH → protamine (full); LMWH → protamine (partial); dabigatran → idarucizumab; rivaroxaban/apixaban → andexanet alfa**.
- **Low FVII + normal FV = vitamin K deficiency; low FV = liver failure.**
- Target **INR 2.0–3.0** (2.5–3.5 for mechanical valves); always **overlap warfarin and parenteral anticoagulant ≥5 days**.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — *"Coagulation Disorders"* (vitamin K cycle, γ-carboxylation, GGCX/VKORC1, vitamin K deficiency, factor half-lives, FV vs FVII) and *"Antiplatelet, Anticoagulant, and Fibrinolytic Drugs"* (warfarin mechanism/pharmacology/INR/reversal; heparin, LMWH, fondaparinux; DOACs and their antidotes).
- CMDT 2026 — *"Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy"* (vitamin K deficiency management, phytonadione dosing, protamine neutralisation, DOAC perioperative handling).
- Coverage note: The spec-listed specialty text *DeVita's Cancer Principles & Practice* does not substantively cover this coagulation/anticoagulation topic (only a tangential note that progestational agents raise plasma warfarin levels); depth here derives from Harrison and CMDT. Protein Z, osteocalcin/matrix Gla protein, the "1972" mnemonic, PIVKA and protamine 1 mg/100 U are standard textbook haematology included for completeness.

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Dermatology & psychiatry

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Bipolar disorder

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

Definition / Introduction — Bipolar disorder is a chronic, recurrent **mood disorder** characterised by unpredictable swings of mood, energy and activity between **mania (or hypomania)** at one pole and **depression** at the other, separated by periods of relative euthymia. It is a *major affective (mood) disorder* distinguished from major depressive disorder by the presence, current or past, of at least one **manic or hypomanic episode**. It affects ~1.5% of the population, has a strong genetic loading (monozygotic concordance approaching 80%), typically begins between 20–30 years of age, and carries a very high lifetime risk of suicide and psychosocial disability.

Epidemiology and classification (Bipolar spectrum)

- **Prevalence:** Bipolar I ~1.0–1.5% (lifetime ~3.3% and Bipolar II ~1.1% in the NESARC survey); cross-national bipolar *spectrum* ~2.4%. Cyclothymic disorder ~0.4–2.5%.
- **Onset:** typically ~20 years (often late adolescence); men tend to have onset ~4–5 years earlier and more **manic** episodes, women more **depressive** episodes and rapid cycling.
- **Sex ratio:** overall ~1:1 (unlike MDD which is ~2:1 female), but women predominate in Bipolar II, mixed/dysphoric mania and rapid cycling; pure (unipolar) mania is commoner in men.

Subtype	Defining requirement	Key feature
Bipolar I	≥1 lifetime **manic episode** (≥1 week, or any duration if hospitalised)	Depressive/hypomanic episodes usual but not required

Subtype	Defining requirement	Key feature
Bipolar II	≥1 **hypomanic episode** + ≥1 **major depressive episode**; *never* a full manic episode	Depression-predominant; high suicide/comorbidity risk
Cyclothymic disorder	≥2 years (≥1 year in children) of fluctuating hypomanic and depressive symptoms that *never* meet full episode criteria	Chronic, temperamental; 15–50% convert to Bipolar I/II
Substance/medication-induced & due to another medical condition	Manic/hypomanic symptoms attributable to a drug or organic cause	Secondary mania
Other specified (subthreshold)	Bipolar-like phenomena, e.g. short-duration hypomania	Bipolar spectrum

Clinical features (episode definitions)

- **Manic episode (Bipolar I):** a distinct period of abnormally **elevated, expansive or irritable mood** *with* persistently increased goal-directed activity/energy, lasting **≥1 week** (or any duration if hospitalisation is required), causing **marked functional impairment, hospitalisation, or psychotic features**. DSM-5-TR requires **≥3 (or ≥4 if mood only irritable)** of: inflated self-esteem/**grandiosity**; **decreased need for sleep** (rested after 3 h); pressured/over-talkativeness; **flight of ideas/racing thoughts**; distractibility; increased goal-directed activity or **psychomotor agitation**; and excessive involvement in high-risk pleasurable activities (buying sprees, sexual indiscretions, foolish investments). Severe mania may include **delusions and paranoia indistinguishable from schizophrenia**.
- **Hypomanic episode (Bipolar II):** same symptom list, lasting **≥4 consecutive days**, an *unequivocal change in functioning observable by others*, but **NOT severe enough to cause marked impairment or hospitalisation, and no psychotic features** (psychosis automatically makes the episode manic).
- **Major depressive episode:** depressed mood/anhedonia ≥2 weeks with ≥5 of 9 symptoms (sleep/appetite/weight change, fatigue, worthlessness/guilt, poor concentration, psychomotor change, suicidal ideation). Depressive phases dominate disability and suicide risk.
- **Mixed states:** about **one-half** of patients present not with euphoria but with a mixture of **psychomotor agitation/activation plus dysphoria, anxiety and irritability** — difficult to distinguish from agitated depression and carrying high suicide risk.
- **Rapid cycling: ≥4 mood episodes (mania, hypomania or depression) in one year**; occurs in ~15% of patients, mostly women; linked to underlying **thyroid dysfunction** or **iatrogenic antidepressant** exposure.
- **Course:** untreated episodes last weeks to 8–12 months; ~half have sustained occupational/psychosocial impairment, depressive phases being more disabling than mania.

Etiology and pathophysiology

- **Genetic:** strongest of the psychiatric disorders — monozygotic concordance **~80%**; a first-degree relative raises risk ~**10-fold**. Replicated risk loci include the L-type **calcium channel α-subunit**

CACNA1C, teneurin **ODZ4 (TENM4)**, ankyrin-3 (**ANK3**), neurocan (**NCAN**) and **TRANK1**; common variants individually small but collectively account for ~25% of heritability, with shared loci (pleiotropy) overlapping schizophrenia and autism.

- **Neurobiology:** evidence for **circadian rhythm dysregulation**, **calcium dysregulation**, oxidative stress, and mitochondrial/microRNA/endoplasmic-reticulum abnormalities; MRI shows grey-matter thinning in frontal, temporal and parietal cortex.
- **Precipitants:** stressful life events, sleep deprivation and circadian disruption can trigger episodes; the link to acute stressors weakens as the number of prior episodes increases (kindling). Comorbid **alcohol/substance use** is common.

Differential diagnosis and recognising "hidden" bipolarity

- **Secondary mania** must be excluded: stimulant/sympathomimetic drugs, **hyperthyroidism**, AIDS, **Huntington's** and **Wilson's disease**, frontotemporal dementia, and **cerebrovascular accidents**; corticosteroids and antidepressants can also induce mania.
- Recognising bipolarity in a patient presenting *only* with depression is **essential**, because antidepressants may be contraindicated and can precipitate a **manic switch or accelerate cycling**. Features predictive of bipolar (vs unipolar) depression (Kaplan/Akiskal): **early age at onset**, psychotic depression before 25 years, postpartum depression (especially with psychotic features), **rapid onset/offset short (<3-month) episodes**, recurrent depression (>5 episodes), marked **psychomotor retardation**, **atypical/reverse vegetative** features (hypersomnia, weight gain), **seasonality**, **bipolar family history**, cyclothymic/hyperthymic temperament, **antidepressant-induced hypomania**, and **repeated loss of antidepressant efficacy** after initial response.

Management

General principles: confirm the diagnosis and stage (acute mania, bipolar depression, or maintenance); ensure safety (suicide/violence risk, hospitalisation for severe mania); withdraw antidepressants/stimulants; treat comorbid thyroid and substance use; **psychoeducation, adherence support and social-rhythm therapy** are integral.

Acute mania

- **Lithium carbonate** — mainstay; response **70–80%**, effect in 1–2 weeks. Start 300 mg bid/tid, titrate to a **therapeutic level 0.8–1.2 mEq/L**.
- **Valproic acid/divalproex** — first-line, *preferred* for **rapid-cycling and mixed/dysphoric mania**; level **50–125 µg/mL**.
- **Carbamazepine** (4–12 µg/mL; 800–1600 mg/day) / **oxcarbazepine** (off-label, safer hepatic profile).
- **Second-generation antipsychotics** (FDA-approved for acute mania): **aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone**; injectable olanzapine/haloperidol for behavioural emergency.
- **Adjuncts** for agitation/insomnia until mood stabiliser acts: lorazepam 1–2 mg or clonazepam 0.5–1 mg.

Bipolar depression — quetiapine, lurasidone, cariprazine, lumateperone, and olanzapine–fluoxetine (Symbyax); **lamotrigine** as adjunct/monotherapy. Antidepressant monotherapy is avoided (switch risk).

Maintenance / prophylaxis — required because of the recurrent course. A sustained **lithium level ≥0.8 mEq/L** gives optimal prophylaxis and uniquely **reduces suicide risk**. **Quetiapine XR, olanzapine, risperidone and lamotrigine** are approved as maintenance monotherapy (lamotrigine especially prevents depressive relapse but is *not* effective in acute mania). Combinations are often needed; antidepressants are generally avoided in maintenance.

Mood stabiliser	Therapeutic level	Key toxicities / cautions
Lithium	0.8–1.2 mEq/L (acute); 0.6–1.0 maintenance	Fine tremor, polyuria/polydipsia (nephrogenic DI), **hypothyroidism/goitre**, weight gain, hypercalcaemia, leukocytosis; toxicity >2 mEq/L (ataxia, dysarthria, myoclonus, seizures, coma) → **haemodialysis**; levels ↑ by thiazides, NSAIDs, tetracyclines, dehydration
Valproate	50–125 µg/mL	Weight gain, tremor, alopecia; rare **hepatotoxicity, pancreatitis**; **teratogenic (neural-tube defects)**
Carbamazepine	4–12 µg/mL	Sedation, hyponatraemia (SIADH), agranulocytosis, **Stevens-Johnson** (screen **HLA-B*1502** Han Chinese, HLA-A*3101 N-Europeans); hepatic enzyme inducer
Lamotrigine	(titrate slowly from 25 mg/d)	**Stevens-Johnson syndrome/TEN** — any rash needs review

Lithium pre-treatment work-up: CBC, **T4/TSH**, urea/creatinine and electrolytes, urinalysis, and **ECG** (>45 y or cardiac history); draw levels **12 h post-dose**; monitor thyroid and renal function 4–6 monthly. **Electroconvulsive therapy** is effective for severe, refractory, psychotic, catatonic or pregnant cases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Mood-vs-time (life-chart) graph:** horizontal euthymia baseline; plot peaks above for **Mania (Bipolar I)** and smaller peaks for **Hypomania (Bipolar II)**; troughs below for **Major depression**; small ripples for **Cyclothymia**; mark a **mixed episode** and a **rapid-cycling** segment (≥4 episodes/year). Labels: *Mania, Hypomania, Euthymia, Major depressive episode, Mixed state, Rapid cycling, ≥1 week (mania), ≥4 days (hypomania), ≥2 weeks (depression).*
- **Treatment-stage box diagram:** three boxes — *Acute mania* (Lithium / Valproate / SGA + benzodiazepine), *Bipolar depression* (Quetiapine / Lurasidone / Lamotrigine / Olanzapine-fluoxetine), *Maintenance* (Lithium ≥0.8 mEq/L — reduces suicide; avoid antidepressants).

Clinical / Diagnostic significance

- **Suicide:** risk is **state-dependent** — highest during severe depressive and **mixed/dysphoric** episodes, very low in euphoric mania; **lithium** is the only mood stabiliser proven to reduce suicide.

- **Misdiagnosis as unipolar depression** delays appropriate treatment and risks antidepressant-induced switching/cycle acceleration — always screen a depressed patient for *past hypomania*.
- **Organic screen** in new-onset mania: TFTs, drug/toxicology screen, neuroimaging, and consider Wilson's/Huntington's/HIV when atypical or late-onset.
- **Lithium monitoring is mandatory** — narrow therapeutic index; counsel on hydration, NSAID/diuretic interactions, thyroid and renal surveillance; choose **valproate/lamotrigine alternatives** (with contraception advice) in women of child-bearing potential because of teratogenicity.
- High **medical comorbidity** (cardiovascular disease, diabetes, substance use) elevates mortality independent of suicide.

High-yield exam pointers

- **Bipolar I = ≥1 manic episode (≥1 week); Bipolar II = hypomania (≥4 days) + major depression, never mania.**
- **Mania needs ≥3 symptoms (≥4 if irritable)** — mnemonic **DIGFAST** (Distractibility, Indiscretion, Grandiosity, Flight of ideas, Activity↑, Sleep↓, Talkativeness).
- **Hypomania:** no marked impairment, no psychosis, no hospitalisation; psychosis ⇒ episode is *manic* by definition.
- **Rapid cycling = ≥4 episodes/year** (~15%, mostly women) — favour **valproate**; check thyroid; stop antidepressants.
- **Monozygotic concordance ~80%**; risk genes **CACNA1C, ANK3, ODZ4, NCAN, TRANK1**; first-degree relative ↑ risk ~10×.
- **Lithium** acute level **0.8–1.2 mEq/L** (response 70–80%); toxicity **>2 mEq/L** → haemodialysis; thiazides/NSAIDs raise levels; causes hypothyroidism and nephrogenic DI.
- **Lamotrigine** prevents depressive relapse but is **ineffective in acute mania** and risks **Stevens-Johnson syndrome**.
- **Avoid antidepressant monotherapy** — manic switch and cycle acceleration.
- **Cyclothymia** = ≥2 years subthreshold hypomanic + depressive symptoms; 15–50% progress to Bipolar I/II.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Psychiatric Disorders" (Mood Disorders: Bipolar Disorder; Table 463-8 Criteria for Bipolar I Disorder; Table 463-9 Clinical Pharmacology of Mood Stabilizers).
- **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — Mood Disorders: epidemiology/correlates and "Features of a Depressive Episode Predictive of Bipolar Disorder" (Akiskal); Pharmacologic Treatment of Bipolar Disorders.
- **DSM-5-TR** — Bipolar and Related Disorders (Bipolar I, Bipolar II, Cyclothymic Disorder criteria).
- **CMDT 2026** — "Psychiatric Disorders": Treatment of Bipolar Disorder — lithium, valproate, carbamazepine, lamotrigine and antipsychotic regimens, dosing and monitoring.

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Delirium tremens

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Delirium tremens* (DTs) is the most severe and life-threatening expression of the **alcohol withdrawal syndrome**, defined as a **severe, agitated delirium** (mental confusion, fluctuating consciousness and disorientation) accompanied by a coarse tremor and marked **autonomic hyperactivity** (tachycardia, hypertension, hyperthermia, diaphoresis), occurring when blood alcohol falls abruptly in a chronic heavy drinker. It complicates roughly **1% of individuals in withdrawal** (Harrison; <5% in Kaplan; <10% develop "dramatic" withdrawal in DSM-5-TR), typically appears **48–72 h after the last drink**, and is a **medical emergency** with an untreated mortality up to ~5%. By DSM-5-TR it requires the patient to satisfy criteria for **both delirium AND alcohol withdrawal** (alcohol withdrawal delirium, F10.231).

Pathophysiology (brief, to anchor the answer)

- Chronic ethanol is a CNS depressant that **enhances inhibitory GABA-A** tone and **suppresses excitatory NMDA-glutamate** transmission. The brain adapts by **down-regulating GABA-A and up-regulating NMDA** receptors.
- Abrupt cessation removes the depressant → unopposed **glutamatergic/adrenergic hyperexcitability** → tremor, seizures, autonomic storm and, at its extreme, delirium.
- Additional drivers: **low thiamine**, hypomagnesaemia, hypokalaemia, dehydration and intercurrent illness, all of which lower the threshold for DTs.

Spectrum and time-course of alcohol withdrawal

Withdrawal is a continuum; DTs sits at the severe end. Knowing the **temporal sequence** is high-yield and is best shown as a timeline.

Syndrome	Typical onset after last drink	Key features
Minor (early) withdrawal / tremulousness	**6–12 h** (Harrison 5–10 h; CMDT 6–36 h)	Tremor ("shakes"), anxiety, insomnia, nausea/vomiting, tachycardia, sweating; intact sensorium
Withdrawal seizures ("rum fits")	**8–48 h**, peak ~day 2	Generalised tonic-clonic, brief, usually self-limiting; ~1–3% of patients
Alcoholic hallucinosis	**12–48 h**	Visual/tactile (± auditory) hallucinations with a **clear sensorium** and intact orientation — distinguishes it from DTs
Delirium tremens	**48–72 h** (may appear up to **7–10 days** later)	Agitated, fluctuating delirium + autonomic storm; lasts 3–5 days

- Minor symptoms peak on day 2–3 and improve by day 4–5; a **protracted** abstinence syndrome (anxiety, insomnia, autonomic lability) may linger **3–6 months**.
- DTs develops in ~**50%** of patients who have had a withdrawal seizure, but **can occur without a preceding seizure**.

Clinical features of delirium tremens

- **Delirium (core):** acute onset over hours-to-days, **fluctuating** course, **inattention**, disorientation to time/place/person, impaired short-term memory, disorganised thinking; typically **hyperactive** form with agitation, but can fluctuate.
- **Perceptual disturbance:** vivid, frightening **visual hallucinations** (classically crawling insects/snakes — *Lilliputian/zoopsia*), tactile (*formication*), less often auditory; **sensory hyperacuity**.
- **Coarse tremor** of hands and whole body, psychomotor agitation, picking/restlessness.
- **Autonomic hyperactivity (hallmark):** marked **tachycardia, hypertension, fever, profuse diaphoresis**, mydriasis, tachypnoea.
- **Metabolic/complications:** dehydration, **hypokalaemia, hypomagnesaemia**, hypophosphataemia, cardiac **arrhythmias**, rhabdomyolysis, aspiration, seizures and, if untreated, **cardiovascular collapse and death**.
- Often **unmasked in a hospitalised patient** admitted for an unrelated problem (trauma, surgery, sepsis) on day 2–3 — DTs should be suspected in **any heavy drinker with unexplained delirium**.

Diagnosis

DTs is essentially a **clinical diagnosis** in a chronic drinker with the typical temporal profile; the key task is to **confirm withdrawal AND exclude mimics**.

- **DSM-5-TR alcohol withdrawal criteria:** (A) cessation/reduction of heavy, prolonged alcohol use; (B) **≥2 of** — autonomic hyperactivity (sweating/pulse >100), increased hand tremor, insomnia, nausea/vomiting, **transient visual/tactile/auditory hallucinations or illusions**, psychomotor agitation, anxiety, **generalised tonic-clonic seizures**; (C) clinically significant distress/impairment; (D) not due to another condition. *Specifier:* "**with perceptual disturbances**" when hallucinations/illusions occur with intact reality testing.

- **DSM-5-TR delirium criteria (must also be met for DTs):** (A) disturbance of **attention and awareness**; (B) develops over hours-days, **fluctuates**; (C) additional cognitive disturbance (memory, orientation, perception); (D) not explained by another neurocognitive disorder/coma; (E) caused by a medical condition or **substance withdrawal**.
- **Severity scoring — CIWA-Ar** (Clinical Institute Withdrawal Assessment for Alcohol, revised): 10 items — nausea/vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile, auditory and visual disturbances, headache, and **orientation/clouding of sensorium**; **maximum 67**. Score **<8** = minimal; **8–15** mild; **16–20** moderate; **>20** severe / impending DTs. Drives **symptom-triggered** dosing.
- **Risk stratification — PAWSS** (Prediction of Alcohol Withdrawal Severity Scale): score **≥4** predicts complicated withdrawal and the need for inpatient prophylaxis.
- **Investigations:** CBC, **electrolytes incl. K^+, Mg^{2+}, Ca^{2+}, phosphate**, glucose (bedside), renal and **liver biochemistry**, amylase/lipase, blood alcohol level, **urine toxicology** (co-ingestants), ECG; **CT head** if focal signs, head trauma, atypical/late or first seizure, or failure to improve — to exclude **subdural haematoma**.
- **Differential diagnosis:** sedative-hypnotic/benzodiazepine withdrawal, **Wernicke encephalopathy**, hepatic encephalopathy, sepsis/meningoencephalitis, hypoglycaemia, electrolyte derangement, hypoxia, drug intoxication (anticholinergic, stimulant, serotonin syndrome), thyroid storm, non-convulsive status, and **subdural haematoma**. *Alcoholic hallucinosis* (clear sensorium) and *withdrawal seizures* are part of the same spectrum but are distinct entities.

Management

DTs is an emergency best managed in an **ICU/high-dependency** setting with close monitoring; it tends to run a **3–5 day** course regardless of therapy, so the aim is to **control agitation/autonomic drive, prevent injury and treat reversible contributors**.

- **General/supportive:** ICU admission, continuous cardiac and **pulse-oximetry** monitoring, quiet well-lit room, reorientation, fall/aspiration precautions, treat the **precipitating illness** (infection, GI bleed, pancreatitis, trauma).
- **Fluids & electrolytes:** correct dehydration; **replace Mg^{2+}, K^+, phosphate**; treat hypoglycaemia. (In uncomplicated withdrawal patients are often normo/over-hydrated — give IV fluids only when indicated.)
- **Thiamine FIRST: thiamine 100 mg IV** (high-dose, e.g. 500 mg IV TDS if Wernicke suspected) **before any glucose** to prevent precipitating **Wernicke encephalopathy/Korsakoff**; add multivitamins and folate. *Caine criteria* (≥2 of: dietary deficiency, oculomotor abnormality, cerebellar signs, altered mentation) prompt empirical Wernicke treatment.
- **Benzodiazepines — mainstay** (only proven agents to prevent/treat DTs; they reduce mortality, seizures and agitation):
  - **Long-acting, self-tapering** agents preferred — **diazepam or chlordiazepoxide** (smoother course, fewer breakthrough seizures).
  - **Lorazepam or oxazepam** preferred in **significant liver disease/cirrhosis or the elderly** (shorter half-life, no active metabolites, glucuronidated → safer).

- **Symptom-triggered (CIWA-Ar-guided)** dosing reduces total dose and duration vs fixed-dose; established DTs usually needs aggressive **fixed + PRN** loading.
- In severe withdrawal/DTs: e.g. **IV lorazepam 1–2 mg every 15 min** titrated until calm-but-rousable; **high doses** are often required (Harrison cites up to **~800 mg/day chlordiazepoxide**; CMDT caps chlordiazepoxide at 600 mg/24 h). Once stable 24 h, taper dose ~20%/day.
- **Hold** benzodiazepine if over-sedated or **respiratory rate <10/min**; do not bolus lorazepam **>4 mg IV**; use a **single agent**, titrated.

- **Refractory DTs (benzodiazepine-resistant):**
  - Add **phenobarbital** (synergistic at GABA-A) **or** escalate to **propofol** (usually requires **intubation/ventilation** for airway protection).
  - **Dexmedetomidine** (α2-agonist, 0.2–0.7 μg/kg/h) as an **adjunct** to blunt hyperadrenergic output — *not* monotherapy (does not prevent seizures or delirium).
- **Antipsychotics: not** first-line; benzodiazepines are preferred because **antipsychotics lower the seizure threshold**. Low-dose **haloperidol** may be added **only** as an adjunct for severe agitation/hallucinations not controlled by adequate benzodiazepines.
- **Withdrawal seizures:** treated with **adequate benzodiazepines**; **phenytoin is ineffective** and routine anticonvulsants are unnecessary unless there is an independent seizure disorder; manage status epilepticus aggressively.
- **After the acute phase:** screen and treat AUD — **brief intervention/motivational interviewing (FRAMES)**, relapse-prevention CBT, **AA/12-step**, and anti-craving pharmacotherapy (**naltrexone**, **acamprosate**, or supervised **disulfiram**) once withdrawal is complete.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Timeline of alcohol withdrawal** (x-axis = hours/days since last drink; y-axis = severity), labelling each band: *Minor withdrawal/tremulousness 6–12 h*, *Withdrawal seizures 8–48 h (peak 24 h)*, *Alcoholic hallucinosis 12–48 h (clear sensorium)*, *Delirium tremens 48–72 h, up to 7–10 days*.
- **CIWA-Ar "clock" / bar of the 10 domains**, labelled: *Nausea/vomiting, Tremor, Paroxysmal sweats, Anxiety, Agitation, Tactile, Auditory, Visual disturbances, Headache, Orientation/clouding of sensorium* — with cut-offs *<8 minimal · 8–15 mild · 16–20 moderate · >20 severe (ICU)*; **max score 67**.

Clinical / Diagnostic significance

- DTs is a **preventable** cause of death — early identification of at-risk drinkers (PAWSS ≥4, prior DTs/seizures, high intake, intercurrent illness) and **adequate benzodiazepine prophylaxis** sharply reduces progression.
- **Suspect DTs in any chronic drinker with unexplained delirium**, especially on **day 2–3 of an unrelated admission**; missing it (mistaking it for "ICU agitation") is a classic exam trap.
- Always **exclude structural and metabolic mimics** — subdural haematoma, hepatic encephalopathy, Wernicke, sepsis, hypoglycaemia — as several can **coexist** with withdrawal.

- **Thiamine before glucose** and **magnesium/potassium correction** are simple, high-impact, often-forgotten steps.

High-yield exam pointers

- DTs = most severe alcohol withdrawal; **~1% of withdrawals**, onset **48–72 h** (up to 7–10 days), course **3–5 days**, mortality **up to ~5%**.
- Triad to write: **agitated fluctuating delirium + coarse tremor + autonomic storm**, with vivid **visual hallucinations** (insects/snakes).
- **Alcoholic hallucinosis = clear sensorium**; DTs = **clouded/fluctuating** sensorium — the key distinguishing point.
- DSM-5-TR: alcohol withdrawal needs **≥2 features within hours–days**; DTs requires **delirium criteria + withdrawal criteria** together.
- **CIWA-Ar** (10 items, **max 67**, treat at **≥8–10**) guides symptom-triggered therapy; **PAWSS ≥4** flags complicated withdrawal.
- **Benzodiazepines are first-line and the only proven prophylaxis**; long-acting (diazepam/chlordiazepoxide) preferred, **lorazepam/oxazepam in liver disease**.
- Refractory DTs → **phenobarbital / propofol (intubate) / dexmedetomidine adjunct**; **antipsychotics lower seizure threshold** and are adjuncts only.
- **Thiamine before glucose**; correct **Mg^{2+}/K^{+}**; **phenytoin does not work** for withdrawal seizures.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Alcohol and Alcohol Use Disorders" (withdrawal time-course, DTs ~1% rate and ~5% mortality, benzodiazepine dosing incl. chlordiazepoxide/diazepam, high-dose/propofol/dexmedetomidine for DTs, cautions on antipsychotics and phenytoin); "Delirium" (clinical/diagnostic framing).
- **Kaplan & Sadock's Comprehensive Psychiatry (2024)** — alcohol withdrawal, alcohol withdrawal delirium, DSM-5 withdrawal criteria (Table 11.2-6), detoxification and severe-withdrawal/DTs management.
- **DSM-5-TR** — diagnostic criteria for **Alcohol Withdrawal** (with perceptual-disturbances specifier) and **Delirium**; alcohol withdrawal delirium (F10.231).
- **CMDT 2026** — "Substance Use Disorders" (categories/time-course table, CIWA-Ar, PAWSS, symptom-triggered vs fixed dosing, agent choice in liver disease, dexmedetomidine/phenobarbital/propofol, Caine criteria, thiamine-before-glucose).

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Depression

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

Definition / Introduction — Depression is a **mood (affective) disorder** characterised by a sustained disturbance in the regulation of mood, behaviour and affect. A **major depressive episode** is defined as depressed mood and/or loss of interest occurring on a daily basis for a minimum of **2 weeks**, accompanied by neurovegetative and cognitive symptoms causing clinically significant distress or functional impairment. **Major depressive disorder (MDD)** is distinguished from bipolar disorder by the *absence of any manic or hypomanic episode*. In the WHO Global Burden of Disease Study (2019), depression was the **single largest contributor to disability worldwide**, with disability-adjusted life-years (DALYs) having risen 61% since 1990.

Classification of Depressive Disorders (DSM-5-TR)

- **Major depressive disorder (MDD)** — single or recurrent major depressive episode(s); the core unipolar syndrome.
- **Persistent depressive disorder (dysthymia)** — chronic (≥2 years), low-grade depressive symptoms; less severe but functionally equally disabling; ~2% population prevalence. A superimposed major depressive episode produces *"double depression"*.
- **Disruptive mood dysregulation disorder** — chronic irritability and temper outbursts in children (onset before age 10).
- **Premenstrual dysphoric disorder (PMDD)** — affective and somatic symptoms in the late luteal phase.
- **Substance/medication-induced depressive disorder** and **depressive disorder due to another medical condition**.
- *Mood disorders broadly* = (1) depressive (unipolar) disorders, (2) bipolar disorders, and (3) depression secondary to medical illness or substance use.

Aetiology and Pathophysiology

- **Genetic** — monozygotic-twin concordance (**46%**) far exceeds dizygotic (**20%**), with little effect of shared family environment. Early-onset depression (before age 25) is *largely genetic*. Large GWAS have identified several hundred risk loci, some overlapping with other psychiatric disorders (pleiotropy); epigenetic change also contributes.
- **Monoamine hypothesis** — the original observation that **TCAs inhibit serotonin/noradrenaline reuptake** and **MAOIs** are effective antidepressants led to the view that depression reflects a *deficiency of monoamines* (serotonin, noradrenaline, dopamine). This is an over-simplification — therapeutic effects emerge over weeks despite reuptake inhibition within hours, implicating **adaptive changes in second-messenger systems, neurotrophic and transcription factors**.
- **Neuroendocrine (HPA axis)** — increased **cortisol** and **CRH** secretion; **dexamethasone non-suppression**; a **blunted TSH response to TRH**. These normalise with successful treatment.
- **Neurobiological** — altered pro-inflammatory cytokines (raised **IL-6, TNF-α**) and neurotrophins, increased oxidative stress, cellular ageing, **telomere shortening**, mitochondrial dysfunction and gut-microbiome change. A subset shows a small reduction in **hippocampal** volume. The limbic circuitry of mood spans the **prefrontal cortex, amygdala, hippocampus, nucleus accumbens and**

hypothalamus, modulated by monoaminergic projections (noradrenaline from locus coeruleus, serotonin from dorsal raphe, dopamine from VTA).

- **Sleep architecture** — reduced **REM latency**, increased **REM density**, and decreased **stage IV (delta) slow-wave sleep**.
- **Psychosocial** — negative life events (death of a relative, assault, severe relationship problems) precipitate episodes; genes influence sensitivity to these stressors.

Clinical Features and DSM-5-TR Criteria

- **Core**: persistent depressed mood (sad, empty, hopeless) and/or **anhedonia** (loss of interest/pleasure in nearly all activities).
- Diagnosis requires **≥5 of 9 symptoms** over the same 2-week period, at least one being depressed mood OR loss of interest/pleasure — usefully recalled by the mnemonic ***SIG-E-CAPS***:

Letter	Symptom (DSM-5-TR Criterion A)
S — Sleep	Insomnia or hypersomnia nearly every day
I — Interest	Markedly diminished interest/pleasure (anhedonia)
G — Guilt	Feelings of worthlessness or excessive/inappropriate guilt
E — Energy	Fatigue or loss of energy
C — Concentration	Diminished ability to think/concentrate; indecisiveness
A — Appetite	Significant weight/appetite change (>5% body weight/month)
P — Psychomotor	Agitation or retardation (observable by others)
S — Suicidality	Recurrent thoughts of death, suicidal ideation, plan or attempt
(+ depressed mood)	Depressed mood most of the day, nearly every day

- Criteria B–C: symptoms cause **significant distress/impairment** and are **not attributable to a substance or medical condition**; there has **never been a manic/hypomanic episode** (else bipolar).
- *Melancholic* features: profound anhedonia, mood worse in the morning (diurnal variation), early-morning awakening, marked guilt, psychomotor change.
- **Course**: ~15% of the population has a major depressive episode in their lifetime; 6–8% of primary-care outpatients qualify. Onset is usually in early adulthood; **50–60% of first-episode patients have at least one or two recurrences** — the *best predictor of future risk is the number of past episodes*. Depression is **twice as common in women** as in men.
- **Important variants**: *psychotic depression* (mood-congruent delusions/hallucinations), *pseudodementia* (cognitive deficits mimicking dementia in the elderly), and **seasonal affective disorder** (anergy, fatigue, weight gain, hypersomnia, carbohydrate craving; commoner in women; prevalence rises with distance from the equator; responds to light therapy).

Specifiers (DSM-5-TR)

- With **anxious distress**, with **mixed features**, with **melancholic features**, with **atypical features**, with **mood-congruent / mood-incongruent psychotic features**, with **catatonia**, with **peripartum onset**, with **seasonal pattern**.

Differential Diagnosis

- **Bipolar depression** — always screen for past mania/hypomania; antidepressant monotherapy can trigger a switch or cycle acceleration. Red flags for bipolarity: childhood onset, antidepressant treatment failure, atypical features (hypersomnia, weight gain), marked irritability/impulsivity.
- **Grief/bereavement** — predominant affect is *emptiness and loss* occurring in waves ("pangs"), self-esteem preserved; contrast with the persistent low mood, worthlessness and self-loathing of an MDE.
- **Secondary depression (10–15%)** — hypothyroidism, Cushing's, stroke (especially left dorsolateral frontal), Parkinson's disease, dementia, multiple sclerosis, malignancy (pancreatic, oropharyngeal), HIV, hepatitis C; and **drug-induced** (antihypertensives, glucocorticoids, interferon-α, anticonvulsants).
- **Persistent depressive disorder**, adjustment disorder with depressed mood, substance-induced mood disorder.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HPA-axis dysregulation in depression** — vertical cascade: *Hypothalamus* → *CRH* → *Anterior pituitary* → *ACTH* → *Adrenal cortex* → *Cortisol (↑)*; show **loss of negative feedback** with a dashed line and label **"Dexamethasone non-suppression"** and **"blunted TSH response to TRH."**
- **Limbic neural circuitry of mood** — label **Prefrontal cortex (PFC)**, **Amygdala (Amy)**, **Hippocampus (HP)**, **Nucleus accumbens (NAc)**, **Hypothalamus (Hyp)**, with monoaminergic inputs: **Locus coeruleus (noradrenaline)**, **Dorsal raphe (serotonin)** and **VTA (dopamine)**.

Clinical / Diagnostic significance

- **Screening**: validated tools (e.g., PHQ-9); always **directly assess suicide risk** — risk factors include prior attempts, profound hopelessness, concurrent medical illness, substance abuse, social isolation, and co-existing anxiety/panic/agitation. **~4–5% of depressed patients die by suicide**, and most have consulted a physician within 1 month of death.
- **Investigations** to exclude secondary causes: TSH/free T4, electrolytes/calcium, blood glucose, renal/hepatic function, B12, and toxicology where indicated; imaging if focal neurology or atypical late-onset presentation.
- **Comorbidity matters**: depression worsens prognosis in **post-MI/cardiac disease** (reduced heart-rate variability, increased mortality) and in diabetes (mood severity tracks hyperglycaemia). **TCAs are contraindicated** in bundle-branch block and significant cardiovascular disease; **SSRIs are preferred** as they cause no significant ECG change.

- **General management principles**: combine *acute* (induce remission) with *maintenance* (prevent recurrence); 60–70% respond to any adequately dosed drug given for **6–8 weeks**; review response at ~2 months; continue for **6–9 months** after remission; **indefinite maintenance** after ≥2 episodes. Psycho-education, stress reduction and avoiding alcohol are essential.
- **Pharmacotherapy (CMDT/STAR*D approach)**:
  - **First-line: SSRIs** (e.g., sertraline 25→200 mg, escitalopram 10–20 mg) — fewer anticholinergic/cardiac effects; adverse effects: GI upset, insomnia, sexual dysfunction, akathisia and **serotonin syndrome** (myoclonus, agitation, hyperpyrexia, hypertension). Escitalopram is most P450-neutral.
  - **SNRIs** (venlafaxine 75–375 mg, duloxetine 40–60 mg) — useful with comorbid neuropathic pain; monitor BP.
  - **TCAs** — therapeutic dose ~150–200 mg imipramine/amitriptyline (level 150–300 ng/mL); **lethal in overdose (~2 g)**, desipramine carrying the greatest risk — prescribe limited supplies when suicide is a risk.
  - **MAOIs** — effective in **atypical depression** but risk **hypertensive (tyramine) crisis**; transdermal selegiline at 6 mg needs no dietary restriction. Never combine with SSRIs (serotonin syndrome).
  - **Mirtazapine** (α2/5-HT2/5-HT3 blocker; sedation, weight gain) and **bupropion** (noradrenergic-dopaminergic; few sexual effects, lowers seizure threshold).
  - **Treatment-resistant strategies** (STAR*D): switch vs augment with **lithium, liothyronine (thyroid), l-methylfolate, atypical antipsychotics** (aripiprazole, quetiapine-XR, brexpiprazole) or **olanzapine-fluoxetine (Symbyax)**.
- **Non-pharmacological / device therapy**: **ECT** is the most effective treatment, reserved for treatment-resistant, psychotic and delusional depression (remission 60–90% in psychotic depression); **rTMS** and **VNS** are approved for treatment-resistant depression. **Intranasal esketamine / IV ketamine** give rapid (often single-dose) benefit and reduce suicidality. **Brexanolone (IV)** and oral **zuranolone** are neuroactive-steroid options for **postpartum depression**.
- **Psychotherapy**: **cognitive-behavioural therapy (CBT)** and **interpersonal therapy (IPT)** are evidence-based; combined drug + psychotherapy outperforms medication alone.

High-yield exam pointers

- MDE = depressed mood/anhedonia ≥2 weeks + **≥5/9 SIG-E-CAPS** symptoms; **no manic/hypomanic episode** ever (else bipolar).
- Lifetime prevalence ~**15%**; **twice as common in women**; MZ:DZ concordance **46%:20%**.
- Biology: **↑cortisol/CRH, dexamethasone non-suppression, blunted TSH-to-TRH, ↓REM latency, ↑REM density**.
- Always assess **suicide risk**; **~4–5% die by suicide**; the best predictor of recurrence is the **number of past episodes**.
- **SSRIs first-line**; TCAs lethal in overdose; **MAOIs best in atypical depression** (tyramine crisis); SSRI + MAOI → serotonin syndrome.

- **ECT** = most effective and treatment of choice for **psychotic/delusional and treatment-resistant** depression.
- Continue antidepressant **6–9 months** post-remission; **indefinite maintenance after ≥2 episodes**.
- **Postpartum depression** → brexanolone / zuranolone; **seasonal affective disorder** → light therapy; **persistent depressive disorder** = dysthymia (≥2 years).
- Distinguish **grief** (emptiness, in waves, self-esteem preserved) from MDE (persistent worthlessness, self-loathing).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Psychiatric Disorders"* (mood/depressive disorders, DSM-5-TR major depressive episode criteria, antidepressant tables, treatment algorithm) and *"Biology of Psychiatric Disorders"* (monoamine hypothesis, HPA axis, neural circuitry of depression).
- **DSM-5-TR** — classification and specifiers of depressive disorders; major depressive episode criteria.
- **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — depressive disorders classification and epidemiology.
- **CMDT 2026** — *"Psychiatric Disorders"* (current pharmacotherapy, STAR*D augmentation, ECT in psychotic depression, antidepressant dosing).

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Major depressive disorder — pathophysiology and differentials

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

Definition / Introduction — Major depressive disorder (MDD) is a primary mood disorder defined by ≥5 of 9 DSM-5-TR symptoms (at least one being *depressed mood* or *anhedonia*) present nearly every day for ≥2 weeks, causing significant distress/impairment, in the absence of any manic/hypomanic episode and not attributable to a substance, medical illness or psychotic disorder. It is among the largest single contributors to global disability (DALYs). No single lesion or biomarker explains MDD; rather it arises from disturbance of several interacting **neuro-regulatory systems** — monoaminergic, neuroendocrine (HPA, thyroid), glutamate/GABA, neurotrophic, neuro-immune and large-scale limbic circuits. Because depressive syndromes are produced by many drugs and medical diseases, a careful **exclusionary differential diagnosis** is mandatory before the label "MDD" is applied.

Overview of neuro-regulatory systems implicated in MDD

System	Key dysregulation in MDD	Clinical / therapeutic correlate
Monoaminergic (NE, 5-HT, DA)	Altered "fine-tuning" of networks; ↓ or dissociated NE (MHPG), 5-HT (5-HIAA), DA (HVA) signalling	TCAs, SSRIs, SNRIs, MAOIs, bupropion

System	Key dysregulation in MDD	Clinical / therapeutic correlate
HPA axis / stress	↑ CRH → ↑ ACTH → hypercortisolaemia; impaired glucocorticoid feedback (dexamethasone non-suppression)	DST positivity; melancholia; relapse marker
Thyroid / other endocrine	Blunted TSH response to TRH; ↑ basal TSH; ↓ GH response to clonidine	Hypothyroidism mimic; T3 augmentation
Glutamate / GABA / neurosteroid	Extrasynaptic NMDA excitotoxicity; ↓ cortical GABA & SST interneurons; ↓ allopregnanolone	Ketamine/esketamine; brexanolone/zuranolone
Neurotrophic / neuroplasticity	↓ BDNF, ↓ GDNF, ↓ hippocampal neurogenesis, hippocampal volume loss	Delayed (weeks) antidepressant action
Neuro-immune / inflammation	↑ IL-6, TNF-α, CRP; NF-κB/NLRP3; microglial activation; kynurenine/QUIN	Inflammatory subtype; cytokine antagonists
Limbic circuits / networks	Hyperactive amygdala & subgenual Cg25; hypoactive NAc; DMN hyperconnectivity	DBS of Cg25/NAc; rTMS of dlPFC
Sleep / circadian	↓ REM latency, ↑ REM density, ↓ slow-wave (stage IV) sleep	Trait marker; predicts relapse
Genetic / epigenetic	Polygenic; MZ:DZ concordance 46%:20%; DNA-methylation/histone changes	Early-onset = higher heritability

Monoaminergic and neuroendocrine systems

- **Monoamine hypothesis (historical basis):** the depressogenic effect of *reserpine* (a monoamine depleter) and the antidepressant action of agents that raise synaptic monoamines (TCAs inhibit NE/5-HT reuptake; MAOIs inhibit their breakdown) led to the view that depression is a *deficiency of monoamines*. This is now regarded as an oversimplification — antidepressants raise synaptic monoamines within hours yet take **weeks** to act, implicating downstream adaptive changes in second messengers, transcription factors and neurotrophins.
- **Noradrenergic:** cell bodies in the **locus coeruleus (LC)** project diffusely; mediate arousal and the medial-forebrain-bundle reward pathway. NE metabolite = **3-methoxy-4-hydroxyphenylglycol (MHPG)**. There is a subgroup with low MHPG and an overlapping subgroup with elevated/hyper-aroused NE.
- **Serotonergic:** dorsal/median **raphe** project widely; regulate mood, sleep, appetite, libido, aggression and circadian rhythm; metabolite = **5-hydroxyindoleacetic acid (5-HIAA)**, low CSF levels linked to impulsivity/aggression. SSRIs "normalise" amygdala over-reactivity.
- **Dopaminergic: VTA → mesolimbic/mesocortical** pathways subserve reward, motivation and hedonic capacity; metabolite = **homovanillic acid (HVA)**; reduced CSF HVA correlates with severe psychomotor-retarded ("hypodopaminergic") depression and anhedonia.
- **Modern reformulation:** monoamines are now seen as broad **neuromodulators** that "tune" the activity and coupling of large-scale networks; their disturbances may be secondary/compensatory rather than the primary cause.

- **Other neuroendocrine axes:** *Thyroid* — blunted TSH response to TRH (20–30%) and occult hypothyroidism (≈5–10%); *Growth hormone* — blunted GH response to the α2-agonist **clonidine**; *Prolactin* — blunted response to 5-HT agonists.

Stress–HPA axis, neurotrophic, glutamate/GABA and neuro-immune systems

- **HPA axis (the clearest stress–depression link):** stress activates hypothalamic **CRH → pituitary ACTH → adrenal cortisol**. A subset of patients show **hypercortisolaemia** with loss of glucocorticoid feedback, demonstrated by the **dexamethasone suppression test (DST)** — failure of 0.5–2 mg dexamethasone to suppress cortisol (non-suppression) or early "escape". HPA overactivity is seen in ~20–40% of outpatients and ~40–60% of inpatients (especially melancholic/psychotic/older patients), correlates with melancholia, and persistent non-suppression after treatment predicts relapse. Excess glucocorticoids are implicated in **hippocampal atrophy/volume loss**.
- **Neurotrophic/neuroplasticity hypothesis:** chronic stress and glucocorticoids reduce **brain-derived neurotrophic factor (BDNF)** and suppress hippocampal **neurogenesis**; antidepressants (and ECT, rTMS, exercise) raise BDNF and reverse this — accounting for their delayed onset. **GDNF** is also reduced.
- **Glutamate / GABA / neurosteroid:** activation of **synaptic NMDA receptors (GluN2A, neuroprotective)** promotes BDNF, whereas **extrasynaptic NMDA (GluN2B)** activation causes excitotoxicity and suppresses BDNF. Sub-anaesthetic **ketamine / intranasal esketamine** (NMDA antagonists, AMPA-mediated, mTOR-dependent) produce *rapid* (hours) antidepressant effects in treatment-resistant depression. **GABA** is reduced (plasma/CSF/cortex), with loss of **somatostatin-expressing (SST) interneurons**; the neurosteroid **allopregnanolone** (a positive allosteric modulator of GABA-A) is low, the rationale for **brexanolone** and **zuranolone** in peripartum depression.
- **Neuro-inflammation/immune:** a subgroup shows raised **IL-6, TNF-α and CRP** (CRP >3 mg/L in ~30–45%), driven by NF-κB and the **NLRP3 inflammasome**, with **microglial activation**. Cytokines induce **indoleamine-2,3-dioxygenase (IDO)**, shunting tryptophan from serotonin toward neurotoxic **kynurenine/quinolinic acid (QUIN)** (an NMDA agonist). Inflammation preferentially produces **anhedonia, psychomotor slowing and suicidality** via the basal ganglia; therapeutic IFN-α reliably induces MDD in 30–50% of recipients.

Neural circuits, sleep and genetic systems

- **Limbic mood circuit:** dysfunction of the **prefrontal cortex (PFC), anterior cingulate, hippocampus and amygdala**, with monoaminergic input from VTA (DA), LC (NE) and raphe (5-HT). Imaging shows **amygdala hyper-reactivity** to negative stimuli, **reduced nucleus accumbens (NAc)** response to reward, and **hyperactivity of subgenual cingulate (area 25/Cg25)** — the basis for **deep brain stimulation (DBS)** of Cg25 or NAc in refractory cases.
- **Large-scale networks:** depression involves hyperconnectivity of the **default-mode network (DMN)** (rumination/self-focus), impaired **central-executive/cognitive-control network (CEN/CCN)** (poor concentration), aberrant **salience network (SAN)** and reduced **sensorimotor**

network (SMN) activity (psychomotor retardation), all "updated" through the **cortico–striatal–thalamo–cortical (CSTC)** loop.

- **Sleep/circadian:** characteristic **reduced REM latency, increased REM density and decreased slow-wave (stage IV) sleep**, with diurnal mood variation (worse in morning) — partly heritable, trait-like markers.
- **Genetic/epigenetic:** GWAS implicate >100 loci; monozygotic concordance ~46% vs dizygotic ~20%; early-onset depression is most heritable; epigenetic (DNA-methylation, histone) changes mediate stress effects.

Diagnosis and differential diagnoses to exclude before diagnosing MDD

Diagnosis is clinical (DSM-5-TR major depressive episode). Before labelling MDD, exclude conditions across three DSM "gatekeeper" criteria — **Criterion C** (not due to a substance or medical condition), **Criterion D** (not better explained by a psychotic disorder) and **Criterion E** (no past mania/hypomania).

Category	Conditions to exclude	Distinguishing clue
Bipolar spectrum (Criterion E)	Bipolar I / II, cyclothymia, mixed/irritable mania	Any past manic/hypomanic episode → not MDD; childhood onset, antidepressant-induced switch, hypersomnia/weight gain suggest bipolarity
Other depressive disorders	Persistent depressive disorder (dysthymia)/"double depression", premenstrual dysphoric disorder, disruptive mood dysregulation disorder	Chronicity ≥2 yrs (dysthymia); luteal-phase timing (PMDD)
Psychotic disorders (Criterion D)	Schizophrenia, schizoaffective, schizophreniform, delusional disorder	Mood-incongruent psychosis; psychosis ≥2 wks without mood episode (schizoaffective)
Normal reactions	Bereavement/grief, normal sadness, adjustment disorder with depressed mood	Grief = emptiness/loss in waves, self-esteem preserved; sub-threshold severity/duration
Depressive disorder due to a medical condition (Criterion C)	*Endocrine:* hypo-/hyperthyroidism, Cushing, Addison, diabetes; *Neurologic:* stroke (esp. left dorsolateral-frontal — major depression in 1 in 5), Parkinson, dementia, MS, traumatic brain injury, Huntington, partial-complex epilepsy; *Malignancy:* pancreatic & oropharyngeal cancer (40–50%); *Infective:* HIV, hepatitis C; *Other:* chronic fatigue syndrome, fibromyalgia, anaemia/nutritional deficiency	History, examination and targeted labs (TSH, glucose, electrolytes, B12/folate, HIV) reveal a causal medical illness
Substance/ medication-induced (Criterion C)	Reserpine, clonidine, methyldopa, β-blockers, corticosteroids, interferon-α, retinoids (isotretinoin), digitalis, antiparkinsonian drugs, anticonvulsants, disulfiram; alcohol/sedative/opioid use; stimulant (cocaine) withdrawal	Temporal link to drug/withdrawal; resolves on removal

Category	Conditions to exclude	Distinguishing clue
Neurocognitive	Dementia vs depressive **"pseudodementia"**	Pseudodementia: rapid onset, "don't-know" answers, reversible with treatment
Other psychiatric	Anxiety/panic disorder, ADHD, eating disorders, somatic symptom disorder	Co-morbid; diagnose both if full criteria met

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Neurobiology of MDD" composite:** Draw the **HPA axis** (Hypothalamus → CRH → Anterior pituitary → ACTH → Adrenal cortex → Cortisol, with a dashed negative-feedback arrow from cortisol to hippocampus/pituitary marked "impaired feedback → DST non-suppression"). Beside it draw three brainstem monoamine nuclei with arrows to cortex/limbic system — label **Locus coeruleus → NE (MHPG)**, **Raphe nuclei → 5-HT (5-HIAA)**, **VTA → DA (HVA)**. Add boxes for **↓BDNF / ↓neurogenesis**, **↑IL-6/TNF-α/CRP → microglia → kynurenine/QUIN**, and **extrasynaptic NMDA (GluN2B) → excitotoxicity**.
- **Diagram 2 — Limbic mood circuit:** Outline a sagittal brain labelling **Prefrontal cortex (dlPFC)**, **Subgenual cingulate (area 25 / Cg25)**, **Amygdala (hyperactive)**, **Hippocampus (atrophy)** and **Nucleus accumbens / VTA (reward, hypoactive)**; mark **DBS targets = Cg25 and NAc**.

Clinical / Diagnostic significance

- **Screen and confirm criteria:** use validated tools (PHQ-9, Hamilton/Montgomery-Åsberg, QIDS-SR) and always **assess suicide risk directly** (Columbia Suicide Severity Rating Scale); ~4–5% of depressed patients die by suicide.
- **Mandatory medical work-up before diagnosing primary MDD:** TSH/free T4, fasting glucose/HbA1c, electrolytes, calcium, renal/hepatic panel, B12 and folate, FBC, and HIV where relevant; neuroimaging (CT/MRI) for first late-onset episode, focal signs, or psychotic features.
- **Biological tests are research/adjunctive, not diagnostic:** DST, TRH-stimulation and EEG-sleep abnormalities are sensitive markers of biological/melancholic depression but lack specificity.
- **Mechanism-guided therapeutics:** SSRIs/SNRIs first-line; **ketamine/esketamine** for rapid effect and acute suicidality; **brexanolone/zuranolone** for peripartum depression; **ECT, rTMS, VNS, DBS (Cg25/NAc)** for treatment-resistant cases; T3/lithium/atypical-antipsychotic augmentation (STAR*D).

High-yield exam pointers

- MDD requires **≥5/9 symptoms ≥2 weeks**, one being depressed mood or anhedonia — and **no history of mania/hypomania** (Criterion E is the single most important exclusion → rules out bipolar disorder).
- Core neuro-systems: **monoamine, HPA, thyroid, glutamate/GABA, neurotrophic (BDNF), neuro-immune, and limbic networks** — name at least four for full marks.
- Monoamine metabolites: **NE → MHPG, 5-HT → 5-HIAA, DA → HVA.**

- **Dexamethasone non-suppression** = impaired glucocorticoid feedback; hypercortisolaemia → **hippocampal atrophy**.
- **Ketamine/esketamine** = NMDA antagonists with *rapid* antidepressant action; **brexanolone/zuranolone** = GABA-A neurosteroids for postpartum depression.
- Inflammation (**IL-6, TNF-α, CRP**, kynurenine/QUIN) drives an **anhedonia–psychomotor-slowing–suicidality** subtype.
- Sleep signature: **short REM latency, ↑ REM density, ↓ slow-wave sleep.**
- Exclude **bipolar disorder, psychotic disorders, grief/bereavement, dysthymia, drug/substance-induced depression, and medical mimics (hypothyroidism, Cushing, stroke, Parkinson, pancreatic cancer, HIV, B12 deficiency, pseudodementia)**.
- **Left dorsolateral-frontal stroke → major depression in 1 in 5;** pancreatic & oropharyngeal cancers carry 40–50% depression prevalence.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Biology of Psychiatric Disorders" (monoamine/HPA/BDNF/glutamate-ketamine, neuro-inflammation, limbic circuitry, subgenual Cg25/DBS) and "Psychiatric Disorders" (Major Depressive Episode criteria, neuroendocrine/sleep abnormalities, depression in medical illness, treatment).
- **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — "Mood Disorders: Neurobiology" (monoaminergic systems and metabolites, HPA/thyroid/GH axes, DST, glutamate/GABA & neurosteroids, BDNF/GDNF, neuro-immune/kynurenine, functional networks DMN/CEN/SAN/SMN/CSTC, sleep neurophysiology) and "Mood Disorders: Clinical Features".
- **DSM-5-TR** — Major Depressive Disorder diagnostic criteria and Differential Diagnosis (bipolar, psychotic, substance/medication-induced, depressive disorder due to another medical condition, bereavement).
- **CMDT 2026** — "Psychiatric Disorders" (differential diagnosis, mood disorders secondary to illness/medications, suicide assessment, current management/augmentation).

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Pemphigus vulgaris

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

Definition / Introduction — Pemphigus vulgaris (PV) is an autoantibody-mediated, potentially life-threatening **intraepidermal** blistering disease in which IgG autoantibodies against **desmoglein 3** (and desmoglein 1 in mucocutaneous disease) cause loss of keratinocyte cell–cell adhesion (**acantholysis**), producing flaccid blisters and painful erosions of mucosae and skin. Because PV is driven by *pathogenic autoantibodies*, therapy must aim to **suppress autoantibody production**, not merely local inflammation. Before glucocorticoids, mortality was 60–90% (death within 2–5 years); with modern immunosuppression and B-cell–directed therapy mortality is now ~5%, but much of the residual morbidity and mortality arises from **complications of treatment** itself.

Goals, principles and general/supportive measures

- **Goals:** rapidly gain disease control, achieve remission, then maintain remission on the *lowest possible* glucocorticoid dose to minimise iatrogenic harm. Disease extent and response are tracked with validated scores — **PDAI** (Pemphigus Disease Area Index) and **ABSIS** (Autoimmune Bullous Skin disorder Intensity Score) — and by serial anti-Dsg **ELISA** titres, which correlate with activity.
- Start **systemic therapy as early as possible**; a steroid-sparing agent is usually added from the outset because the disease course is long and adjuvants take weeks to act.
- **Supportive care (severe disease):** hospitalise, bed rest, attention to **fluid, electrolyte, protein and nutritional** balance, wound care of denuded skin, and **secondary-infection** surveillance with systemic/topical antibiotics. **Anaesthetic troches** before meals ease painful oral erosions and maintain oral intake.
- **Drug-induced pemphigus:** review and withdraw culprit drugs — thiol-containing agents (**penicillamine, captopril, enalapril**), other ACE inhibitors, β-lactams, piroxicam, immune-checkpoint inhibitors.

Systemic pharmacotherapy — the therapeutic ladder

Drug	Typical dose	Role / notes
Prednisone (oral)	**1 mg/kg/day** (up to 1–2 mg/kg/day; usually 60 mg/day)	Standard first-line; taper once new-blister formation stops
Pulse IV methylprednisolone	**1 g/day over 2–3 h × 3–5 days** (cardiac monitoring)	Severe/rapidly progressive disease
Rituximab (anti-CD20)	1 g on days 1 & 15, *or* 375 mg/m^2 weekly × 4; maintenance 500 mg q6 months	**FDA-approved, first-line** for moderate–severe PV
Azathioprine	**2–4 mg/kg/day** (100–300 mg/day)	Steroid-sparing; **check TPMT** before starting
Mycophenolate mofetil	**2–3 g/day** (1–3 g/day)	Steroid-sparing; less marrow toxicity, more GI upset
Cyclophosphamide	1–3 mg/kg/day PO, or 500–1000 mg/m^2 IV q4 weeks	Potent anti–B-cell; reserved for refractory disease

Drug	Typical dose	Role / notes
IVIg	**2 g/kg** over 3–5 days, repeated monthly	Non-immunosuppressive; steroid-resistant disease
Plasmapheresis / immunoadsorption	1–2 sessions/week initially	Rapidly lowers autoantibody titre; needs concomitant immunosuppression
Methotrexate / cyclosporine	MTX 7.5–20 mg/week; CsA 3–5 mg/kg/day	Second-line; **cyclosporine shown of no added benefit** in a randomised trial

- **Corticosteroids** remain the mainstay for the rapidity of response; the dose is titrated against the *number of new blisters per day* and rate of healing. If no response in 3–7 days, escalate the dose and/or add an adjuvant.
- **Steroid-sparing immunosuppressants** (azathioprine, MMF, cyclophosphamide) added to prednisone achieve earlier control and higher remission rates and permit steroid tapering. In a randomised trial MMF gave faster, more durable responses than placebo when added to corticosteroids; azathioprine and MMF are of broadly comparable efficacy. Once remission is sustained and prednisone is down to 5–10 mg/day, the adjuvant is carefully tapered and stopped.

Rituximab, biologics and refractory-disease options

- **Rituximab** is a chimeric **anti-CD20** monoclonal antibody that depletes $CD20^+$ B cells (sparing plasma cells) and also reduces desmoglein-specific T-cell responses; onset of benefit is ~8–16 weeks and may last 12–18 months. The pivotal **Ritux 3** trial (first-line rituximab + short-course prednisone vs prednisone alone) showed **complete remission off-therapy in ~89% vs 34%**, with a lower cumulative steroid dose and fewer severe adverse events — establishing rituximab as **first-line** therapy (endorsed by international expert and EADV S2 guidelines). Humanised anti-CD20 agents (**obinutuzumab, ofatumumab**) and intralesional rituximab are emerging options.
- **IVIg** acts via **neonatal Fc-receptor (FcRn) blockade** (reducing IgG recycling), anti-idiotypic antibodies and immunomodulation; effective and safe in steroid-resistant PV in a randomised trial.
- **Plasmapheresis / immunoadsorption** physically removes circulating autoantibody for severe, unresponsive disease; **must** be combined with immunosuppression to prevent a rebound autoantibody surge.
- **Novel/targeted: efgartigimod**, an **FcRn inhibitor**, gave early disease control in 28 of 31 PV/PF patients in a phase II trial; **DSG3-CAART** (chimeric autoantibody-receptor T cells targeting Dsg3-specific B cells) received FDA orphan-drug designation in 2020 — both reflect the move toward antigen-specific immunosuppression.
- **Topical/local adjuncts:** superpotent (Class I) topical corticosteroids and intralesional corticosteroids for persistent localised lesions; **topical ciclosporin mouthwash** for refractory oral disease; topical antibiotics for secondary infection. **Dapsone** is an adjunct in mild disease and the drug of choice in IgA pemphigus/pemphigus herpetiformis.

Complications

Complications fall into two groups — those of the **disease** and those of its **treatment**.

Disease-related complications	Treatment-related complications
Secondary bacterial infection of erosions → ***S. aureus* septicaemia** (most frequent cause of death)	**Corticosteroids:** Cushingoid features, osteoporosis/avascular necrosis, diabetes, hypertension, peptic ulcer, cataract, myopathy, psychosis, **adrenal suppression**, opportunistic infection
Fluid, electrolyte and protein loss through denuded skin; impaired barrier/thermoregulation	**Azathioprine:** dose-dependent **myelosuppression**, nausea, hepatotoxicity (worse if low **TPMT**)
Nutritional compromise from painful oral erosions, dysphagia, odynophagia	**Mycophenolate mofetil:** GI toxicity, marrow suppression
Oesophageal/laryngeal/pharyngeal involvement — hoarseness, mucosal cast, stricture risk	**Cyclophosphamide:** haemorrhagic cystitis, **gonadal failure/sterility**, leukopenia, long-term **bladder carcinoma**; chlorambucil → leukaemia risk
Post-inflammatory hyperpigmentation; scarring only at infected/traumatised sites	**Rituximab:** infusion reactions, **hepatitis B reactivation**, **PML**, late-onset neutropenia, infection
Untreated disease is **fatal** (death within ~5 years)	**IVIg:** headache, flu-like illness, hypotension, **anaphylaxis in IgA deficiency**; **Plasmapheresis:** rebound antibody, line sepsis, hypovolaemia

- **Bad prognostic factors:** advanced age, widespread involvement, and a requirement for **high-dose glucocorticoids** (± other immunosuppressants) for control.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
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> - **Desmoglein compensation theory of PV (skin vs mucosa):** draw the epidermis with a triangle gradient — label **Dsg1 (superficial)**, **Dsg3 (basal/parabasal)**; show **anti-Dsg3 IgG → mucosal erosions (mucosal-dominant PV)** and **anti-Dsg3 + anti-Dsg1 IgG → suprabasal split + skin blisters (mucocutaneous PV)**. Label **suprabasal acantholysis**, **"row of tombstones" basal cells**, **acantholytic (Tzanck) cells**.
> - **Therapeutic ladder schematic:** vertical ladder labelled **Supportive care → Topical/intralesional steroids → Systemic prednisone 1 mg/kg/day → Steroid-sparing (azathioprine / MMF) → Rituximab (first-line, moderate–severe) → IVIg / plasmapheresis / cyclophosphamide / efgartigimod (refractory)**.

Clinical / Diagnostic significance

- **Confirm the diagnosis before immunosuppression:** lesional biopsy (suprabasal acantholysis), **DIF** of perilesional skin (intercellular "chicken-wire" IgG ± C3), **IIF** on monkey oesophagus, and **anti-Dsg1/Dsg3 ELISA** — the latter also guides dosing as titres track activity.
- **Pre-treatment screen:** baseline glucose, BP, bone-density assessment and PPI/calcium-vitamin D + osteoporosis prophylaxis for steroids; **TPMT** before azathioprine; **hepatitis B/C, HIV, latent TB and immunoglobulin levels** before rituximab/IVIg; contraception counselling before cyclophosphamide.

- **Monitor** FBC/LFTs on azathioprine/MMF/cyclophosphamide; urinalysis (haematuria) on cyclophosphamide; CD19/CD20 counts and anti-Dsg titres after rituximab to anticipate relapse.
- Exclude **drug-induced pemphigus** and, where the picture is atypical (severe stomatitis, palmoplantar/lichenoid lesions, bronchiolitis obliterans), **paraneoplastic pemphigus** — search for underlying lymphoma/Castleman disease/thymoma.

High-yield exam pointers

- PV target antigen = **Dsg3** (mucosal) ± **Dsg1** (mucocutaneous); split is **suprabasal**.
- **Prednisone 1 mg/kg/day** is standard first-line; **rituximab is FDA-approved first-line** for moderate–severe PV (**Ritux 3**: CR off-therapy ~89% vs 34%).
- **Rituximab regimens:** 1 g days 1 & 15, *or* 375 mg/m^2 weekly × 4; maintenance 500 mg q6 months.
- **IVIg 2 g/kg** monthly works via **FcRn blockade**; **efgartigimod** is a new FcRn inhibitor.
- **Cyclophosphamide** → haemorrhagic cystitis, sterility, **bladder cancer**; check **TPMT** before azathioprine.
- Most frequent cause of death = ***Staphylococcus aureus* septicaemia**; untreated PV is fatal within ~5 years.
- Disease severity/response measured by **PDAI** and **ABSIS**; antibody titre by **anti-Dsg ELISA**.
- Always **screen for HBV** before rituximab (reactivation risk) and exclude **IgA deficiency** before IVIg (anaphylaxis).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Immunologically Mediated Skin Diseases" (Pemphigus vulgaris: pathogenesis, mortality figures, glucocorticoid/rituximab/IVIg/plasmapheresis treatment, prognostic factors).
- **Bolognia Dermatology, 5e** — "Pemphigus" (therapeutic ladder with doses and evidence levels, complications of individual agents, PDAI/ABSIS, efgartigimod, DSG3-CAART).
- **Rook's Textbook of Dermatology, 10e** — "Immunobullous Diseases" (azathioprine/TPMT, MMF, rituximab first-line and Ritux 3 data, IVIg mechanism, immunoadsorption, drug toxicities).
- **CMDT 2026** — "Dermatologic Disorders: Pemphigus" (current management including rituximab maintenance dosing, supportive measures, complications and prognosis).

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Eating disorders

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

Definition / Introduction — Feeding and eating disorders are a group of psychiatric conditions in which there is a **persistent disturbance of eating or eating-associated behaviour that significantly impairs the individual's physical health or psychosocial functioning**. In **DSM-5-TR**, the described categories (with the exception of pica) are defined to be **mutually exclusive in a given episode** — although phenotypically similar, they differ in course, prognosis and effective treatment. They are of direct relevance to the internist because their complications are **multisystemic and potentially life-threatening**: untreated anorexia nervosa carries the **highest mortality of any psychiatric condition**.

Classification (DSM-5-TR)

Disorder	Cardinal feature	Key differentiating point
Pica	Eating non-nutritive, non-food substances (clay, starch, soap, paper, ash) for ≥1 month in a person aged >2 years, requiring medical attention	Culturally approved practices must be excluded; diagnosed only when the behaviour increases medical risk
Rumination disorder	Repeated regurgitation of food after eating, which is re-chewed, re-swallowed or spat out, daily, for ≥1 month	No demonstrable gastrointestinal or other medical cause
Avoidant/restrictive food intake disorder (ARFID)	Avoidance/restriction of food intake from lack of interest in or distaste of food, with weight loss, nutritional deficiency, dependence on supplements or psychosocial impairment	**No fear of weight gain and no body-image distortion** (this distinguishes it from anorexia nervosa)
Anorexia nervosa (AN)	Caloric restriction producing **significantly low body weight** + fear of gaining weight + disturbed body image	Two subtypes — restricting vs binge-eating/purging
Bulimia nervosa (BN)	Recurrent binge eating (≥1/week for 3 months) **with compensatory behaviours** (vomiting/purging, enemas, laxatives, excessive exercise)	Weight is **normal or somewhat above normal**
Binge-eating disorder (BED)	Recurrent binges with distress and loss of control	**No compensatory behaviour** and no inter-episode restriction

Anorexia nervosa

- **Diagnosis**: restriction of caloric intake so that body weight deviates significantly from **age, gender, health and developmental norms**, *plus* an intense **fear of gaining weight** and an associated **disturbance of body image**. Determining "significantly low weight" is complex and must be **individualised**, using all historical information and comparison with **international body-mass (BMI) norms and guidelines**.
- **Subtypes** (more *state*- than *trait*-specific — patients transition between them over time):
  - **Restricting type** — weight loss achieved predominantly by restricting intake and/or **excessive exercise**.

- **Binge-eating/purging type** — recurrent binge eating and/or purging by **self-induced vomiting, enemas, laxatives or diuretics**.

- **Psychopathology**: patients frequently **lack insight** and are in **denial** of the medical consequences; they are characteristically **not comforted by achieved weight loss** and persist despite reaching previously self-set weight goals.
- **Neurobiology**: alterations in the circuitry of **reward sensitivity and executive function**, implicating disturbed **frontal cortex and anterior insula** regulation of **interoceptive awareness of satiety and hunger**. Neurochemical findings (including the role of **ghrelin**) remain controversial.
- **Epidemiology**: onset most commonly in **adolescence** (later-life onset can occur); marked female preponderance; **lifetime prevalence in women up to 4%**; most prevalent in **post-industrialised, urbanised countries**; frequently comorbid with **pre-existing anxiety disorders**.
- **Course and prognosis**: variable — recovery after a single episode, recurrent episodes, or a chronic course. **Untreated AN has a mortality of 5.1 per 1000 — the highest among psychiatric conditions** (deaths from medical complications and suicide). Most treated individuals achieve **remission within 5 years** of diagnosis.

Medical complications of anorexia nervosa (system-wise)

System	Findings
General / metabolic	Hypometabolic state — **hypotension, hypothermia, sinus bradycardia**; elevated blood urea nitrogen
Haematological	**Leukopenia with relative lymphocytosis**
Electrolytes / acid–base	**Metabolic alkalosis and hypokalaemia** when purging is present
Endocrine	**Hypogonadism (amenorrhoea in females), growth-hormone resistance, hypercortisolaemia**
Skin	**Petechiae, lanugo hair, dryness**
Skeletal	**Osteoporosis** (long-term concern)
Cardiac	Bradycardia, hypotension; with purging — **cardiac conduction abnormalities** secondary to electrolyte disturbance
Refeeding	Over-rapid nutritional rehabilitation precipitates the **refeeding syndrome** (hallmark **hypophosphataemia**, with fluid shifts and arrhythmia risk) — hence weight-gain target of only **0.5–1 lb (~0.25–0.5 kg) per week**

Bulimia nervosa

- **Diagnosis**: recurrent, frequent episodes of **binge eating — at least once a week for 3 months** — followed by **compensatory behaviours**: self-induced purging/vomiting, enemas, laxative use or excessive exercise to avoid weight gain.
- A **binge** is defined as excessive food intake within a prescribed period of time, **usually <2 hours**, with a subjective **loss of control**; patients express **shame**, and episodes are often triggered by **negative self-esteem or social stresses**.

- Body-image disturbance occurs as in AN, **but weight is normal or somewhat above normal** — the key clinical separator from AN binge-purge type (which requires significantly low weight).
- **Epidemiology**: lifetime prevalence in women **~2%**, female-to-male ratio **10:1**; typically begins in **adolescence** and may persist for years; **transition to anorexia nervosa occurs in only 10–15%** of cases.
- **Medical risks** parallel those of AN and are a direct consequence of **purging**: **fluid and electrolyte disturbances** (hypokalaemia, metabolic alkalosis) and **cardiac conduction abnormalities**.
- **Physical examination** is often unremarkable; the classical signs are **dental erosion** (perimolysis from gastric acid) and **parotid gland enlargement**; calluses over the dorsum of the hand from repeated self-induced vomiting (*Russell's sign*) are a standard accompanying sign.

Binge-eating disorder and the other feeding disorders

- **Binge-eating disorder (BED)**:
  - Distinguished from BN by the **absence of compensatory behaviours** after a binge and by a **lack of effort to restrict weight between episodes**.
  - Shares the **distress and loss of control** — eating more rapidly or in greater amounts than intended, or eating when not hungry.
  - **12-month prevalence in females 1.6%**, with a **much lower female-to-male ratio than BN**; prognosis is **markedly better** than other eating disorders (both natural course and treatment response); transition to other eating disorders is thought to be **rare**.
- **Pica**: onset most common in childhood; can occur with other major psychiatric conditions in adults; an **association with pregnancy** is observed, but the diagnosis is made only when the behaviour increases medical risk (e.g., toxicity, obstruction, infection). It is **not commonly caused by a specific nutritional deficiency**.
- **Rumination disorder**: onset in infancy typically between **3 and 12 months**; **weight loss and malnutrition** are common sequelae; patients may conceal the behaviour (covering the mouth, social avoidance while eating); may remit spontaneously or recur.
- **ARFID**: onset usually in infancy/early childhood but may persist into adulthood; **equal prevalence in males and females**; frequently comorbid with **anxiety, cognitive and attention-deficit disorders** and situations of **familial stress**; long-standing unrecognised disease causes **developmental delay and functional deficits**.

Management

Disorder	Psychological treatment (first-line)	Pharmacotherapy	Medical management
Anorexia nervosa	**MANTRA** (*Maudsley Anorexia Nervosa Treatment for Adults*) and **eating-disorder–focused CBT**; strict **behavioural contingencies** when weight loss becomes critical	**No drug is specifically beneficial**; treat comorbid depression and anxiety on their own merits	Gradual nutritional rehabilitation — **0.5–1 lb/week** weight gain to **prevent refeeding syndrome**; monitor electrolytes (especially phosphate, potassium), ECG; hospitalise for severe bradycardia, hypotension, hypothermia, marked electrolyte derangement or critical low weight

Disorder	Psychological treatment (first-line)	Pharmacotherapy	Medical management
Bulimia nervosa	**Cognitive-behavioural**, **emotion-regulation** or **interpersonal** psychotherapies	**SSRI antidepressants**, usually combined with psychotherapy (fluoxetine is the standard agent, used at higher dose, e.g., 60 mg/day)	Correct hypokalaemia/alkalosis; dental review for enamel erosion
Binge-eating disorder	CBT-based approaches; responds markedly better than other eating disorders	SSRIs/CBT as for BN-spectrum illness (lisdexamfetamine is an approved option in standard practice)	Address obesity-related comorbidity
Pica / Rumination / ARFID	Behavioural therapy, family-based management of stressors; nutritional supplementation in ARFID	—	Treat the medical consequence (toxicity, malnutrition, deficiency states)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Multisystem complications of anorexia nervosa" (labelled human figure).** Labels: *Brain* — lack of insight, altered frontal cortex–anterior insula interoceptive circuitry; *Skin* — lanugo hair, petechiae, dryness; *Heart* — sinus bradycardia, hypotension, conduction abnormalities; *Blood* — leukopenia with lymphocytosis; *Kidney/metabolic* — raised BUN, hypokalaemia, metabolic alkalosis (purging); *Endocrine* — amenorrhoea/hypogonadism, GH resistance, hypercortisolaemia; *Bone* — osteoporosis; *Whole body* — hypothermia, weight significantly below norms.
- **Diagram 2 — "Diagnostic algorithm for eating disorders" (flow chart).** Boxes: *Significantly low body weight?* → YES + fear of weight gain + body-image disturbance → **Anorexia nervosa** (→ restricting type vs binge-eating/purging type); YES but NO fear of weight gain/body-image distortion → **ARFID**; NO (normal/overweight) + binge ≥1/week × 3 months → *Compensatory behaviour?* → YES → **Bulimia nervosa**; NO → **Binge-eating disorder**.

Clinical / Diagnostic significance

- **Internist's screen**: unexplained **amenorrhoea, bradycardia, hypokalaemic metabolic alkalosis, dental erosion or parotid swelling** in a young woman should prompt directed questioning for disordered eating; physical examination in BN is often normal, so the diagnosis rests on history.
- **Laboratory panel**: electrolytes (K^+, and phosphate during refeeding), urea, glucose, complete blood count (leukopenia with lymphocytosis), and **ECG** (bradycardia, conduction abnormalities — risk of arrhythmic death when hypokalaemic).

- **Distinguish organic disease**: weight loss with intact body image and genuine loss of appetite suggests malignancy, malabsorption, thyrotoxicosis, adrenal insufficiency or depression rather than AN; in AN the patient *fears* weight gain and is *not relieved* by weight loss.
- **Refeeding syndrome** is the most important iatrogenic hazard — gradual calorie escalation, phosphate/potassium/magnesium monitoring and a weight-gain ceiling of **0.5–1 lb/week**.
- **Psychiatric comorbidity** (anxiety disorders in AN; depression in BN/BED) must be actively treated; suicide contributes to the excess mortality of AN.
- **Hospitalisation/behavioural contingency** is indicated when weight loss becomes critical or vital signs/electrolytes are dangerously deranged.

High-yield exam pointers

- **DSM-5-TR feeding and eating disorders**: pica, rumination disorder, ARFID, anorexia nervosa, bulimia nervosa, binge-eating disorder — mutually exclusive in a given episode (except pica).
- **AN = low weight + fear of weight gain + body-image disturbance**; two subtypes — restricting vs binge-eating/purging; subtype is state-, not trait-specific.
- **ARFID vs AN**: ARFID has **no fear of weight gain and no body-image distortion**.
- **BN vs AN binge-purge type**: BN patients are of **normal weight or overweight**; binge ≥1/week for 3 months, binge usually **<2 h**.
- **BED vs BN**: BED has **no compensatory behaviour**; lowest female predominance; **best prognosis** of all eating disorders.
- Untreated AN mortality **5.1/1000 — highest of all psychiatric disorders**; lifetime prevalence in women up to **4%** (BN ~2%, 10:1 F:M; BED 12-month prevalence 1.6% in females).
- AN examination: **lanugo, petechiae, dry skin, hypotension, hypothermia, sinus bradycardia, amenorrhoea**; labs: **leukopenia with lymphocytosis, ↑BUN, hypokalaemic metabolic alkalosis (purging), hypogonadism, GH resistance, hypercortisolaemia, osteoporosis**.
- BN examination: **dental erosion + parotid enlargement** (± Russell's sign).
- Treatment one-liners: **AN — MANTRA / ED-focused CBT, no specific drug, refeed at 0.5–1 lb/week; BN — SSRI + CBT/interpersonal therapy; BED — best treatment response**.
- Neurobiology of AN: **frontal cortex–anterior insula** interoceptive circuitry; **ghrelin** data controversial.

SOURCE & COVERAGE

Harrison 22e — Ch 463 "Psychiatric Disorders" (section: *Feeding and Eating Disorders*). **Coverage note**: Harrison 22e has no dedicated eating-disorders chapter; the topic is covered briefly within Ch 463, and this answer reflects that coverage. A few universally standard exam points absent from the provided text were added for completeness and are flagged as standard practice: *Russell's sign*, hypophosphataemia as the hallmark of refeeding syndrome, high-dose fluoxetine for BN, lisdexamfetamine for BED, and explicit hospitalisation criteria (consistent with CMDT/standard psychiatry teaching).

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Eczema

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

Definition / Introduction — *Eczema* (Greek *ekzema*, "to boil over") is a **clinico-histological reaction pattern of skin inflammation** rather than a single disease, characterised clinically by pruritus, erythema, oozing, vesiculation, scaling and (when chronic) lichenification, and histologically by **spongiosis** (intercellular oedema of the epidermis) with acanthosis and a perivascular lymphohistiocytic infiltrate. The terms *eczema* and *dermatitis* are used synonymously. It is the **final common pathway of many disorders** of diverse aetiology; **atopic dermatitis (AD)** is the prototype and commonest endogenous form. Eczema accounts for ~10–25% of dermatology consultations and AD carries the highest disability-adjusted life-year burden of any skin disease.

Classification of eczematous disorders

Best classified by **aetiology** (where known) and by **endogenous vs exogenous** origin; morphological labels (e.g. nummular, dyshidrotic) cut across causes.

Category	Examples
Endogenous (constitutional)	Atopic eczema; seborrhoeic dermatitis; nummular (discoid) eczema; asteatotic (xerotic / "winter itch") eczema; stasis (venous/gravitational) eczema; hand eczema incl. pompholyx; lichen simplex chronicus; pityriasis alba; juvenile plantar dermatosis
Exogenous (contact)	Allergic contact dermatitis (type IV, e.g. nickel, *Toxicodendron*/urushiol); irritant contact dermatitis (soaps, detergents, wet-work); photoallergic / photo-irritant eczema; infective dermatitis; post-traumatic eczema; dermatophytide ("id" reaction)
By morphology / acuity	Acute (wet, oedematous, vesicular) → subacute → chronic (dry, lichenified, fissured)

Atopic dermatitis — pathophysiology (the exam favourite)

AD is the cutaneous expression of the **atopic state** (familial tendency to asthma, allergic rhinitis, eczema). Pathogenesis is a **three-way interaction** of barrier defect, immune dysregulation and microbiome alteration, on a strong genetic background (monozygotic twin concordance ~77% vs ~15% dizygotic; if **both parents affected >80%** of children develop AD).

- **Epidermal barrier dysfunction — loss-of-function mutations in the filaggrin gene (*FLG*)** are the single strongest genetic risk factor (also cause ichthyosis vulgaris). Filaggrin aggregates keratin in the stratum corneum; deficiency → ↑ transepidermal water loss, ↑ skin pH, xerosis, and easier penetration of irritants, allergens and microbes. *FLG* null carriers manifest **hyperlinear palms, keratosis pilaris and ichthyosis vulgaris**; penetrance of AD is ~40% with one and ~90% with two null alleles.
- **Immune dysregulation** — barrier breach lets keratinocytes release "alarmins" **TSLP** (the "master switch of allergic inflammation"), **IL-25 and IL-33**, driving a **Th2-skewed** response. *Acute* lesions are Th2-dominant (**IL-4, IL-5, IL-13, IL-31** — IL-31 is the key pruritogen); *chronic* lesions shift to **Th1/Th17/Th22** cytokines. Th2 cytokines themselves suppress filaggrin, loricrin and

antimicrobial peptides, perpetuating the barrier defect. Result: ↑ **IgE synthesis, eosinophilia, impaired delayed-type hypersensitivity**.

- **Microbiome** — reduced diversity with **>90% colonisation by *Staphylococcus aureus***; staphylococcal exotoxins act as **superantigens** amplifying inflammation; reduced antimicrobial peptide (β-defensin, cathelicidin) production predisposes to viral superinfection (eczema herpeticum).
- **Epicutaneous sensitisation** through defective skin is thought to initiate the "**atopic march**" — AD in infancy → food allergy → asthma → allergic rhinoconjunctivitis.

Atopic dermatitis — clinical features by age

Pruritus ("**an itch that rashes**") is the cardinal symptom in all ages; the course is chronically relapsing. **45% present in first 6 months, 60% in first year, ~85% by age 5**; ~40% persist into adult life.

Phase	Age	Distribution / features
Infantile	0–2 yr	Weeping, crusted patches on **cheeks, face, scalp, neck and extensor** surfaces; napkin area spared
Childhood / adolescent	2 yr–puberty	**Flexural** dermatitis — antecubital & popliteal fossae, wrists, ankles, neck; lichenification
Adult	post-puberty	Flexures, **hand eczema**, head-and-neck, nipple/eyelid eczema; often localised lichen simplex chronicus

- **Atopic stigmata / minor signs:** xerosis, **Dennie–Morgan infraorbital fold**, infraorbital darkening ("allergic shiners"), perioral/midfacial pallor, **hyperlinear palms**, keratosis pilaris, **pityriasis alba**, white dermographism, anterior neck folds, **keratoconus and anterior subcapsular cataract**.

Diagnostic criteria

AD is a **clinical diagnosis** (no confirmatory test except skin biopsy).

- ***Hanifin & Rajka criteria* (1980)** — require **≥3 of 4 major** plus **≥3 minor**.
  - *Major:* (1) pruritus; (2) typical morphology & age-specific distribution (flexural in adults, facial/extensor in infants); (3) chronic or chronically relapsing course; (4) personal/family history of atopy.
  - *Minor (selected):* xerosis; ichthyosis/palmar hyperlinearity/keratosis pilaris; elevated serum IgE / immediate (type I) skin-test reactivity; early age of onset; tendency to cutaneous infections (*S. aureus*, HSV); non-specific hand/foot dermatitis; nipple eczema; cheilitis; recurrent conjunctivitis; Dennie–Morgan fold; keratoconus; anterior subcapsular cataract; orbital darkening; facial pallor; pityriasis alba; itch on sweating; wool intolerance; white dermographism; food intolerance; course influenced by environment/emotion.
- ***UK Working Party (Williams) criteria*** — validated, simplified for population studies (80% PPV, 97% NPV). **Must have an itchy skin condition** in the last 12 months **plus ≥3 of:** onset <2 yr; history of flexural involvement; history of generally dry skin; personal history of other atopic disease (or atopy in a first-degree relative if <4 yr); visible flexural dermatitis.
- **Severity scoring: SCORAD, EASI, POEM** (patient-oriented), vIGA-AD.

Other clinically important eczema variants

Variant	Key features
Lichen simplex chronicus	Circumscribed lichenified plaque from chronic rubbing; nape, ankles, dorsum of feet
Nummular (discoid)	"Coin-shaped" crusted scaly plaques, extensor limbs; middle-aged men; dry skin
Asteatotic (xerotic)	"Crazy-paving"/cracked dry skin, shins of the elderly in winter
Stasis dermatitis	Medial ankle, venous incompetence, haemosiderin pigmentation, brawny oedema; *bilateral* (vs unilateral cellulitis); may precede venous ulcer
Seborrhoeic dermatitis	Greasy yellow scale on scalp, eyebrows, nasolabial folds; *Malassezia*; associated with Parkinson's, HIV
Hand eczema / pompholyx	Wet-work/occupational; dyshidrotic — intensely pruritic deep vesicles on sides of fingers, palms
Contact dermatitis	Allergic (type IV, patch-test positive) vs irritant (dose-dependent, no prior sensitisation)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Distribution of atopic dermatitis by age" — three body silhouettes.** Labels: *Infantile* — cheeks/face, scalp, neck, **extensor** limbs, napkin sparing; *Childhood* — **antecubital fossa, popliteal fossa**, wrists, ankles, neck; *Adult* — flexures, hands, eyelids, head-and-neck.
- **"Pathogenesis triad of AD" — three interlocking circles.** Labels: **(1) Epidermal barrier defect** (*FLG* mutation, ↑TEWL, xerosis); **(2) Immune dysregulation** (TSLP/IL-33 → Th2: IL-4, IL-13, IL-31; chronic Th1/Th17/Th22; ↑IgE); **(3) Microbiome** (*S. aureus* superantigens, ↓antimicrobial peptides); central output → **chronic pruritic eczema → atopic march**.

Clinical / Diagnostic significance

- **Investigations:** largely clinical; serum IgE/eosinophilia support but are not diagnostic; **patch testing** if allergic contact dermatitis suspected or AD is recalcitrant; **KOH/culture** to exclude dermatophyte (esp. hand eczema); skin/viral swabs in weeping flares.
- **Complications:** secondary **impetiginisation** with *S. aureus*/*S. pyogenes* (infra-auricular fissure is a cardinal sign); **eczema herpeticum** (*Kaposi varicelliform eruption*) — monomorphic punched-out "scalloped" erosions with haemorrhagic crusts + fever; a dermatological emergency needing **systemic aciclovir**; predisposition to widespread **molluscum contagiosum**. Risk of erythroderma. Associations: asthma, allergic rhinitis, food allergy, ADHD, anxiety/depression, and ↑ cardiovascular risk in adults.
- **Management ladder (AD):**
  - *General* — gentle skin care, avoid irritants/wool/soaps, bathe ≤ once daily in warm water, **liberal emollients** (≈30 g covers an adult; apply within minutes of bathing); identify triggers.

- *First line* — **topical corticosteroids** (potency matched to site/severity; low-potency on face/flexures to avoid atrophy); **topical calcineurin inhibitors** (tacrolimus, pimecrolimus — steroid-sparing, safe on face, no atrophy), **crisaborole** (PDE-4 inhibitor), **ruxolitinib/roflumilast** cream. *Proactive* twice-weekly anti-inflammatory to flare-prone sites prevents relapse.
- *Adjuncts* — **dilute sodium hypochlorite (bleach, ~0.005%) baths** + intranasal mupirocin to reduce *S. aureus*; **wet-wrap therapy** (diluted steroid + inner wet/outer dry layer, ≤2 weeks) for acute flares; sedating antihistamines (hydroxyzine, doxepin) at night for sleep; treat secondary infection (dicloxacillin/cephalexin; cover CA-MRSA with cotrimoxazole/doxycycline/clindamycin per culture).
- *Severe/refractory* — **phototherapy (NB-UVB)**; systemic immunosuppressants (ciclosporin, methotrexate, azathioprine, mycophenolate); **biologics — dupilumab** (anti–IL-4Rα, blocks IL-4/IL-13; approved ≥6 months), **tralokinumab** (anti–IL-13); **oral JAK inhibitors — upadacitinib, abrocitinib**. Systemic corticosteroids only for short severe exacerbations (rebound on withdrawal).

High-yield exam pointers

- Eczema = **spongiosis** histologically; "the itch that rashes."
- **Filaggrin (*FLG*) loss-of-function** = strongest genetic risk for AD; links to ichthyosis vulgaris, hyperlinear palms, keratosis pilaris.
- Acute AD is **Th2** (IL-4/IL-13/IL-31, ↑IgE); chronic shifts to **Th1/Th17/Th22**; **TSLP** is the alarmin "master switch."
- **Hanifin & Rajka** (≥3 major + ≥3 minor) and **UK Working Party** criteria; severity by **SCORAD/EASI/POEM**.
- **Dennie–Morgan fold, allergic shiners, hyperlinear palms, pityriasis alba, white dermographism** = atopic stigmata.
- **Eczema herpeticum (Kaposi varicelliform eruption)** = monomorphic punched-out erosions → **aciclovir** urgently.
- **Stasis dermatitis is usually bilateral**; unilateral red leg favours cellulitis.
- **Dupilumab (IL-4Rα), tralokinumab (IL-13), upadacitinib/abrocitinib (JAK)** are the modern systemic agents; FDA *black-box warning* on topical calcineurin inhibitors (theoretical lymphoma — absolute risk very low).
- Topical steroid potency: **low-potency on face/flexures** to avoid atrophy/striae.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders" (atopic dermatitis, contact/hand/nummular/asteatotic/stasis/seborrhoeic dermatitis, lichen simplex chronicus, treatment).
- **Rook's Textbook of Dermatology, 10e** — "Eczematous Disorders" (classification, nomenclature) and "Atopic Eczema" (diagnostic criteria, filaggrin genetics, epidemiology, complications).
- **Bolognia, Dermatology, 5e** — "Atopic Dermatitis" (pathogenesis triad, atopic march, Th2/Th1-Th17-Th22 cytokines, diagnostic features table, eczema herpeticum, severity scores).
- **CMDT 2026** — "Dermatologic Disorders: Atopic Dermatitis" (current stepwise management, topical non-steroidals, biologics/JAK inhibitors, wet wraps, bleach baths).

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Erythema nodosum

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Erythema nodosum (EN) is the commonest and best-known form of **panniculitis** (inflammation of subcutaneous fat), presenting as an acute, self-limited eruption of **tender, erythematous, non-ulcerating subcutaneous nodules**, classically symmetrical over the **pretibial shins**. It is widely regarded as a **delayed (type IV) hypersensitivity reaction** to diverse antigenic stimuli (infections, drugs, systemic inflammatory disease) and is histologically the **prototype of a septal panniculitis without vasculitis**. Because of its strong links to systemic disease, EN is an important *skin sign of internal disease* — diagnosis is only the first step; the cause must be sought.

Pathogenesis

- A **delayed-type hypersensitivity response** to varied antigens; lesional skin and blood show a **Th1 cytokine pattern** (interferon-γ, IL-2) characteristic of DTH.
- **Immune-complex deposition** in septal venules and a **neutrophil-driven** early phase: circulating neutrophils generate reactive oxygen intermediates that provoke tissue damage; later, **granuloma formation** predominates, in which **TNF** plays a central role (explaining both response to, and paradoxical induction by, TNF inhibitors).
- Endothelial up-regulation of adhesion molecules (**VCAM-1/CD106, PECAM-1/CD31, E-selectin, HLA-DR**) with VLA-4/L-selectin on infiltrating cells.
- A **TNF promoter polymorphism** correlates with sarcoidosis-associated EN, linking deregulated TNF to granuloma formation.

Causes / Aetiology

A precipitant is identifiable in roughly half; the rest are idiopathic. Crohn disease associates more strongly than ulcerative colitis.

Category	Specific causes (high-yield)
Idiopathic	Largest single group — **one-third to one-half** of cases
Infections (≈1/3 of cases)	**Streptococcal URTI** = commonest *infectious* cause; viral URTI; bacterial gastroenteritis (**Yersinia > Salmonella, Campylobacter**); **Mycobacterium tuberculosis**; **coccidioidomycosis** (and histoplasmosis, blastomycosis); brucellosis, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*/*C. trachomatis*, hepatitis B, HIV, COVID-19
Sarcoidosis	10–20% of cases; **Löfgren syndrome** (see below)
Inflammatory bowel disease	**Crohn disease > ulcerative colitis**
Drugs	Oral contraceptives/**oestrogens**, **sulfonamides, penicillins**, **bromides, iodides**, **TNF inhibitors** (etanercept, infliximab, adalimumab), immune **checkpoint inhibitors**, **BRAF inhibitors** (vemurafenib, dabrafenib), tyrosine-kinase inhibitors (imatinib, dasatinib)
Neutrophilic dermatoses	**Behçet disease**, **Sweet syndrome** (EN in Behçet often resembles erythema induratum)
Pregnancy / hormonal	Pregnancy itself; OCP use
Malignancy	Acute myeloid leukaemia, Hodgkin lymphoma (may overlap with Sweet syndrome)
Miscellaneous	Acne fulminans (incl. isotretinoin-associated), diverticulitis, granulomatous mastitis, lupus erythematosus, MonoMAC syndrome (*GATA2*)

- ***Löfgren syndrome*** — acute, spontaneously resolving sarcoidosis = **EN + bilateral hilar lymphadenopathy + fever + polyarthritis (peri-ankle) + uveitis**; carries a benign, self-limited prognosis.

Clinical features

- **Crops of tender, warm, erythematous nodules 1–10 cm**, bilateral and symmetrical, on the **anterior shins** (occasionally thighs, forearms; trunk/face/neck rare — atypical sites should prompt an alternative diagnosis).
- Lesions **do not ulcerate** and **resolve without scarring** over ~**6 weeks**, evolving through **bruise-like (contusiform) colour changes** — hence the synonym *erythema contusiformis*.
- **Constitutional symptoms** common even without an identified systemic cause: fever, malaise, **arthralgia/arthritis**, leukocytosis, raised ESR.
- **Up to one-third recur**; annual recurrences typical of idiopathic disease. Chronic/migratory variants = *subacute nodular migratory panniculitis (erythema nodosum migrans)*, often unilateral with centrifugal spread and central clearing.

Histopathology

Biopsy requires a deep incisional/excisional specimen capturing generous subcutaneous fat — a punch biopsy is usually inadequate.

- **Prototypic septal (interlobular) panniculitis WITHOUT true vasculitis.**

- **Septa are thickened and oedematous**, infiltrated by inflammatory cells concentrated at the **septal–lobular interface**, extending into the lobule periphery in a *lace-like* pattern.
- **Early lesions**: oedematous septa, often **neutrophil-rich**; **late lesions**: mixed, **granulomatous** infiltrate with **epithelioid histiocytes and multinucleated giant cells**, eventual **septal fibrosis**.
- ***Miescher radial microgranulomas*** — the characteristic (though not strictly pathognomonic) hallmark: small nodular aggregates of **histiocytoid cells arranged radially around a central stellate / banana-shaped cleft**, located within or at the edge of septa.
- A **mild superficial and deep perivascular lymphocytic infiltrate** is usually present in the overlying dermis.
- Leukocytoclastic vasculitis is **absent** (its presence, with venular/venous involvement, suggests EN-like lesions of severe Behçet disease).

Evaluation / Investigations

- **Confirm the diagnosis clinically** (classic bilateral pretibial tender non-ulcerating nodules in a young adult, F:M ≈ 10:1, 2nd–4th decades); biopsy only when atypical (few lesions, unusual site, duration >6 weeks, or ulceration suggesting another panniculitis).
- **Search for an underlying cause** — directed by *findings that predict a systemic association*: synovitis, diarrhoea, abnormal CXR, preceding URTI, raised ASO/anti-DNase B, positive TST/IGRA.
- **First-line work-up:** FBC, **ESR/CRP**, throat swab + **two serial ASO / anti-DNase B titres 2–4 weeks apart**, **chest X-ray** (hilar adenopathy → sarcoidosis/Löfgren, TB, lymphoma), **tuberculin skin test or IGRA (QuantiFERON-TB / T-SPOT.TB)**.
- **Targeted tests:** stool culture + **faecal calprotectin** (if GI symptoms) for IBD/enteric infection; **serum amylase/lipase** if pancreatic panniculitis suspected; **serum β-hCG** in women of child-bearing age; viral hepatitis panel; coccidioidin/fungal serology in endemic areas; review of drug history.
- **Differential diagnosis of subcutaneous nodules:**

Entity	Distinguishing feature
Erythema induratum (nodular vasculitis)	**Posterior calf**, **ulcerates**; lobular panniculitis with vasculitis; *M. tuberculosis* DNA by PCR
Pancreatic panniculitis	Fat necrosis with saponification/"ghost cells"; ↑amylase/lipase; arthritis, serositis
Lupus panniculitis	Cheeks, upper arms, buttocks; heals with **depressed scars**
Cutaneous polyarteritis nodosa	Nodules + ulcers within **fixed livedo reticularis**; medium-vessel arteritis
Superficial thrombophlebitis	Linear cord along a vein

Management

- **General (all patients):** stop any causative drug; **diagnose and treat the underlying cause**; **bed rest, leg elevation, compression**.

Line	Agents
First-line	**NSAIDs**, salicylates, **potassium iodide (SSKI)**
Second-line (only after infection excluded/treated)	**Colchicine** (esp. Behçet-associated), hydroxychloroquine, **TNF inhibitors** (infliximab/adalimumab/etanercept — useful in IBD-associated EN), mycophenolate mofetil
Third-line	**Systemic corticosteroids** (avoid if infection unexcluded), thalidomide, ciclosporin, dapsone

- **Potassium iodide (SSKI):** adult dose commonly **300 mg three times daily** (range ~450–1500 mg/day); CMDT quotes **5–15 drops three times daily**; improvement within ~2 weeks via inhibition of neutrophil chemotaxis and cell-mediated immunity.
- **Caveat:** NSAIDs and KI may flare IBD; corticosteroids are contraindicated if an underlying infection (e.g. TB, deep mycosis) has not been excluded/treated.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Histology of EN (septal panniculitis):** label *epidermis*, *dermis with superficial + deep perivascular lymphocytic infiltrate*, *widened oedematous/fibrotic interlobular septum*, *fat lobule*, *Miescher radial microgranuloma (histiocytes around central stellate cleft)*, *multinucleated giant cells*, and *absence of vasculitis*.
- **Clinical distribution figure:** front-of-legs silhouette showing **bilateral symmetrical tender nodules over both shins (pretibial)**, with a colour key for *erythema → contusiform/bruise-like resolution, non-ulcerating*.

Clinical / Diagnostic significance

- EN is a **paraclinical marker of systemic disease** — it may **precede or accompany an IBD flare**, herald **sarcoidosis** or **primary TB/coccidioidomycosis**, or signal drug reaction.
- It carries **prognostic value**: EN denotes a **benign, self-limited course in sarcoidosis (Löfgren)** and a **protective effect against dissemination in coccidioidomycosis**.
- A normal CXR, negative IGRA/TST and negative streptococcal serology in an otherwise well young woman support an **idiopathic, benign** course; only a small minority develop significant illness within the following year.
- **Persistent, ulcerating, posterior-leg or unilateral lesions argue against EN** and mandate biopsy for an alternative panniculitis.

High-yield exam pointers

- EN = **commonest panniculitis**; **septal panniculitis without vasculitis**; **never ulcerates, heals without scar**.
- **Miescher radial microgranuloma** = histological hallmark (histiocytes around a central stellate/banana-shaped cleft).
- **Streptococcal URTI** = commonest infectious cause; **idiopathic** = commonest overall; **sarcoidosis 10–20%**.

- **Löfgren syndrome** = EN + bilateral hilar lymphadenopathy + fever + arthritis + uveitis (good prognosis).
- **Crohn > ulcerative colitis**; **Yersinia** = leading enteric trigger; drugs — **OCP, sulfonamides, penicillins, bromides/iodides, BRAF inhibitors**.
- Core work-up: **CXR + ASO/anti-DNase B (×2) + TST/IGRA + ESR ± stool studies + β-hCG**.
- Treatment ladder: **NSAIDs / potassium iodide → colchicine, HCQ → steroids** (only after excluding infection); always **treat the cause**.
- **DDx mnemonic by site:** EN = **shin (anterior)**; erythema induratum = **calf (posterior, ulcerates, TB)**; lupus panniculitis = **buttocks/arms (scars)**.

SOURCE & COVERAGE

- **Bolognia, *Dermatology* (5e) — "Panniculitis"** (primary source: aetiology Table, pathogenesis, septal histopathology with Miescher microgranulomas, treatment ladder and potassium iodide dosing).
- **Rook's *Textbook of Dermatology* (10e) — "Panniculitis"** (Miescher radial granuloma morphology; septal-panniculitis-without-vasculitis confirmation; Löfgren/sarcoid associations).
- **Harrison's *Principles of Internal Medicine* (22e) — "Skin Manifestations of Internal Disease"** (EN as a sign of systemic disease; differential of subcutaneous nodules).
- **CMDT 2026 — "Dermatologic Disorders" (Erythema Nodosum)** (clinical essentials, evaluation algorithm, NSAID/SSKI/colchicine/dapsone management, prognosis).
- *Coverage note:* The spec flagged panniculitis histopathology as potentially thin in Harrison; this was fully resolved using the dedicated dermatology texts (Bolognia and Rook's), which supplied exam-grade histological and therapeutic detail.

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Erythroderma

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

Definition / Introduction — Erythroderma (synonyms: *exfoliative dermatitis*, *exfoliative erythroderma*) is an inflammatory reaction pattern characterised by **generalised erythema and scaling involving ≥80–90% of the body surface area (BSA)**. The term was coined by *Hebra* in 1868 for an eruption affecting >90% of the skin. It is **not a single disease but a striking, potentially life-threatening clinical presentation** that can arise from several underlying dermatoses, drugs or systemic diseases, and is therefore regarded as a **dermatological emergency** requiring a careful aetiological search and management of systemic complications.

Epidemiology and classification

- Estimated incidence **~1–2 per 100,000**; male predominance with **M:F ratio 2:1 to 4:1**; mean age of onset **~52 years**.

- **By onset/course**: *Primary* erythroderma (erythema begins de novo, often on the trunk, and generalises over days–weeks) vs *Secondary* erythroderma (generalisation of a pre-existing dermatosis, e.g. psoriasis, atopic dermatitis — up to **50%** have a prior localised skin disease).
- **Idiopathic erythroderma** persists despite thorough work-up in ~**25%** of adults — typically **elderly men** with chronic pruritus, palmoplantar keratoderma and dermatopathic lymphadenopathy; historically termed *"red man syndrome"* or *"l'homme rouge"* (**not** to be confused with the vancomycin rapid-infusion reaction of the same name). These cases mandate longitudinal review, as some evolve into CTCL.

Aetiology

The major causes are **(1)** primary cutaneous dermatoses, **(2)** drugs, **(3)** systemic disease (chiefly CTCL), and **(4)** idiopathic. In adults the four commonest are **dermatitis, psoriasis, drug reactions and CTCL**.

Category	Approx. frequency	Diagnostic clues
Psoriasis	~20–27%	Pre-existing plaques (elbows/knees/scalp), nail pits / oil-drop sign / onycholysis, sterile pustules, arthritis; often spares central face
Dermatitis (atopic > contact > seborrhoeic / stasis)	~20–24%	Pre-existing flexural lesions, intense pruritus, lichenification (incl. eyelids), raised IgE, eosinophilia, atopy history
Drug reactions	~15–19%	Preceding morbilliform/scarlatiniform exanthem, facial oedema, rapid onset; may be part of **DRESS/DIHS**
CTCL (Sézary syndrome > erythrodermic mycosis fungoides)	~8–18%	Leonine facies, *melanoerythroderma*, painful fissured keratoderma, alopecia, lymphadenopathy, severe pruritus
Idiopathic	~25% (often older men)	Chronic, relapsing; palmoplantar keratoderma, dermatopathic lymphadenopathy
Uncommon	—	Pityriasis rubra pilaris, pemphigus foliaceus, bullous pemphigoid, paraneoplastic (lymphoma > solid tumours, thymoma), crusted (Norwegian) scabies, dermatophytosis, GVHD, sarcoidosis, connective-tissue disease, papuloerythroderma of Ofuji

- **Implicated drugs**: allopurinol, **β-lactams/penicillins, sulfonamides, sulfasalazine**, **aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital)**, gold salts, lithium, cimetidine, antimalarials, dapsone, isoniazid, immune checkpoint inhibitors.
- **Neonatal/infantile erythroderma** ("the red baby") — distinct causes: **inherited ichthyoses** (congenital ichthyosiform erythroderma — *TGM1*; epidermolytic ichthyosis — *KRT1/KRT10*; **Netherton syndrome** — *SPINK5*/LEKTI, *trichorrhexis invaginata* "bamboo hair"), **primary immunodeficiencies** (**Omenn syndrome** — *RAG1/RAG2*; Wiskott–Aldrich — *WAS*), psoriasis, atopic/seborrhoeic dermatitis (*Leiner phenotype*), and **staphylococcal scalded skin syndrome**.

Pathogenesis

- A massive, generalised inflammatory response produces a **marked increase in germinative keratinocytes and their mitotic rate** with **shortened epidermal transit time**.

- Consequently scale (rich in nucleic acids, amino acids and soluble protein) is shed in excess — daily loss rises from a normal **0.5–1 g to 20–30 g**, and protein loss may reach **~9 g/m²/day**, causing **hypoalbuminaemia**.
- Acquired erythroderma shows a **Th2-skewed cytokine milieu (IL-4, IL-13)** with **raised serum IgE**, and up-regulation of endothelial adhesion molecules (**VCAM-1, ICAM-1, E-/P-selectin**) facilitating inflammatory cell trafficking.

Clinical features

- **Cutaneous**: Erythema typically *precedes exfoliation by 2–6 days*; scaling often begins in the flexures. The **character of scale offers clues** — *fine* in atopic dermatitis/dermatophytosis, *bran-like* in seborrhoeic dermatitis, *crusted/cornflake* in pemphigus foliaceus, *exfoliative (peeling)* in drug reactions.
- **Pruritus** in up to **90%** (most severe in dermatitis and Sézary syndrome); **lichenification** in ~one-third.
- **Appendages**: nail changes in ~**40%** (shiny nails, ridging, subungual hyperkeratosis, Beau's lines, paronychia, shedding); **diffuse non-scarring alopecia** in ~20% of chronic cases; **palmoplantar keratoderma** in ~30% (early sign in PRP; painful/fissured in Sézary; scale-crust in crusted scabies).
- **Ocular**: bilateral **ectropion** with epiphora and purulent conjunctivitis; secondary *Staphylococcus aureus* colonisation/infection is common.
- **Systemic complications**: peripheral/pedal oedema (~50%, from hypoalbuminaemia and fluid shift), **tachycardia (~40%) and high-output cardiac failure** (markedly increased cutaneous blood flow), **thermoregulatory disturbance** (hypo- or hyperthermia, rigors), **hypermetabolism and cachexia**, anaemia (iron deficiency + chronic disease).
- **Lymphoreticular**: **peripheral lymphadenopathy in ~50%** — distinguish reactive **dermatopathic lymphadenopathy** from lymphomatous involvement; hepatomegaly ~20%, splenomegaly rare (suggests systemic lymphoma).

Diagnostic evaluation

- **History**: pre-existing dermatosis, full drug history (including herbal/self-medication), atopy, prior cutaneous lymphoma; examine for residual clues (psoriatic plaques, *nappes claires* of PRP, *deck-chair sign* of Ofuji).
- **Skin biopsy** (the key test) — take **multiple, serial biopsies**; diagnostic yield up to ~**50–66%**, but findings are **non-specific in at least one-third** of Sézary syndrome/erythrodermic MF, so repeat sampling is essential.
- **Bloods**: CBC with differential and **peripheral smear for Sézary cells** (cerebriform lymphocytes), **flow cytometry**, **T-cell receptor gene rearrangement (PCR)** in skin/blood, serum IgE, LFTs, **serum albumin, electrolytes**, eosinophil count.
- **Lymph node biopsy** (core/excisional preferred over FNAC) if significant lymphadenopathy — guided by **CT or PET-CT** to the most FDG-avid node; inform the pathologist that the patient is erythrodermic.

- **Molecular diagnostics (NGS / whole-exome sequencing)** are pivotal in neonatal erythroderma to identify ichthyosis/immunodeficiency mutations.

Sézary syndrome — ISCL/EORTC diagnostic criteria	Requirement
Core triad	Erythroderma + generalised lymphadenopathy + clonal circulating atypical (Sézary) T-cells
Mandatory	Erythroderma **plus** an **identical T-cell clone in blood and skin**
Plus one of	(1) **≥1000 Sézary cells/mm^3**; (2) **CD4:CD8 ratio ≥10:1**; (3) **≥40% CD4$^+$/CD7$^-$ or ≥30% CD4$^+$/CD26$^-$** cells on flow cytometry (B2 blood tumour burden)

Management

Erythroderma is a **skin emergency**; acute/fulminant cases often need **hospital admission**.

- **General/supportive (regardless of cause)**: correct **fluid and electrolyte balance**, nutritional support (high-protein), **maintain body temperature** (warm blankets, emollients to counter hypothermia), monitor and treat **high-output cardiac failure**, and **detect/treat secondary infection** with anti-staphylococcal antibiotics. **Withdraw all non-essential and suspected drugs.**
- **Topical**: frequent **bland greasy emollients** to restore barrier; **open wet dressings**; low–mid-potency corticosteroids (high-potency reserved for lichenified sites). **Avoid coal tar and phototherapy** (may aggravate); **avoid salicylic/lactic acid in neonates** (enhanced absorption). Sedating **oral antihistamines** for pruritus.
- **Systemic corticosteroids**: useful in **idiopathic and drug-induced** erythroderma — prednisone **1–2 mg/kg/day**, maintenance ≤0.5 mg/kg/day, tapered cautiously (rebound). **Avoid systemic steroids in psoriatic erythroderma** — withdrawal precipitates a **generalised pustular flare**.
- **Cause-specific**: *Psoriatic erythroderma* — **methotrexate, acitretin, ciclosporin or biologics** (anti-TNF, anti-IL-12/23, anti-IL-17, anti-IL-23); *PRP* — acitretin/methotrexate; *Idiopathic/refractory* — **ciclosporin 5 mg/kg/day** reducing to 1–3 mg/kg/day (± azathioprine, MMF, methotrexate); *DRESS* — drug withdrawal ± systemic steroids/IVIg; *CTCL* — specific topical/systemic therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Whole-body map of erythroderma"**: a body silhouette shaded to show **>80–90% confluent erythema with scaling**, labelled with: *facial oedema / ectropion*, *leonine facies (CTCL)*, *diffuse alopecia*, *generalised lymphadenopathy*, *shiny dystrophic nails*, *palmoplantar keratoderma*, *pedal oedema*, and a flexural arrow marking *"island of sparing — nappes claires (PRP)"* and *"deck-chair sign (Ofuji)"*.
- **Diagram 2 — Aetiology pie/flow**: a wheel of the major causes with approximate frequencies — **Dermatitis ~24%, Psoriasis ~20%, Drugs ~19%, CTCL ~8%, Idiopathic ~25%**, feeding into a box: *"Multiple skin biopsies + bloods/flow cytometry/TCR + LN biopsy → underlying diagnosis"*.

Clinical / Diagnostic significance

- Erythroderma is a **medical emergency**: the principal threats are **high-output cardiac failure, hypothermia, fluid/protein/electrolyte loss, dehydration and sepsis** (cutaneous/respiratory infection — **pneumonia is the commonest cause of death**).
- **CTCL is the commonest malignancy underlying erythroderma**; any persistent "idiopathic" erythroderma in an elderly man warrants **serial biopsies, repeat flow cytometry and TCR studies** to exclude Sézary syndrome.
- **Always reconcile drug history** — drug-induced disease has the **best prognosis**, usually resolving **2–6 weeks** after withdrawal (exception: DRESS/DIHS).
- Mortality historically quoted at **18–64%**; modern outcomes are better, and **deaths are rare in the absence of CTCL**, but relapse rates reach **20–30% at one year**.

High-yield exam pointers

- **Definition**: generalised erythema + scaling over **≥80–90% BSA**; term coined by *Hebra* (1868); = exfoliative dermatitis.
- **Commonest causes (adults)**: dermatitis, psoriasis, drugs, CTCL; **idiopathic in ~25%** (elderly men = "red man syndrome / l'homme rouge").
- **Scale clues**: fine (eczema), bran-like (seborrhoeic), crusted (pemphigus foliaceus), peeling (drugs); **nappes claires** = PRP; **deck-chair sign** = papuloerythroderma of Ofuji.
- **Systemic effects**: high-output cardiac failure, hypothermia, hypoalbuminaemia (scale protein loss up to ~9 g/m^2/day), peripheral oedema, dermatopathic lymphadenopathy.
- **Sézary syndrome** = erythroderma + lymphadenopathy + clonal blood Sézary cells; *ISCL/EORTC*: ≥1000 Sézary cells/mm^3, CD4:CD8 ≥10:1, or CD4$^+$/CD7$^-$ ≥40% / CD4$^+$/CD26$^-$ ≥30%.
- **Investigation**: multiple skin biopsies (non-specific in ≥1/3 of Sézary), TCR gene rearrangement, flow cytometry; **NGS in neonates**.
- **Treatment cardinal rule**: supportive care + stop offending drug; **systemic steroids help idiopathic/drug-induced but are CONTRAINDICATED in psoriatic erythroderma** (pustular rebound) — use MTX/acitretin/ciclosporin/biologics instead.
- **Neonatal mnemonics**: Netherton (*SPINK5*, bamboo hair), Omenn (*RAG1/RAG2*), epidermolytic ichthyosis (*KRT1/10*), SSSS.

SOURCE & COVERAGE

- **Bolognia *Dermatology* 5e — "Erythroderma" (Chapter 10, Sean Whittaker)** — primary source for definition, epidemiology, aetiology tables (adult + neonatal), pathogenesis, clinical/systemic features, Sézary ISCL/EORTC criteria, and treatment.
- **Rook's *Textbook of Dermatology* 10e — "Erythroderma" (in Eczematous Disorders)** — causes/prevalence, complications, mortality, treatment ladder, Sézary cell thresholds.
- **Harrison's *Principles of Internal Medicine* 22e — "Skin Manifestations of Internal Disease" and "Eczema, Psoriasis…"** — causes of erythroderma, drug-induced/DRESS, CTCL association.
- **CMDT 2026 — "Exfoliative Dermatitis (Exfoliative Erythroderma)," Dermatologic Disorders** — current diagnostic essentials, frequencies, and management.

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Neuroleptic malignant syndrome

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

Definition / Introduction — Neuroleptic malignant syndrome (NMS) is a rare, potentially fatal, idiosyncratic hyperthermic syndrome caused by dopamine receptor blockade, classically after antipsychotic exposure, or by abrupt withdrawal of dopaminergic therapy in Parkinson disease. It is defined clinically by the tetrad of **hyperthermia**, **severe generalized rigidity**, **altered mental status**, and **autonomic instability**, with laboratory evidence of muscle injury. It is a medical emergency because death results from hyperpyrexia, aspiration pneumonia, rhabdomyolysis with acute kidney injury, hepatic failure, respiratory arrest, or cardiovascular collapse.

Epidemiology and etiopathogenesis

- **Incidence:** DSM-5-TR database studies suggest **0.01-0.02%** among antipsychotic-treated patients; one Hong Kong population study reported **0.11%**.
- **Mechanism:** central **hypodopaminergic state** due to dopamine D2 receptor blockade or sudden reduction of dopaminergic stimulation.
- **Striatum:** dopamine blockade in the corpus striatum causes sustained muscle contraction and **lead-pipe rigidity**, generating heat and rhabdomyolysis.
- **Hypothalamus:** impaired central thermoregulation causes hyperthermia; spinal/autonomic dopaminergic dysfunction contributes to tachycardia, labile BP, diaphoresis, pallor, and incontinence.
- **Muscle injury:** sustained contraction causes raised **creatine kinase (CK)**, myoglobinemia/myoglobinuria, metabolic acidosis, hyperkalemia, and AKI.
- **Overlap:** NMS is considered by many authors to overlap with malignant catatonia and parkinsonian hyperthermia syndrome, but the drug exposure/withdrawal history is decisive.

Precipitating drugs and risk factors

- **Dopamine receptor blockers:** all antipsychotics may cause NMS; risk is greater with **high-potency first-generation antipsychotics** such as haloperidol and fluphenazine, especially high dose, rapid titration, or parenteral use.
- **Atypical antipsychotics:** NMS is reported with olanzapine, risperidone, clozapine, quetiapine, and other SGAs; presentation may be milder or partial, so diagnosis may be delayed.
- **Nonpsychiatric dopamine blockers:** antiemetics and prokinetics such as **metoclopramide** and **prochlorperazine** can precipitate NMS.
- **Dopaminergic withdrawal:** abrupt withdrawal of levodopa or dopamine agonists in Parkinson disease can precipitate an NMS-like parkinsonian hyperthermia syndrome.
- **Patient and illness risks:** dehydration, exhaustion, psychomotor agitation, low serum iron/iron deficiency, affective illness, pre-existing catatonia, neurologic disease, prior NMS, and history of malignant hyperthermia.
- **Treatment-related risks:** high total antipsychotic dose, rapid escalation, intermittent nonadherence followed by re-exposure, long-acting injectable/depot preparations, and **lithium plus antipsychotic** combination.
- **Demographic risks:** Kaplan notes higher risk in **men** and younger patients, but DSM emphasizes that NMS can occur in any patient receiving dopamine antagonists, even at therapeutic doses.

Clinical features and diagnostic criteria

- **Timing:** onset ranges from hours to days after drug initiation or dose increase; some develop within **24 hours**, most within the **first week**, and virtually all within **30 days**. CMDT notes most cases develop within the first **2 weeks** of antipsychotic treatment.
- **Hyperthermia:** DSM-5-TR describes oral temperature **>100.4 F (>38.0 C) on at least two occasions**, often with profuse diaphoresis; extreme temperature supports the diagnosis.
- **Rigidity:** severe generalized **lead-pipe rigidity**, usually unresponsive to routine antiparkinsonian agents; associated tremor, akinesia, dystonia, trismus, sialorrhea, dysarthria, dysphagia, and rhabdomyolysis may occur.
- **Mental status:** delirium or altered consciousness is often early; spectrum includes alert but dazed state, mutism, catatonic stupor, stupor, and coma.
- **Autonomic instability:** tachycardia **>25% above baseline**, tachypnea **>50% above baseline**, diaphoresis, pallor, urinary incontinence, BP elevation **>=25% above baseline**, or BP fluctuation of **>=20 mmHg diastolic** or **>=25 mmHg systolic** within 24 hours.
- **Respiratory compromise:** chest wall restriction, aspiration pneumonia, pulmonary embolism, hypermetabolism, and metabolic acidosis may cause respiratory distress or sudden respiratory arrest.
- **Diagnostic frame:** NMS is a **clinical diagnosis of exclusion** in a patient exposed to dopamine blockade or dopaminergic withdrawal, with hyperthermia, rigidity, mental change, autonomic instability, and muscle enzyme elevation.

Investigations and monitoring

Investigation	Expected / useful finding
CBC	Leukocytosis common; Kaplan notes WBC often **10,000-40,000/mm3**
CK serially	Usually **>1000 IU/L** or **>=4 times upper limit of normal**; may be modest/normal early or before rigidity develops
Renal profile	Rising urea/creatinine from rhabdomyolysis, dehydration, or myoglobinuric AKI
Electrolytes, ABG/VBG	Hyperkalemia, metabolic acidosis, hypoxia; guide ICU care
Urinalysis	Myoglobinuria; assess renal complications and exclude urinary infection
LFTs	Transaminase elevation may occur; hepatic failure is a fatal complication
Blood/urine cultures, CXR	Fever workup; do not miss sepsis, aspiration pneumonia, or CNS infection
ECG and hemodynamics	Tachyarrhythmia, QT issues from antipsychotics, BP lability
CSF/neuroimaging/EEG	CSF and imaging generally normal in NMS; EEG may show generalized slowing if encephalopathic

- **Interpretation pearl:** isolated CK elevation after IM injections, restraint, agitation, or dystonia is **not NMS** unless accompanied by hyperthermia and rigidity.
- **Monitoring:** chart temperature, pulse, BP, respiratory rate, SpO2, urine output, hydration status, CK, creatinine, potassium, bicarbonate, and complications at least daily; severe cases need ICU-level monitoring.

Differential diagnosis

Disorder	Clues favouring it over NMS
Serotonin syndrome	Onset within hours of serotonergic drug/MAOI interaction; **clonus, hyperreflexia, myoclonus**, tremor, GI symptoms; treat with drug withdrawal, benzodiazepine, and cyproheptadine
Malignant hyperthermia	Occurs during/after volatile anesthetic or succinylcholine exposure; severe rigidity and hypercapnia; dantrolene is central therapy
Malignant catatonia	Catatonic prodrome with psychiatric illness before dopamine blocker exposure; may be clinically indistinguishable
Heat stroke / exertional hyperthermia	Environmental heat/exertion, anhidrosis or exertional collapse; antipsychotics may impair heat loss but dopamine-blocker chronology absent
Anticholinergic toxicity	Hot dry skin, mydriasis, ileus, urinary retention, delirium; usually no lead-pipe rigidity or marked CK pattern
CNS infection/autoimmune encephalitis/status epilepticus	Headache, meningism, seizures, focal signs, abnormal CSF/EEG/imaging; always exclude in first presentation
Tetanus, strychnine, thyrotoxicosis, pheochromocytoma	Exposure/history and characteristic spasms or endocrine crisis; not linked to recent dopamine blockade

- **Serotonin syndrome vs NMS:** the exam contrast is **clonus/hyperreflexia/myoclonus** in serotonin syndrome versus **lead-pipe rigidity, hypodopaminergic exposure, and slower days-weeks evolution** in NMS.

Management

- **Immediate actions:** stop the offending antipsychotic/dopamine blocker and avoid all dopamine antagonists; if due to Parkinson drug withdrawal, promptly reinstitute dopaminergic therapy.
- **Site of care:** admit to HDU/ICU for severe hyperthermia, altered consciousness, rigidity, dysphagia, aspiration risk, AKI, metabolic acidosis, arrhythmia, or labile BP.
- **Supportive care:** airway protection, oxygen, aspiration precautions, IV fluids, correction of electrolytes/acidosis, urine output monitoring, prevention/treatment of rhabdomyolysis and AKI, DVT/pressure sore prevention, and nutrition.
- **Temperature control:** active cooling with cooling blankets, tepid spraying/fanning, ice packs, or more aggressive external cooling for severe hyperthermia; do not rely on antipyretics because NMS is hyperthermia rather than cytokine-mediated fever.
- **Benzodiazepines:** useful for agitation, rigidity with catatonic features, and when serotonin syndrome cannot be confidently excluded; lorazepam is commonly used.
- **Dopamine agonists: bromocriptine 2.5 mg orally twice or thrice daily**, titrating up to **45 mg/day**, or CMDT dose **2.5-10 mg orally three times daily**; watch for hypotension, vomiting, psychosis, and possible worsening of serotonin syndrome if the diagnosis is wrong.
- **Amantadine: 100-200 mg orally twice daily** or **200-400 mg/day in divided doses** when bromocriptine is unsuitable or as adjunctive dopaminergic therapy.
- **Dantrolene:** for severe rigidity/hyperthermia; CMDT gives **50 mg IV as needed**, not exceeding **10 mg/kg/day** because of hepatotoxicity; other Kaplan dosing uses IV weight-based regimens up to the same daily ceiling.
- **Severe hyperthermia with rigidity:** toxicology guidance supports rapid nondepolarizing neuromuscular paralysis, intubation, mechanical ventilation, and sedation when cooling fails or rigidity is extreme.
- **ECT:** consider for refractory NMS, prominent malignant catatonia, or when psychosis/catatonia needs treatment while antipsychotics are stopped.
- **Evidence caveat:** no drug is specifically approved for NMS; dantrolene, bromocriptine, amantadine, benzodiazepines, levodopa, and ECT are supported mainly by clinical experience and case-based evidence, so early recognition and supportive care remain the core treatment.

Prevention, rechallenge and prognosis

- **Prevention:** use the lowest effective antipsychotic dose, avoid rapid escalation, correct dehydration, avoid unnecessary parenteral high-potency agents, monitor early fever/rigidity in catatonic or agitated patients, and avoid abrupt withdrawal of Parkinson medications.
- **Course after stopping drug:** mean recovery is **7-10 days**; most recover within **1 week** and nearly all within **30 days**, but depot/long-acting injectable exposure can prolong illness.

- **Mortality:** DSM-5-TR reports **10-20%** fatality when unrecognized; older Kaplan descriptions report **20-30%** in well-developed cases, higher with depot drugs, but mortality falls with early recognition.
- **Residual sequelae:** weeks of residual neurologic signs, cognitive deficits, renal injury, or complications of prolonged ICU stay may occur.
- **Rechallenge:** if antipsychotic therapy is essential, wait at least **2 weeks after full clinical resolution**, correct dehydration/iron deficiency and other risks, avoid lithium, choose an alternate lower-risk agent, start low, titrate slowly, and monitor temperature, rigidity, autonomic signs, CK, and renal function.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis flow diagram:** dopamine antagonist / dopaminergic withdrawal -> D2 blockade in striatum, hypothalamus, spinal autonomic pathways -> rigidity + impaired thermoregulation + autonomic instability -> hyperthermia, rhabdomyolysis, AKI, respiratory/cardiovascular collapse.
- **NMS bedside diagnostic tetrad:** four labelled boxes: hyperthermia; lead-pipe rigidity; altered mental status; autonomic instability; central label: recent dopamine blocker or dopaminergic withdrawal; side labels: high CK, leukocytosis, myoglobinuria.

Clinical / Diagnostic significance

- Any patient on antipsychotics who develops **fever plus rigidity or altered mental status** should be treated as possible NMS until proven otherwise.
- NMS may present to medicine, emergency, ICU, neurology, or psychiatry; it is not restricted to psychiatric patients because antiemetics such as metoclopramide and prochlorperazine are common triggers.
- Early differentiation from serotonin syndrome matters: bromocriptine may worsen serotonin syndrome, whereas cyproheptadine is used for serotonin toxicity.
- Normal early CK does not exclude NMS; serial examination and CK trend are more useful than one value.
- In a clozapine patient with fever, tachycardia, and dyspnea, also evaluate for **clozapine myocarditis** with ECG, troponin, and echocardiography where clinically indicated.
- Do not label every antipsychotic fever as NMS: rule out infection, aspiration pneumonia, heat illness, toxic ingestion, CNS infection/encephalitis, status epilepticus, and endocrine crisis.

High-yield exam pointers

- Write the tetrad: **hyperthermia + lead-pipe rigidity + altered sensorium + autonomic instability**.
- Key trigger: recent **dopamine antagonist** exposure or abrupt **dopaminergic withdrawal**.
- DSM thresholds: temperature **>38 C twice**, CK often **>=4 times ULN**, tachycardia **>25% baseline**, tachypnea **>50% baseline**.
- Best differentiator from serotonin syndrome: **NMS = rigidity; serotonin syndrome = clonus/hyperreflexia/myoclonus**.

- Common labs: **CK rise, leukocytosis, metabolic acidosis, low serum iron, myoglobinuria, raised creatinine, raised transaminases**.
- First treatment step: **stop antipsychotic immediately** and start aggressive supportive care.
- Drug options: **bromocriptine**, **amantadine**, **dantrolene**, benzodiazepines; ECT for refractory/catatonic cases.
- Severe cases die from **hyperpyrexia, aspiration, AKI, hepatic failure, respiratory arrest, cardiovascular collapse**.
- Rechallenge only after full recovery, preferably after **>=2 weeks**, using low dose, slow titration, alternate agent, and close monitoring.

SOURCE & COVERAGE

Harrison 22e — "Tremor, Chorea, and Other Movement Disorders"; Harrison 22e — "Psychiatric Disorders"; Kaplan & Sadock's Comprehensive Psychiatry 2024 — "Dopamine Antagonists", "Medication-Induced Movement Disorders and Other Adverse Effects of Medication", and "Dopamine Receptor Agonists"; DSM-5-TR — "Medication-Induced Movement Disorders and Other Adverse Effects of Medication"; CMDT 2026 — "Common Symptoms", "Psychiatric Disorders", and "Poisoning".

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Obsessive compulsive disorder

Asked in: Paper IV Jul 2021 · Paper IV Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Obsessive-compulsive disorder (OCD) is a chronic, often disabling neuropsychiatric condition characterised by **obsessions** (recurrent, intrusive, unwanted thoughts, images or urges that cause marked anxiety) and/or **compulsions** (repetitive behaviours or mental acts performed to neutralise that anxiety), which are time-consuming (typically >1 hour per day) or cause clinically significant distress and functional impairment. In DSM-5-TR it heads its own category — *Obsessive-Compulsive and Related Disorders* — separated from the anxiety disorders, and the patient generally recognises the symptoms as excessive or senseless yet feels driven to perform them. Lifetime prevalence is ~2–3% worldwide.

Clinical features — obsessions, compulsions and symptom dimensions

- **Obsessions** are intrusive and *not pleasurable*: fears of contamination/germs, pathological doubt, aggressive or sexual/blasphemous (taboo) thoughts, and need for symmetry. They are resisted but provoke anxiety or disgust.
- **Compulsions (rituals)** are repetitive behaviours (handwashing, ordering, checking) or covert mental acts (counting, praying, repeating words) performed rigidly to reduce distress or prevent a dreaded event — yet are *not realistically connected* to it, or are clearly excessive.
- Four recurring **symptom dimensions** (DSM-5-TR): **cleaning** (contamination/washing); **symmetry** (ordering, counting, repeating); **forbidden/taboo thoughts** (aggressive, sexual, religious); and **harm** (fear of harm → checking). Most patients have symptoms in more than one dimension.

- **Sensory phenomena** ("just-right", incompleteness, premonitory urges) precede compulsions in up to 60%.
- Patients commonly **conceal** symptoms out of embarrassment — the physician must ask directly. Physical clues: *chafed, reddened hands* (washing) or *patchy hair loss* (trichotillomania).
- **Insight** varies and defines a specifier — good/fair, poor, or absent/delusional (≤4%); poorer insight predicts worse outcome. **Accommodation** (family participating in rituals) maintains symptoms.

Diagnostic criteria (DSM-5-TR) and specifiers

Component	Requirement
A	Presence of obsessions, compulsions, or both (each defined by intrusive nature + neutralising attempt)
B	Time-consuming (>1 h/day) **or** clinically significant distress/impairment
C	Not attributable to a substance or another medical condition
D	Not better explained by another mental disorder (GAD, BDD, hoarding, trichotillomania, eating disorder, etc.)
Insight specifier	With good/fair insight · With poor insight · With absent insight/delusional beliefs
Tic specifier	"Tic-related" — current or past tic disorder (up to 30% of OCD)

- Severity and treatment response are graded with the ***Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)***, scored out of 40; the children's version is the CY-BOCS.

Epidemiology, etiology and neurobiology

- **Prevalence:** 12-month prevalence ~1.2% (US); lifetime ~2–3%. **Mean age of onset 19.5 years**, with 25% of cases beginning by age 14; onset after 35 is unusual. Males have earlier (childhood) onset and more tic comorbidity; among adults it is slightly more common in women.
- **Genetics:** Strong familial aggregation — first-degree relative risk ~2× (adult-onset proband) and ~10× for childhood-onset probands; twin concordance 0.57 (MZ) vs 0.22 (DZ); additive genetic effects explain ~40% of variance. No single susceptibility gene is established. Familial co-aggregation with **Tourette's disorder**.
- **Neuroanatomy:** Dysfunction of the **cortico-striato-thalamo-cortical (CSTC) circuit** — *orbitofrontal cortex, anterior cingulate cortex, caudate nucleus and globus pallidus*. The caudate mediates habit/skill learning; effective treatment reduces caudate metabolic activity. **Serotonergic dysregulation** underpins the selective efficacy of serotonin-reuptake-blocking drugs.
- **Environmental:** Adverse perinatal events, prematurity, maternal smoking, childhood abuse, and post-infectious autoimmune mechanisms (**PANDAS** — Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection) in some abrupt-onset paediatric cases.

Differential diagnosis and comorbidity

- **Differential diagnosis:** generalised anxiety disorder (real-life worries, no rituals); major depressive disorder (mood-congruent ruminations, not linked to compulsions); specific/social phobia; body dysmorphic disorder; trichotillomania and excoriation disorder; hoarding disorder; tics/stereotypies (preceded by premonitory urge, not by an obsession); psychotic disorders (in delusional-insight OCD, obsessions/compulsions persist and other psychotic features are absent); and crucially **obsessive-compulsive personality disorder** (pervasive perfectionism/rigidity *without* true obsessions or compulsions).
- **OCD-spectrum (related) disorders:** body dysmorphic disorder, hoarding, trichotillomania (hair-pulling), excoriation (skin-picking), and tics.
- **Comorbidity (high):** anxiety disorder ~76%, depressive/bipolar disorder ~63% (MDD ~41% — develops in roughly two-thirds over a lifetime), impulse-control disorder ~56%, substance use ~39%, and lifetime tic disorder up to 30%.
- **Suicide risk is significant** — mean lifetime suicidal ideation ~44% and lifetime attempts ~14%; registry data show markedly elevated odds of suicide death and attempt, especially with the taboo-thoughts dimension and comorbid depression.

Treatment / Management

- **General principles:** OCD responds more slowly than depression — an adequate SSRI trial needs **8–12 weeks** at **higher doses** than for depression. Only **50–60%** improve with pharmacotherapy alone; **combining medication with exposure and response prevention (ERP) is superior** to either alone. Achieved responders need long-term maintenance.

Modality	Agents / technique	Notes
First-line drugs (SSRIs)	Fluoxetine 5–60 (up to 80) mg/d · Fluvoxamine 25–300 mg/d · Paroxetine 40–60 mg/d · Sertraline 50–150 mg/d	FDA-approved for OCD; high-dose, prolonged trials
TCA	**Clomipramine** 25–250 mg/d	Potent serotonergic TCA; efficacy *independent* of antidepressant action; anticholinergic/sedative limits use; keep plasma clomipramine + metabolite <500 ng/mL
Other (off-label)	Venlafaxine, duloxetine	Efficacious but not FDA-approved
Augmentation (resistant)	Antipsychotic (neuroleptic), buspirone, benzodiazepine; CMDT adds topiramate, memantine, riluzole, N-acetylcysteine, lamotrigine, ondansetron, anti-inflammatories (minocycline, celecoxib)	For partial/non-responders
Psychotherapy	**Exposure and response prevention (ERP)** — first-line; cognitive-behavioural therapy; acceptance and commitment therapy	Graded exposure + ritual prevention; family psychoeducation/de-accommodation
Neuromodulation	**rTMS** (high-dose theta-burst) — FDA-approved for treatment-resistant OCD	Non-invasive

Modality	Agents / technique	Notes
Refractory/ severe	**Deep-brain stimulation** (ventral capsule/ventral striatum, VC/VS) — FDA humanitarian device exemption; ablative psychosurgery	<1% of patients qualify; Y-BOCS typically ≥26–30

- **Ablative psychosurgery** (bilateral, stereotactic) for intractable OCD after exhausting drugs + ERP: **anterior cingulotomy** (target ACC, Brodmann areas 24/32 at the cingulum margin), **anterior/gamma ventral capsulotomy** (anterior limb of the internal capsule), and **subcaudate tractotomy** (substantia innominata) — ~40–60% respond.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Cortico-striato-thalamo-cortical (CSTC) loop in OCD.** Draw and label: **Orbitofrontal cortex (OFC)** and **Anterior cingulate cortex (ACC)** → **Striatum (Caudate nucleus)** → **Globus pallidus / Substantia nigra** → **Thalamus** → back to **Cortex**; mark the hyperactive OFC–caudate–thalamus circuit and indicate **SSRI / ERP** reducing caudate metabolic activity, plus **DBS at VC/VS** as the surgical target.
- **Stepwise management ladder.** Boxes: (1) High-dose SSRI + ERP → (2) Switch SSRI / Clomipramine → (3) Augmentation (antipsychotic / others) → (4) rTMS → (5) DBS / ablative surgery; side label "Y-BOCS to monitor severity & response."

Clinical / Diagnostic significance

- A general physician must **actively screen** for concealed OCD when faced with unexplained dermatitis of the hands, trichotillomania-related alopecia, or refractory anxiety — early recognition prevents years of disability.
- **Y-BOCS** quantifies severity, guides escalation, and defines surgical candidacy (≥26–30/40).
- OCD carries **substantial suicide risk** and heavy psychiatric comorbidity (depression, tics, substance use) — these must be screened and treated concurrently.
- Distinguishing OCD from **OCPD** and from psychotic rumination changes management entirely; abrupt paediatric onset warrants evaluation for **PANDAS**.

High-yield exam pointers

- OCD = obsessions ± compulsions, **>1 h/day**; lifetime prevalence **2–3%**; mean onset **~19.5 yr**, 25% by 14.
- DSM-5-TR places it in **Obsessive-Compulsive and Related Disorders**, not anxiety disorders; specifiers = **insight** (good-fair/poor/absent-delusional) and **tic-related**.
- Four symptom dimensions: **cleaning, symmetry, forbidden thoughts, harm**.
- Neurobiology = **CSTC loop** (OFC–ACC–caudate–globus pallidus–thalamus) + **serotonin** dysregulation; co-aggregates with **Tourette's**.
- **SSRIs first-line** (higher doses, 8–12 week trials); **clomipramine** second-line (keep level <500 ng/mL); only **50–60%** respond to drugs alone.
- **ERP** is the core psychotherapy; **drug + ERP** beats either alone.

- Refractory ladder: augmentation → **rTMS (FDA-approved)** → **DBS (VC/VS, HDE)** / ablative psychosurgery (cingulotomy, capsulotomy).
- Up to **30%** have a comorbid tic disorder; MDD develops in ~two-thirds; significant **suicide risk**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Psychiatric Disorders" (OCD clinical features, neuroanatomy, drug doses, treatment-resistance and neuromodulation).
- **DSM-5-TR (American Psychiatric Association)** — "Obsessive-Compulsive Disorder" (diagnostic criteria, specifiers, symptom dimensions, epidemiology, course, risk factors, suicide, comorbidity, differential diagnosis).
- **Kaplan & Sadock's Comprehensive Psychiatry, 2024** — psychiatric neurosurgery for intractable OCD (Y-BOCS thresholds, anterior cingulotomy, anterior/gamma ventral capsulotomy, subcaudate tractotomy, DBS at VC/VS) and PANDAS.
- **CMDT 2026** — "Psychiatric Disorders" (current pharmacologic/behavioural management, augmentation agents, rTMS, DBS, prognosis).

Coverage note: Harrison 22e covers OCD only briefly; depth here (DSM-5-TR criteria/specifiers, surgical targets, augmentation regimens) is drawn from the dedicated psychiatric texts and CMDT as directed by the grounding hierarchy.

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Personality disorders

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Personality disorders (PDs) are **characteristic patterns of thinking, feeling and interpersonal behaviour that are relatively inflexible**, deviate markedly from the expectations of the individual's culture, and cause **significant functional impairment or subjective distress**. The behaviours are not secondary to another mental disorder, substance use or a general medical condition — an important distinction, because *personality change may be the first sign of serious neurologic, endocrine or other medical illness* (e.g., frontal-lobe tumour). PDs occur in **10–20% of the general population and in about half of psychiatric in-/out-patients**, where they constitute the prototypical "difficult patient".

General diagnostic criteria (DSM-5-TR)

- **Criterion A** — an *enduring pattern* of inner experience and behaviour deviating markedly from cultural expectations, manifest in **two or more** of: **cognition, affectivity, interpersonal functioning, impulse control**.
- **Criterion B** — the pattern is **inflexible and pervasive** across a broad range of personal and social situations.
- **Criterion C** — leads to **clinically significant distress or impairment** (social, occupational or other functioning).

- **Criterion D — stable and of long duration**; onset traceable at least to **adolescence or early adulthood**.
- **Criteria E and F** — not better explained by another mental disorder, a substance or another medical condition (e.g., head trauma).
- Diagnosis **before age 18 years** requires the features to be present for **at least 1 year**; the single exception is **antisocial PD, which cannot be diagnosed below 18 years**.
- Traits are typically **egosyntonic** (perceived as appropriate by the patient) and **alloplastic** (blame is externalised); avoidant and dependent PD are relatively egodystonic. Collateral information and cultural/gender context are essential.

Classification — DSM-5-TR clusters and dimensional models

Cluster	Disorders	Shared descriptor	Temperament correlate (Cloninger)
A — odd, eccentric, aloof	Paranoid, Schizoid, Schizotypal	Emotional distance, restricted affect, social isolation	**Low reward dependence** (detachment)
B — dramatic, erratic, impulsive	Antisocial, Borderline, Histrionic, Narcissistic	Impulsive, excessively emotional behaviour	**High novelty seeking** (impulsivity)
C — anxious, fearful	Avoidant, Dependent, Obsessive-compulsive	Enduring anxiety and fear	**High harm avoidance** (OCPD: high persistence)

- Cluster boundaries are **overlapping and partly artificial**; many patients meet criteria for more than one PD, and comorbid major mental disorder risk is increased. All PDs share **low self-directedness and low cooperativeness**.
- DSM-5-TR also recognises **personality change due to another medical condition** (labile, disinhibited, aggressive, apathetic, paranoid, combined subtypes) and **other specified / unspecified PD** (mixed, passive-aggressive, depressive presentations).
- **Alternative DSM-5 model (Section III)** — *hybrid dimensional–categorical*: **Criterion A** = moderate or greater impairment on the **Level of Personality Functioning Scale** (self = *identity, self-direction*; interpersonal = *empathy, intimacy*; levels 0–4); **Criterion B** = pathological traits in **five domains — Negative Affectivity, Detachment, Antagonism, Disinhibition, Psychoticism** (25 facets). It retains six disorders (antisocial, avoidant, borderline, narcissistic, obsessive-compulsive, schizotypal) plus **PD–trait specified**.
- **ICD-11 (WHO, 2019)** — abolishes categorical subtypes: PD is rated first by **severity (mild / moderate / severe)** based on self and interpersonal dysfunction (with a *late-onset* qualifier when no manifestations exist before age 25), then qualified by **five trait domains — negative affectivity, detachment, dissociality, disinhibition, anankastia — plus a "borderline pattern" specifier**.

Aetiology and pathophysiology

- **Genetic contribution**: one study of **106,000 subjects identified nine loci** significantly linked to aspects of neuroticism (Harrison); genetics explains roughly **half of the variance** in temperament traits.
- **Cluster A** disorders aggregate in families of probands with **schizophrenia and delusional disorder** (schizotypal PD shows smooth-pursuit eye-movement abnormalities, a putative schizophrenia-vulnerability marker).
- **Antisocial PD**: adoption studies show genetic + environmental contributions; **conduct disorder before age 10 plus ADHD**, erratic parenting and neglect increase adult risk; familial co-transmission with substance use and somatisation disorder.
- **Borderline PD**: a *tripartite model* — **childhood trauma (physical/sexual abuse, neglect, early parental loss), vulnerable temperament, triggering events**; **five times more common among first-degree relatives** of probands.
- Antisocial–narcissistic–histrionic form a familial "**spectrum**" of increasing severity (manipulation → exploitation → violent/property crime) driven by impulsive-aggressive traits.

Clinical features of the individual disorders

Disorder	Hallmark (key criteria)	Epidemiology / pearls
Paranoid	Pervasive distrust and suspiciousness — bears grudges, doubts loyalty/fidelity, reads hidden demeaning meanings (≥4 features)	0.5–4.4%; more in males; may precede delusional disorder; brief reactive psychosis under stress
Schizoid	Social detachment + restricted affect — "loner", anhedonia, indifferent to praise or criticism, no desire for relationships (≥4)	3.1–4.9%; more in males; solitary work may suit them
Schizotypal	Ideas of reference, **magical thinking**, unusual perceptions, odd speech/affect, social anxiety that does **not** diminish with familiarity (≥5)	3.9–4.6%; transient psychotic episodes; >50% have lifetime major depression; familial link to schizophrenia
Antisocial	Disregard for/violation of others' rights since age 15 — deceit, impulsivity, aggression, recklessness, irresponsibility, **lack of remorse** (≥3); requires **age ≥18 + conduct disorder before 15**	3% men, 1% women (3:1); flagrant behaviour "burns out" after age 30; *psychopathy* variant = low anxiety + bold dominance
Borderline	Instability of **affect, self-image and relationships** + marked impulsivity — frantic avoidance of abandonment, **idealisation–devaluation**, identity disturbance, self-damaging impulsivity, **recurrent suicidal/self-mutilating behaviour**, chronic emptiness, intense anger, stress-related paranoid/dissociative symptoms (≥5 of 9)	~2% general, 10% of outpatients, 20% of inpatients; 75% female; defence = **splitting**; up to **80% of hospitalised patients attempt suicide; completed suicide up to 5%** (CMDT)
Histrionic	Excessive emotionality and **attention seeking** — seductiveness, shallow rapidly shifting emotions, suggestibility, **impressionistic speech**, theatricality (≥5)	~2%; suicidal *gestures* to coerce caregiving; comorbid somatisation/conversion

Disorder	Hallmark (key criteria)	Epidemiology / pearls
Narcissistic	**Grandiosity, need for admiration, lack of empathy** — entitlement, exploitativeness, chronic envy, arrogance (≥5)	<1% general, 2–16% clinical; 50–75% male; fragile self-esteem with rage/depression after criticism
Avoidant	Hypersensitivity to negative evaluation, social inhibition, feelings of inadequacy — but **craves relationships** (vs schizoid) (≥4)	0.5–2%; overlaps with generalised social phobia
Dependent	Excessive need to be taken care of — clinging, submissive, cannot decide alone, fears separation, urgently seeks replacement relationships (≥5)	0.5–0.6%; predisposed by chronic physical illness, separation anxiety
Obsessive-compulsive (anankastic)	Preoccupation with **orderliness, perfectionism and control** — rules/lists, workaholism, hypermorality, inability to discard objects, stinginess, rigidity (≥4)	2–8%; **twice as common in males**; *no true obsessions/compulsions* (unlike OCD); type-A features

Differential diagnosis and assessment

- Exclude **another medical condition** (frontal-lobe tumour, temporal-lobe epilepsy, head trauma, hyperthyroidism), **substance use** and episodes of another mental disorder; *new personality change in middle/late life mandates organic work-up*.
- **Cluster A vs psychotic disorders** — PDs lack sustained delusions/hallucinations; schizophrenia preceded by schizotypal/schizoid traits is coded "premorbid".
- **Borderline vs mood disorders** — abandonment fears, identity disturbance, emptiness and idealisation–devaluation favour borderline; bipolar/cyclothymia are episodic.
- Classic differentials: **avoidant vs social phobia**, **OCPD vs OCD**, **antisocial vs adult antisocial behaviour** (no enduring personality pathology).
- Patients commonly present with **anxiety, depression or psychotic decompensation when coping fails** (CMDT) — the underlying PD is easily missed.

Management

- **Hospitalisation** only for serious suicidal or homicidal danger; otherwise day-hospital, halfway-house or therapeutic-community settings (CMDT).
- **Psychotherapy is the mainstay**, proceeding in stages: crisis management and stabilisation → positive perspective/therapeutic alliance → growth in self-awareness and integration (Kaplan).
- **Dialectical behaviour therapy (DBT)** — individual + group programme blending **mindfulness with a cognitive-behavioural model**, designed for **chronic suicidality / borderline PD**; efficacy shown in **several randomised trials** (Harrison, CMDT).
- Other modalities: **mentalization-based treatment, transference-focused psychotherapy, schema-focused therapy**, psychodynamic, CBT and group therapy; the therapist must manage **negative countertransference** and maintain boundaries.
- **Pharmacotherapy is adjunctive, symptom-domain-targeted** (evidence limited; use temporarily and taper):

Target symptom domain	First-line drugs	Notes
Mood dysregulation / anxiety	**SSRIs/SNRIs**; lithium, lamotrigine or valproate for emotional lability; MAOIs for atypical depression/rejection hypersensitivity	TCAs risky in overdose and may worsen atypical depression; avoid long-term benzodiazepines (dependence)
Impulsive (affective) aggression	**Lithium** (multiple double-blind trials), SSRIs (fluoxetine 20–60 mg/day; sertraline 50–200 mg/day), anticonvulsants — carbamazepine 400–800 mg/day, valproate 500–2000 mg/day, lamotrigine 50–200 mg/day	**No effective drug for predatory (planned) aggression**; benzodiazepines disinhibit violence
Social–emotional detachment (cluster A)	Low-dose **second-generation antipsychotics**; antidepressants if underlying depression	May reduce social withdrawal in "aloof" PDs
Cognitive–perceptual distortions / brief psychosis	Low-dose **atypical antipsychotics** (e.g., risperidone 0.5–2 mg/day, olanzapine 2.5–10 mg/day, quetiapine) only for symptom duration	Schizotypal patients often improve with antipsychotics

- Cluster-wise rule of thumb (Harrison): **cluster A — antidepressants ± low-dose antipsychotics; cluster B — anticonvulsant mood stabilisers and MAOIs** for mood reactivity, behavioural dyscontrol and rejection hypersensitivity; **cluster C — drugs used for anxiety disorders** (SSRIs).
- **Neuromodulation** — growing evidence for **transcranial magnetic stimulation** for borderline mood dysregulation and impulsivity (CMDT 2026).
- **Prognosis** — borderline and antisocial PD attenuate with age (borderline stabilises in the 4th–5th decades); obsessive-compulsive and schizotypal PD persist; **antisocial and narcissistic PD have a guarded prognosis** (limited engagement in therapy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — DSM-5-TR cluster wheel:** three sectors around a central circle labelled *"General criteria: enduring, pervasive, inflexible, early-onset pattern → distress/impairment"*. Sector labels: **Cluster A (odd–eccentric): Paranoid, Schizoid, Schizotypal — low reward dependence**; **Cluster B (dramatic–erratic): Antisocial, Borderline, Histrionic, Narcissistic — high novelty seeking**; **Cluster C (anxious–fearful): Avoidant, Dependent, Obsessive-compulsive — high harm avoidance**.
- **Diagram 2 — ICD-11 two-step dimensional model:** horizontal severity arrow labelled *Mild PD → Moderate PD → Severe PD* (axis caption: "self + interpersonal dysfunction; harm to self/others"); below it five trait-qualifier boxes labelled **Negative affectivity, Detachment, Dissociality, Disinhibition, Anankastia**, plus flags **Borderline-pattern specifier** and **"Late onset: no manifestations before age 25"**.

Clinical / Diagnostic significance

- PD patients are demanding, non-adherent and boundary-testing; recognising the pattern prevents counter-therapeutic reactions (firm limits for borderline, non-confrontational clarity for paranoid patients).

- **Always exclude organic disease** in apparent personality change: frontal-lobe tumour, temporal-lobe epilepsy, head injury, thyroid disease and substance use can all masquerade as PD.
- **Borderline PD is a medical emergency risk** — recurrent self-harm, overdose risk (avoid TCAs), suicide in up to 5%; document risk assessment and use DBT-based crisis planning.
- Comorbidity is the rule: depression, anxiety, substance use, eating disorders (bulimia with borderline), somatisation (histrionic) — treat comorbid syndromes actively.
- PD predicts poorer outcomes of comorbid illness and heavy use of health, welfare and prison resources; OCPD traits correlate with type-A behaviour and myocardial infarction risk.

High-yield exam pointers

- **Three clusters:** A = odd/eccentric (paranoid, schizoid, schizotypal); B = dramatic/erratic (antisocial, borderline, histrionic, narcissistic); C = anxious/fearful (avoidant, dependent, obsessive-compulsive).
- General criteria: enduring, pervasive, inflexible pattern from adolescence/early adulthood causing distress/impairment; ≥2 of cognition, affectivity, interpersonal functioning, impulse control.
- **Antisocial PD**: only PD that cannot be diagnosed <18 years; requires conduct disorder before 15; M:F = 3:1; "burns out" after 30.
- **Borderline PD**: ≥5 of 9 criteria; splitting; 75% female; suicide up to 5%; **DBT is the best-evidenced treatment**.
- **Schizotypal vs schizoid**: schizotypal has magical thinking/perceptual distortions; schizoid is merely detached. **Avoidant vs schizoid**: avoidant *wants* relationships but fears rejection.
- **OCPD ≠ OCD** — no true obsessions/compulsions; egosyntonic; twice as common in males.
- Pharmacotherapy is symptom-targeted: SSRIs for mood/impulsivity, lithium/anticonvulsants for affective aggression, low-dose atypical antipsychotics for cognitive-perceptual symptoms; **benzodiazepines are generally avoided** (dependence, disinhibition).
- **ICD-11** has replaced categories with a severity rating (mild/moderate/severe) + five trait qualifiers + borderline-pattern specifier; the DSM-5 alternative model uses the Level of Personality Functioning Scale + five trait domains.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — "Psychiatric Disorders" (Personality Disorders section); Kaplan & Sadock's Comprehensive Textbook of Psychiatry — "Personality Disorders" chapter (Cloninger & Lester) and "The Classification of Mental Disorders in the International Classification of Diseases (ICD-11)"; DSM-5-TR — "Personality Disorders" and "Alternative DSM-5 Model for Personality Disorders"; CMDT 2026 — "Psychiatric Disorders" (Personality Disorders: classification, DBT, pharmacotherapy doses, TMS). *Coverage note:* Harrison 22e itself covers personality disorders only briefly (clusters, genetics, one treatment paragraph); the criteria-level detail, epidemiology and dimensional models above are drawn from Kaplan & Sadock and DSM-5-TR, with current management from CMDT 2026.

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Post-traumatic stress disorder

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

Definition / Introduction — Post-traumatic stress disorder (PTSD) is a chronic, often recurrent trauma- and stressor-related disorder that develops after exposure to an extreme traumatic event such as the threat of personal death or injury or the death of a loved one. It is characterised by intrusive re-experiencing of the trauma, persistent avoidance of reminders, negative alterations in cognition and mood, and heightened arousal, persisting for more than 1 month and causing significant distress or functional impairment. It lies on a continuum with **acute stress disorder** (a self-limited reaction occurring shortly after the trauma); when the reaction is delayed or recurrent it is termed PTSD. Between **5 and 10%** of the population will satisfy criteria for PTSD at some point in life, with women affected more often than men.

Etiology, risk factors and epidemiology

- **Inciting event:** exposure to actual or threatened death, serious injury or sexual violence — directly experienced, witnessed, learned to have happened to a close relative/friend, or through repeated/extreme exposure to aversive details (e.g., first responders, police investigating child abuse).
- **Lifetime prevalence:** 5–10% of Americans; **women > men**.
- **Risk factors:** a past psychiatric history; personality traits of **high neuroticism and extroversion**; presence of peritraumatic dissociative symptoms and development of an acute stress disorder at the time of trauma (strongly predict later PTSD).
- **Genetics:** twin studies show a **substantial genetic influence** on all PTSD symptoms, with comparatively less evidence for an environmental effect.
- **Comorbidity:** patients are at high risk of other disorders related to **anxiety, mood, and substance abuse** (especially alcohol).

Clinical features

- **Re-experiencing / intrusion:** the trauma is typically re-experienced through intrusive thoughts, distressing dreams, or **flashbacks**, particularly when cues of the original event are present.
- **Avoidance:** patients actively avoid stimuli that precipitate recollections of the trauma.
- **Hyperarousal:** a resulting increase in **vigilance, arousal and exaggerated startle response**.
- **Emotional numbing / dissociation:** associated **detachment and loss of emotional responsivity**; the patient may feel *depersonalised* and may be unable to recall specific aspects of the trauma.
- **Temporal pattern:** reaction may be acute (acute stress disorder) or delayed and recurrent (PTSD).
- **Screening:** a validated four-item screen, the **PC-PTSD** (Primary Care PTSD screen), is available for case-finding in primary care.

DSM-5-TR diagnostic criteria (Table 463-6) — symptom clusters

PTSD is diagnosed using the DSM-5-TR. Criteria A–H must be satisfied (criteria for adults and children >6 years summarised below).

Criterion	Requirement	Representative features
A — Stressor	Exposure to actual/threatened death, serious injury or sexual violence	Direct experience; witnessing in person; learning it occurred to a close relative/friend (violent or accidental); repeated/extreme exposure to aversive details (work-related)
B — Intrusion (≥1)	Re-experiencing	Intrusive distressing memories; recurrent distressing dreams; **dissociative flashbacks**; intense distress at cues; marked physiological reactions to cues
C — Avoidance (one or both)	Persistent avoidance	Avoidance of distressing memories/thoughts/feelings; avoidance of external reminders (people, places, conversations, objects, situations)
D — Negative cognition/mood (≥2)	Worsening after trauma	Inability to recall an important aspect (dissociative amnesia); exaggerated negative beliefs about self/others/world; distorted self-blame; persistent negative emotional state (fear, horror, anger, guilt, shame); diminished interest; detachment/estrangement; inability to feel positive emotions
E — Arousal/reactivity (≥2)	Worsening after trauma	Irritability/angry outbursts; reckless or self-destructive behaviour; **hypervigilance**; exaggerated startle; impaired concentration; sleep disturbance
F — Duration	**> 1 month** (criteria B, C, D and E)	—
G — Distress	Clinically significant distress or impairment	Social, occupational or other important domains
H — Exclusion	Not due to a substance or another medical condition	—

- **Specify "With dissociative symptoms":** persistent/recurrent **depersonalisation** (detachment, as an outside observer of oneself) and/or **derealisation** (unreality of surroundings), not attributable to a substance or condition such as complex partial seizures.
- **Specify "With delayed expression":** full criteria not met until **≥6 months** after the event (some symptoms may begin immediately).
- *In children ≤6 years*, modified criteria apply — intrusion may manifest as **trauma-specific reenactment in play**, dreams may lack recognisable content, and avoidance/negative-mood items are combined into a single cluster.

Pathophysiology

- It is hypothesised that PTSD involves **excessive release of norepinephrine from the locus coeruleus** in response to stress, with **increased noradrenergic activity at projection sites in the hippocampus and amygdala** — theoretically facilitating the **encoding of fear-based memories**.
- **Greater sympathetic responses** occur to trauma-associated cues, whereas **pituitary-adrenal responses are blunted**.
- Beyond fear learning, documented changes include altered **threat detection (insula overactivity)**, executive dysfunction, impaired **emotional regulation**, and disturbed **contextual learning**.

- Candidate **predictive biomarkers:** increased heart rate and serum lactate, decreased coagulation, insulin resistance, and alterations in glycolysis and fatty-acid uptake.

Treatment / Management

General principles: acute stress reactions are usually self-limited; chronic, recurrent PTSD requires a combined drug-plus-behavioural approach. **Benzodiazepines and SSRIs should NOT be given in the early aftermath of trauma**, and routine **debriefing does not prevent PTSD and may exacerbate symptoms**. Attempts to prevent/ameliorate PTSD in the acute period (escitalopram, hydrocortisone, intranasal oxytocin) have proven **equivocal**.

Modality	Agents / methods	Notes
Acute stress reaction	Short-term **benzodiazepines** + supportive/expressive psychotherapy	Self-limited; benzodiazepines avoided in early post-trauma period for PTSD prevention
First-line drugs (PTSD)	**SSRIs — paroxetine and sertraline (FDA-approved for PTSD)**	Reduce anxiety, intrusion and avoidance
Other useful drugs	**Venlafaxine, fluoxetine, topiramate**	Reduce anxiety, intrusion symptoms and avoidance behaviours
For insomnia	Low-dose **trazodone, mirtazapine** (sedating antidepressants)	Given at night
Emerging adjuncts	**MDMA** as adjunct to intensive psychotherapy; **stellate ganglion block**	MDMA demonstrated efficacy as a psychotherapy adjunct
Psychotherapy (most effective)	**Trauma-focused cognitive-behavioural therapy**; **eye-movement desensitisation and reprocessing (EMDR)**; **prolonged exposure therapy** (augmented / virtual reality)	Dismantle avoidance via stepwise focusing on the traumatic experience; help master fear of recurrence

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **PTSD symptom-cluster wheel / box diagram** — a central box labelled *"Traumatic event (Criterion A)"* with four radiating clusters labelled: **(1) Intrusion / re-experiencing (B)** — flashbacks, nightmares, intrusive memories; **(2) Avoidance (C)** — of thoughts and external reminders; **(3) Negative cognition & mood (D)** — guilt, detachment, negative beliefs, amnesia; **(4) Hyperarousal/reactivity (E)** — hypervigilance, startle, irritability, insomnia. Annotate "Duration >1 month (F)".
- **Neurobiology schematic** — label: *Locus coeruleus → excess norepinephrine*; *Amygdala (fear encoding, ↑)*; *Hippocampus (memory)*; *Insula (threat detection, overactive)*; *Prefrontal cortex (impaired emotional regulation)*; *Blunted HPA / pituitary-adrenal axis.*

Clinical / Diagnostic significance

- **Recognise referral triggers:** PTSD symptoms, like psychosis, mania, severe depression and suicidal/homicidal preoccupation, warrant psychiatric consultation or transfer of care.

- **Screen in primary care** using the four-item **PC-PTSD**, especially after trauma, assault, disaster, combat or serious illness.
- **Differentiate from acute stress disorder** (same symptoms but earlier onset and self-limited; PTSD requires duration >1 month) and from **adjustment, panic, phobic and depressive disorders**.
- **Co-manage comorbidities** — alcohol/substance misuse, depression and other anxiety disorders are frequent and worsen prognosis.
- **Avoid harm:** do not start SSRIs/benzodiazepines in the immediate post-trauma window, and avoid single-session debriefing.
- **Set expectations:** medication relapse rates are high if used alone — combine pharmacotherapy with trauma-focused psychotherapy for durable response.

High-yield exam pointers

- PTSD = trauma-related disorder with **four symptom clusters (B–E)** persisting **>1 month**; <1 month with prominent dissociation = acute stress disorder.
- **Lifetime prevalence 5–10%; women > men;** validated **PC-PTSD** four-item screen.
- **Risk factors:** prior psychiatric history, high neuroticism/extroversion, peritraumatic dissociation; **strong genetic (twin-study) contribution.**
- **Core neurobiology:** ↑ norepinephrine from **locus coeruleus**, ↑ noradrenergic drive to **amygdala & hippocampus** → fear-memory encoding; **blunted HPA axis**; insula overactivity.
- **FDA-approved drugs: paroxetine and sertraline (SSRIs).** Also venlafaxine, fluoxetine, topiramate.
- **Most effective psychotherapies:** trauma-focused CBT, **EMDR**, prolonged exposure therapy.
- **Pitfalls:** do NOT give benzodiazepines/SSRIs in the early aftermath; **debriefing does not prevent PTSD and may worsen it.**
- **Specifiers:** *with dissociative symptoms* (depersonalisation/derealisation); *with delayed expression* (criteria met ≥6 months later).
- Emerging adjuncts: **MDMA-assisted psychotherapy** and **stellate ganglion block**; trazodone/mirtazapine for insomnia.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 463 "Psychiatric Disorders" (Stress Disorders section, Table 463-6 DSM-5-TR criteria, Etiology/Pathophysiology and Treatment of Stress Disorders). Coverage note: the chapter covers PTSD comprehensively for an MD-level answer; DSM-5-TR criteria are reproduced from Table 463-6. The PC-PTSD acronym expansion ("Primary Care PTSD screen") and the standard cluster-count phrasing are universally accepted additions; all drug names, doses-where-stated, FDA approvals, and neurobiological mechanisms are faithful to the source text.

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Psoriasis and its complications

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Psoriasis is a common, chronic, immune-mediated, genetically determined inflammatory skin disease characterised by sharply demarcated, erythematous plaques surmounted by silvery (*micaceous*) scale, affecting up to ~2% of the world population. It is best understood as a **systemic inflammatory disorder**: the IL-23/IL-17 (Th17) axis drives keratinocyte hyperproliferation in skin while the same inflammation underpins articular, metabolic and cardiovascular *complications* — most importantly **psoriatic arthritis (PsA)** and **metabolic syndrome**. There is a fundamental division into **plaque (non-pustular)** and **pustular** forms.

Epidemiology, aetiopathogenesis and genetics

- **Bimodal onset (Type I / Type II):** Type I — early onset (peak 16–22 yr), strong family history, **HLA-C*06:02**-associated, more severe; Type II — late onset (peak 57–62 yr), sporadic, HLA-C*06:02-unrelated, generally milder.
- **Genetics:** lifetime risk 4% / 28% / 65% with neither / one / both parents affected; monozygotic twin concordance gives heritability ~60–90%. Polygenic/multifactorial with >65 susceptibility loci.
  - **PSORS1** (chromosome 6p, MHC class I) — the major determinant; consensus risk allele **HLA-C*06:02**.
  - **PSORS2 = CARD14** — gain-of-function mutations enhance NF-κB signalling in keratinocytes.
  - **IL36RN** loss-of-function (deficiency of IL-36 receptor antagonist) and **AP1S3** — drive **generalised pustular psoriasis**.
- **Pathogenesis:** plasmacytoid dendritic cells/neutrophils release **NETs** and the cathelicidin peptide **LL37**, which (with self-DNA) triggers IFN-α; myeloid dendritic cells secrete **IL-12 (→Th1)** and **IL-23 (→Th17)**; **IL-17A/IL-17F, TNF-α, IL-22** drive keratinocyte hyperproliferation and self-amplifying loops via **JAK-STAT** and **NF-κB** — the rationale for all modern targeted therapy.
- **Triggers / exacerbating factors:** streptococcal pharyngitis (guttate), HIV, **Koebner (isomorphic) phenomenon** (cutaneous trauma, *Heinrich Köbner 1877*), drugs (**lithium, antimalarials, beta-blockers, TNF-α inhibitors [paradoxical], interferon-α, NSAIDs, ACE inhibitors**), **withdrawal of systemic/potent topical corticosteroids**, smoking, alcohol, obesity, psychological stress.

Clinical variants and diagnostic signs

Variant	Key features
Chronic plaque (vulgaris)	Commonest (~80–90%); symmetric well-demarcated plaques on **elbows, knees, scalp, sacrum, extensors**
Guttate (eruptive)	Shower of 2–10 mm "drop-like" papules in children/young adults, ~2 weeks after group A streptococcal pharyngitis
Inverse (flexural)	Glazed, scale-poor plaques in axillae, groin, submammary, natal cleft, umbilicus; obesity-associated
Erythrodermic	>90% body surface; *complication* — skin failure (see below)

Variant	Key features
Pustular	Localised palmoplantar pustulosis, or **generalised (von Zumbusch)**
Nail	**Pitting** (~1 mm), subungual **"oil-drop"/salmon patch** (highly specific), subungual hyperkeratosis, splinter haemorrhages, distal **onycholysis**
Scalp / sebopsoriasis	Often first site; pityriasis amiantacea

- **Diagnostic signs:** *Auspitz sign* (pinpoint bleeding on scale removal from thin suprapapillary epidermis), *ring/halo of Woronoff* (pale rim around resolving plaque), *Koebner phenomenon*; geographic & fissured tongue associations.

Histopathology

- **Confluent parakeratosis** with focal orthokeratosis and near-absence of the granular layer.
- **Regular epidermal hyperplasia** with elongated, clubbed/fused rete ridges and **suprapapillary thinning**.
- **Munro microabscesses** — neutrophils in the (para)keratotic stratum corneum.
- **Spongiform pustule of Kogoj** — neutrophils within the stratum spinosum (prominent in pustular forms).
- Dilated, tortuous papillary capillaries (correlate of the Auspitz sign).

Complications and co-morbidities

Psoriasis (especially severe disease) carries excess morbidity and mortality across most organ systems; **severe disease shortens life expectancy by ~4–6 years**, chiefly from cardiovascular death.

A. Psoriatic arthritis (PsA) — the principal articular complication, a **seronegative spondyloarthritis** occurring in up to ~30–40% of patients; skin precedes joints in ~70%. **Five patterns (Moll & Wright):** asymmetric mono-/oligoarthritis (classically regarded as commonest), symmetric "rheumatoid-like" polyarthritis (~50% in Harrison), **distal interphalangeal-predominant** (distinguishes from RA), **arthritis mutilans** (rare, deforming "telescoping" digits), and **axial disease/spondylitis** (HLA-B27-linked). Hallmarks: **dactylitis** ("sausage digit"), **enthesitis** (Achilles, plantar fascia), nail disease (~80%). Diagnosis by **CASPAR criteria** (≥3 points; sensitivity 99%, specificity 91%):

CASPAR category	Points
Current psoriasis (2) / personal history (1) / family history 1st–2nd degree relative (1)	2 / 1 / 1
Typical psoriatic nail involvement	1
Negative rheumatoid factor	1
Current or past dactylitis	1
Radiographic juxta-articular new bone formation (hands/feet)	1

B. Acute dermatological emergencies (skin failure):

- **Erythrodermic psoriasis** (1–2% of patients; underlies ~25% of all erythroderma) — sepsis, **hypothermia/hyperthermia, hypoalbuminaemia, anaemia, dehydration, high-output cardiac failure**.
- **Generalised pustular psoriasis (von Zumbusch)** — fever, sheets of sterile pustules ("lakes of pus"), leucocytosis; complications: **acute kidney injury, hypoalbuminaemia with hypocalcaemia, neutrophilic cholangitis / cholestatic jaundice, ARDS (aseptic pneumonitis), telogen effluvium, amyloidosis**; mortality 2–16%. GPP confined to pregnancy = **impetigo herpetiformis** (last trimester; placental insufficiency, stillbirth).

C. Systemic co-morbidities (Box 35.2):

- **Metabolic syndrome** (prevalence ~34% vs 26%) — obesity (strongest, often predates psoriasis), hypertension, hyperlipidaemia, type 2 diabetes.
- **Cardiovascular disease** — myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation, venous thromboembolism (risk greatest in young, severe disease/PsA).
- **Other immune-mediated disease** — Crohn's disease, ulcerative colitis, coeliac disease, **uveitis**.
- **Hepatobiliary** — **non-alcoholic fatty liver disease (up to 50%)**, alcoholic liver disease.
- **Malignancy** — non-melanoma skin cancer (esp. post-PUVA), Hodgkin lymphoma.
- **Psychiatric** — depression, anxiety, increased suicidality; alcohol misuse.
- **Miscellaneous** — hyperuricaemia/gout, secondary (AA) amyloidosis, IgA nephropathy (rare).

Management

- **Assess severity** with the **PASI (Psoriasis Area and Severity Index, 0–72)** grading erythema, scaling and induration over four regions, ± **BSA** and **DLQI**; "candidate for systemic therapy" ≈ BSA ≥10%, high-impact sites, or topical failure. Screen at every visit for **PsA, metabolic syndrome and depression**.
- **Topical (limited disease):** mid-/high-potency corticosteroids; **vitamin D analogues** (calcipotriene 0.005% [max 100 g/wk], calcitriol 0.003% [max 200 g/wk] — hypercalcaemia risk); tazarotene; coal tar, salicylic acid, dithranol; **calcineurin inhibitors** (tacrolimus/pimecrolimus) for face/flexures; newer **roflumilast (PDE-4)** and **tapinarof (AhR agonist)** creams.
- **Phototherapy (moderate/widespread): narrowband UVB** (first-line, 3×/week) and **PUVA**; avoid with ciclosporin and in the immunosuppressed (skin-cancer risk).
- **Conventional systemics: methotrexate** (≤25 mg weekly + folic acid 1–2 mg/day; cumulative 3.5–4 g → hepatology); **acitretin** (0.5–0.75 mg/kg/day; teratogen — avoid pregnancy 3 yr; best for pustular); **ciclosporin** (≤5 mg/kg/day; rebound on stopping); **apremilast (PDE-4)**; **deucravacitinib (oral TYK2 inhibitor)**.
- **Biologics:** anti-TNF-α (etanercept, adalimumab, infliximab, certolizumab, golimumab); **anti-IL-12/23 ustekinumab**; **anti-IL-23p19** (guselkumab, risankizumab, tildrakizumab); **anti-IL-17** (secukinumab, ixekizumab, brodalumab, bimekizumab); **anti-IL-36R spesolimab** for GPP. Screen for **TB, HIV, hepatitis B/C** before starting; TNF inhibitors with caution in CHF.
- **Avoid systemic (oral) corticosteroids** — withdrawal precipitates life-threatening pustular/erythrodermic flares. Weight loss improves both disease and response.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled cross-section of a psoriatic plaque (histology):** label *parakeratosis*, *Munro microabscess (neutrophils in stratum corneum)*, *Kogoj spongiform pustule (stratum spinosum)*, *absent/diminished granular layer*, *acanthosis with elongated regular rete ridges*, *suprapapillary thinning*, *dilated tortuous papillary capillary*, *dermal lymphocytic infiltrate*.
- **IL-23/IL-17 immunopathogenesis schematic:** label *plasmacytoid DC → IFN-α*, *myeloid DC → IL-12 (Th1) and IL-23 (Th17)*, *Th17 → IL-17A/IL-17F, IL-22, TNF-α*, *keratinocyte hyperproliferation* — with arrows showing biologic drug targets (anti-TNF, anti-IL-12/23, anti-IL-23, anti-IL-17, TYK2/JAK).

Clinical / Diagnostic significance

- Diagnosis is **clinical**; biopsy reserved for atypical cases. No constant laboratory abnormality; **hs-CRP/ESR** rise in PsA and GPP. KOH/fungal culture distinguishes nail/flexural psoriasis from onychomycosis and candidiasis.
- **Differential diagnosis:** seborrhoeic dermatitis, eczema, lichen planus, pityriasis rosea, pityriasis rubra pilaris, secondary syphilis, mycosis fungoides, tinea, discoid lupus; severe/atypical/treatment-resistant psoriasis should prompt **HIV testing**.
- Recognise **erythrodermic and von Zumbusch GPP as emergencies** needing fluid/electrolyte support, temperature control and rapid systemic therapy (infliximab for severe flares; spesolimab for GPP).
- Treat psoriasis as a **systemic disease** — proactively screen and manage cardiometabolic risk, PsA (early referral prevents irreversible joint destruction) and mood disorder.

High-yield exam pointers

- **IL-23/IL-17 (Th17) axis** is central; **HLA-C*06:02 / PSORS1** is the major genetic determinant; **CARD14** and **IL36RN** drive familial/pustular disease.
- **Auspitz sign**, **Woronoff ring**, **Koebner phenomenon** — classic triad of signs; nail **"oil-drop" sign** is highly specific.
- Histology: **Munro microabscess** (stratum corneum) vs **Kogoj spongiform pustule** (stratum spinosum); parakeratosis + suprapapillary thinning.
- **Guttate** follows streptococcal pharyngitis; **inverse** is scale-poor and flexural; **von Zumbusch** is febrile generalised pustular psoriasis.
- **PsA** = seronegative spondyloarthritis; **5 Moll & Wright patterns**; diagnose by **CASPAR (≥3 points)**; DIP involvement, dactylitis and enthesitis distinguish from RA.
- **Complications:** PsA, metabolic syndrome, MI/stroke, NAFLD, lymphoma/NMSC, depression, amyloidosis; severe disease shortens life by ~4–6 years.
- **Never give systemic steroids** (rebound pustular psoriasis); first-line widespread therapy = **NB-UVB**; **methotrexate** is the workhorse systemic, especially with PsA.
- Screen for **TB/HIV/hepatitis B & C** before biologics; **TNF inhibitors** can paradoxically induce psoriasis and worsen CHF.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders" (clinical types, FDA-approved systemic and biologic therapy tables, PsA subtypes).
- **Rook's Textbook of Dermatology, 10e** — "Psoriasis and Related Disorders" (epidemiology, Type I/II, genetics PSORS1/HLA-C*06:02/CARD14/IL36RN, IL-23/IL-17 pathogenesis, histopathology, clinical variants, PASI, Box 35.2 co-morbidities, von Zumbusch GPP, impetigo herpetiformis, PsA with Moll & Wright and CASPAR criteria).
- **CMDT 2026** — "Dermatologic Disorders: Psoriasis" (current management, drug doses: calcipotriene/calcitriol ceilings, methotrexate, acitretin, etanercept, deucravacitinib, spesolimab).

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Psoriasis — cutaneous and extra-cutaneous manifestations

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

Definition / Introduction — **Psoriasis** is one of the commonest dermatologic diseases, affecting up to **2% of the world's population**. It is a chronic, **immune-mediated** disorder clinically characterised by **erythematous, sharply demarcated papules and rounded plaques covered by silvery micaceous scale**, which are variably pruritic. It is now best regarded as a **systemic "psoriatic disease"**: beyond the skin and nails it carries musculoskeletal (psoriatic arthritis), ocular, gastrointestinal, cardiometabolic and psychiatric burden. Skin lesions contain infiltrates of **activated T cells** that elaborate cytokines driving **keratinocyte hyperproliferation**, with a strong genetic predisposition (positive family history in **30–50%**).

Pathogenesis (in brief)

- T-cell–mediated disorder; activated T cells release proinflammatory cytokines → keratinocyte hyperproliferation → characteristic plaques and scale.
- The **IL-23/IL-17 axis** is central — explaining why agents targeting IL-23, IL-12/23, IL-17 and TNF-α are highly effective.
- **Strong genetic component**: 30–50% report a positive family history; the spondyloarthritis literature links psoriatic disease to **HLA-B*27** (positive in ~20% of all PsA and ~50% of axial PsA).
- **Koebner (isomorphic) phenomenon** — traumatised skin develops new lesions.
- **Exacerbating factors**: infections (streptococcal), psychological stress, and drugs — **lithium, beta blockers, antimalarials**; systemic glucocorticoid withdrawal can precipitate pustular flares.

Cutaneous manifestations — morphology

- **Primary lesion**: sharply demarcated, erythematous plaque with a loosely adherent **silvery (micaceous) scale**; predominantly over **extensor surfaces — elbows, knees, gluteal cleft and scalp**, with a tendency to **symmetry**.

- Course is typically **indolent and chronic**; plaque psoriasis develops slowly and **rarely remits spontaneously**.
- **Auspitz sign** (pinpoint bleeding on removal of scale, reflecting dermal vascular proliferation) and **Munro microabscesses** on histology are classic features (standard textbook; see Coverage note).
- **Histology** (Table 60-2): **acanthosis** with dermal **vascular proliferation**.

Clinical variants of cutaneous psoriasis

Variant	Typical patient / trigger	Distinguishing features
Plaque-type (psoriasis vulgaris)	Commonest variety; adults	Stable, slowly enlarging plaques; elbows, knees, gluteal cleft, scalp; symmetric; indolent
Inverse (flexural) psoriasis	Intertriginous skin	Affects **axillae, groin, submammary region, navel**; also scalp, palms, soles; sharply demarcated plaques that may be **moist and without scale** due to location
Guttate (eruptive) psoriasis	**Children and young adults**; often **after URTI with β-hemolytic streptococci**	Acute onset of **many small erythematous, scaling papules**; DDx — pityriasis rosea, secondary syphilis
Pustular psoriasis	Localised (palms/soles) or generalised; triggers — local irritants, pregnancy, drugs, infection, **systemic glucocorticoid withdrawal**	Erythema studded with **sterile pustules**; generalised form has **fever (39–40°C) for several days**, recurrent episodes; may become **erythrodermic**. **Oral retinoids** are treatment of choice (non-pregnant). Localised form mimics dyshidrotic eczema

Nail involvement

- **Fingernail involvement** may be the only clue when the skin presentation is atypical.
- **Nail matrix disease**: **pitting** (punctate), leukonychia, crumbling, and red spots in the lunula.
- **Nail bed disease**: **onycholysis**, **subungual hyperkeratosis**, **oil-drop (salmon patch) change**, and **splinter haemorrhages**; nail thickening.
- Nail disease is intimately linked to **DIP-joint** psoriatic arthritis (the nail bed is closely related to the DIP joint).
- Frequency: ~**40%** of psoriasis patients *without* arthritis have nail lesions, rising to ~**90%** in those with **PsA** — i.e., nail change is a strong marker of arthritis.

Extra-cutaneous manifestations

1. Psoriatic arthritis (PsA) — the major extra-cutaneous manifestation

- Affects **up to 30%** of psoriasis patients (range 6–42%); incidence ~**3 per 100 patient-years**, rising with severity of skin disease; onset usually **30–50 years**.
- **Moll & Wright (1973)** definition: inflammatory arthritis (peripheral and/or sacroiliitis/spondylitis) **with cutaneous psoriasis** and **absence of RF**; described **five phenotypes** (below); enthesitis and dactylitis added later.

- Temporal pattern: **psoriasis precedes arthritis in ~80%**, simultaneous in ~10%, and **arthritis precedes skin disease in ~10%** ("psoriatic arthritis sine psoriasis").
- Cardinal musculoskeletal features: **peripheral arthritis** (early oligoarticular/asymmetric → later polyarticular/symmetric), **DIP-joint involvement** (typical, linked to nail disease), **axial arthritis/spondylitis** (5% early, ~50% after 20 years), **dactylitis** ("sausage digit" — inflammatory swelling of an entire digit; marker of severity), **enthesitis** (commonest at plantar fascia and Achilles insertion on calcaneum), and **tenosynovitis**.

2. Ocular — **uveitis** in ~5% (commonly **unilateral acute anterior uveitis**; posterior/bilateral also reported); conjunctivitis rare.

3. Gastrointestinal — **inflammatory bowel disease** (Crohn's disease, rarely ulcerative colitis) may coexist; mucous-membrane inflammation with painful mouth ulcers, rarely urethritis.

4. Cardiometabolic / systemic — increased risk of **metabolic syndrome** with raised cardiovascular morbidity and mortality. Patients with psoriasis + PsA have CV risk **as high as in diabetes mellitus**, independent of conventional risk factors, with more severe subclinical atherosclerosis; higher prevalence of **hypertension, type 2 diabetes, obesity, fatty liver, angina and MI**. Obesity worsens disease activity and treatment response. Malignancy is **not** increased.

5. Psychiatric — increased rates of **depression and suicidality**.

Psoriatic arthritis — phenotypes, criteria & imaging

Five clinical phenotypes (Moll & Wright)	Notes
Symmetric polyarticular (~50%)	Resembles rheumatoid arthritis
Asymmetric oligoarticular (~35%)	Any joint; "sausage digits"; early-stage pattern
Distal (DIP) arthritis (~5%)	Classic form; dystrophic nails, pitting
Spondylitis (axial) (~5%)	Inflammatory back/neck pain; sacroiliitis often **unilateral**
Arthritis mutilans (<5%)	Severe, deforming; small joints of hands/feet; end-stage with osteolysis

- **CASPAR criteria** (Table 374-6): in a patient with **inflammatory articular disease** (joint, spine or entheseal), need **≥3 points** from — current psoriasis (**2**) / personal or family history of psoriasis (**1**), typical **nail dystrophy** (1), **RF negative** (1), **dactylitis** (1), **juxta-articular new bone formation** on X-ray (1). **Specificity 98.7%, sensitivity 91.4%.**
- **Radiology**: marginal **erosions with adjacent "fluffy" new bone formation** (characteristic), **"pencil-in-cup" deformity**, bony ankylosis in a **"ray" distribution**, **acro-osteolysis**; **chunky nonmarginal syndesmophytes** and (usually unilateral) sacroiliitis. MRI/ultrasound detect synovitis, enthesitis and erosions earlier than X-ray.
- **Labs**: ESR/CRP raised in ~50%; **RF negative** (low-titre RF or anti-CCP in <10%); **HLA-B27** positive in ~20% (≈50% of axial PsA).

Management (overview)

- **Cutaneous, localised**: skin hydration; **mid-potency topical glucocorticoids** (limited by tachyphylaxis and atrophy); **vitamin D analogue (calcipotriene)** and **retinoid (tazarotene)** — have largely replaced coal tar, salicylic acid and anthralin.
- **Phototherapy** for widespread disease: **UV-B, narrowband UV-B, and PUVA** (UV-A + psoralens); mutagenic (skin-cancer risk); **contraindicated with cyclosporine** and in the immunocompromised.
- **Systemic agents** (Table 60-3): **methotrexate** (weekly; especially with PsA), **acitretin** (teratogenic), **cyclosporine**, **apremilast** (PDE-4 inhibitor; for psoriasis and PsA), **deucravacitinib** (TYK2 inhibitor — blocks IL-23/IL-12/type-1-IFN; plaque psoriasis). **Oral glucocorticoids must NOT be used** — withdrawal can trigger **life-threatening generalised pustular psoriasis**.
- **Biologics** (Table 60-4): **Anti-TNF-α** (etanercept, adalimumab, certolizumab, infliximab, golimumab); **Anti-IL-12/23** (ustekinumab); **Anti-IL-23** (risankizumab, tildrakizumab, guselkumab); **Anti-IL-17** (secukinumab, ixekizumab, brodalumab). Screen for **TB, HIV, hepatitis B/C** before starting; TNF-α inhibitors may worsen **CHF** and cause **paradoxical psoriasiform lesions**.
- **PsA-specific** (Table 374-7): **"treat-to-target"** (minimal disease activity/remission); NSAIDs short-term; **local** glucocorticoid injections (avoid weight-bearing lower-limb entheses — rupture risk); **avoid systemic steroids**; **csDMARDs** (methotrexate preferred if relevant skin disease, sulfasalazine, leflunomide); **bDMARDs** (TNF/IL-12-23/IL-17/IL-23 inhibitors), **PDE-4/TYK2** inhibitors; **JAKi after TNFi failure** (CV black-box warning). For predominant **skin + joint** disease prefer IL-12/23, IL-17 or IL-23 inhibitors over TNF; **avoid IL-17i in active IBD**; prefer **TNF mAbs for uveitis**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled cutaneous psoriasis plaque (cross-section/surface)** — labels: *silvery micaceous scale*, *sharply demarcated erythematous plaque*, *Auspitz sign (pinpoint bleeding)*, *Koebner phenomenon at trauma site*, *extensor distribution (elbows, knees, scalp, gluteal cleft)*.
- **Psoriatic nail + DIP joint schematic** — labels: *nail pitting*, *onycholysis*, *oil-drop sign*, *subungual hyperkeratosis*, *splinter haemorrhage*, *DIP arthritis*, *dactylitis ("sausage digit")*, *"pencil-in-cup" deformity*.

Clinical / Diagnostic significance

- Recognise the **clinical variants** — guttate (post-streptococcal, young), inverse (flexural), pustular (febrile, can be erythrodermic) — as each alters prognosis and therapy.
- **Nail disease and dactylitis** are red flags for psoriatic arthritis; examine **hidden sites** (scalp, umbilicus, natal cleft, nails) when arthritis precedes obvious skin disease.
- **Screen every patient** for cardiometabolic risk (BP, lipids, glucose, weight), IBD, uveitis and **depression/suicidality** — psoriasis is a systemic disease.
- Biopsy (acanthosis, dermal vascular proliferation, Munro microabscesses) helps when the presentation is atypical; **CASPAR criteria** confirm PsA.

- A **multidisciplinary team** (dermatology, rheumatology, ophthalmology, gastroenterology, psychiatry, cardiology) optimises outcomes.

High-yield exam pointers

- Prevalence ~**2%**; **immune-mediated**, T-cell driven via the **IL-23/IL-17 axis**; family history in **30–50%**.
- **Koebner phenomenon**; drug triggers — **lithium, beta blockers, antimalarials**; never use systemic steroids (rebound **pustular** flare).
- **Auspitz sign**, **silvery micaceous scale**, extensor/scalp distribution; **Munro microabscess** on histology.
- Variants: **plaque (commonest)**, **guttate (post-streptococcal)**, **inverse**, **pustular/erythrodermic**.
- **PsA in up to 30%**; **five Moll–Wright phenotypes**; **psoriasis precedes arthritis in ~80%**; nail change in ~**90%** of PsA.
- **CASPAR criteria** (≥3 points; specificity 98.7%); radiology — **"pencil-in-cup"**, fluffy new bone, **acro-osteolysis**, asymmetric (often unilateral) sacroiliitis.
- Extra-cutaneous: **anterior uveitis, IBD, metabolic syndrome, CV disease (risk like diabetes), depression**.
- Therapeutic ladder — topical steroids/calcipotriene/tazarotene → phototherapy (NB-UVB/PUVA) → MTX/acitretin/cyclosporine/apremilast/deucravacitinib → **biologics (TNF, IL-12/23, IL-17, IL-23 inhibitors)**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 60 "Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders"** (cutaneous variants, nail disease, treatment) and **Ch 374 "Spondyloarthritis"** (psoriatic arthritis, extra-cutaneous/systemic manifestations, CASPAR criteria, PsA management).

Coverage note: **Auspitz sign** and **Munro microabscess** are not stated verbatim in the provided chapters but are included as universally-accepted standard dermatology; histology in Table 60-2 explicitly supports **acanthosis with dermal vascular proliferation**. The pithy ranges for PsA phenotype proportions and subtype names are drawn from Ch 60 (symmetric ~50%, asymmetric ~35%, distal ~5%, spondylitis ~5%, arthritis mutilans <5%); Ch 374 frames the same as the five Moll–Wright phenotypes. All drug names, criteria, and numerical figures are taken directly from the two chapters.

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Schizophrenia

Asked in: Paper IV Jun 2024 · Paper IV Dec 2023 (2×) — RGUHS MD General Medicine

Definition / Introduction — Schizophrenia is a chronic, heterogeneous psychotic syndrome characterised by perturbations of perception, thinking, language, affect, social activity and volition, in which the patient progressively loses contact with reality. There is **no pathognomonic feature and no confirmatory laboratory test**; diagnosis is clinical and one of exclusion. It typically begins in late adolescence/early adulthood, has an insidious (less often acute) onset and a frequently poor outcome, and is best conceptualised as a **neurodevelopmental disorder** of multifactorial (genetic, environmental and neurotransmitter) origin. Lifetime prevalence is ~0.3–1.5% (Harrison quotes 0.85% worldwide; CMDT ~1%), and ~10% of patients die by suicide.

Epidemiology and risk factors

- **Prevalence:** ~0.85% worldwide; lifetime ~1–1.5% (Harrison). DSM-5-TR lifetime estimate 0.3–0.7%. ~300,000 acute episodes/year in the USA.
- **Age/sex at onset:** late teens to mid-30s; peak in early–mid 20s in **men** (~18 yr) and late 20s in **women** (~25 yr), with a second mid-life peak in women. Onset before adolescence is rare.
- **Genetic susceptibility** (strongest risk factor): present in ~**6.6% of first-degree relatives**; risk ~**40% if both parents affected**; **monozygotic twin concordance 50% vs 10% for dizygotic**. Sibling of a proband → ~10-fold risk. Most affected individuals nonetheless have no family history.
- **Environmental/developmental:** early developmental insults, **winter/early-spring birth**, advancing paternal age, obstetric complications with hypoxia, prenatal infection/malnutrition/maternal diabetes, urban upbringing, migration/refugee status, childhood trauma and social adversity.

Clinical features

- **Positive symptoms** (added experiences) — *delusions* (often persecutory/somatic), *auditory hallucinations* (characteristically third-person/derogatory; visual hallucinations suggest an organic state), *conceptual disorganisation*, *disorganised (formal thought-disordered) speech* with derailment, neologisms, echolalia and verbigeration, and *grossly disorganised or catatonic behaviour*.
- **Negative symptoms** (lost function) — *affective flattening/diminished emotional expression*, *avolition*, *anhedonia*, *alogia/poverty of speech*, *asociality* and impaired concentration. Predominate in ~one-third of patients and predict **poor long-term outcome and poor drug response**.
- **Cognitive symptoms** — deficits in working/declarative memory, attention, processing speed and executive function; strongly linked to functional/vocational disability and often precede frank psychosis.
- **Schneiderian first-rank symptoms** (classically supportive, not specific) — thought insertion, withdrawal and broadcasting; delusions of control/passivity; third-person auditory hallucinations; delusional perception. **Bleuler's "4 A's"** (loosening of *Associations*, *Affect*

incongruity, *Ambivalence*, *Autism*) and Kraepelin's *dementia praecox* are the classical descriptions.

- **Catatonia** — a non-specific syndrome (≥3 of stupor, cataplexy, mutism, waxy flexibility, stereotypy, etc.) that may complicate schizophrenia but also occurs in mood and medical disorders.
- **Course:** chronic with relapses; positive symptoms attenuate with age while negative/cognitive features persist. Pooled first-episode remission ~56% and recovery ~30%. **Anosognosia (lack of insight)** is the commonest predictor of non-adherence and relapse. ~5–10% commit suicide (20% attempt).

DSM-5-TR diagnostic criteria

Criterion	Requirement
A (core)	**≥2** of the following for ≥1 month (active phase), **at least one being 1, 2 or 3**: (1) delusions; (2) hallucinations; (3) disorganised speech; (4) grossly disorganised/catatonic behaviour; (5) negative symptoms
B	Marked decline in functioning (work, relationships, self-care) below premorbid level
C	**Continuous signs ≥6 months**, including ≥1 month of active-phase (Criterion A) symptoms; may include prodromal/residual phases
D	Schizoaffective and mood disorder with psychotic features excluded
E	Not due to a substance or another medical condition
F	If autism/childhood communication disorder, diagnosis only if prominent delusions/hallucinations also present ≥1 month

- **Related spectrum disorders by duration/content:** *brief psychotic disorder* (>1 day, <1 month, full recovery); *schizophreniform disorder* (1–6 months); *schizoaffective disorder* (mood episode plus active-phase psychosis, with ≥2 weeks of psychosis without mood symptoms); *delusional disorder* (≥1 month delusions, Criterion A never met).
- DSM-5-TR **abandoned the classical subtypes** (paranoid, disorganised/hebephrenic, catatonic, undifferentiated, residual) in favour of a **dimensional 0–4 severity rating** of psychotic domains.

Etiopathogenesis

- **Dopamine hypothesis (four pathways):** clinical antipsychotic potency parallels affinity for **D2/D3 receptors in the ventral striatum**. Mesolimbic **hyperdopaminergia → positive symptoms**; mesocortical **hypodopaminergia → negative/cognitive symptoms**; blockade of the **nigrostriatal** pathway → extrapyramidal symptoms; blockade of the **tuberoinfundibular** pathway → hyperprolactinaemia.
- **Other neurotransmitters:** glutamatergic (NMDA) hypofunction and serotonergic (5-HT2A) signalling — atypical agents have high 5-HT2:D2 ratios; newer targets include D3, 5-HT1A/5-HT7, mGlu2/3 and **muscarinic M1/M4** receptors.
- **Neurodevelopmental/structural changes** (ch462): **enlarged lateral ventricles**, reduced cortical and subcortical grey matter in frontal/temporal lobes and limbic system, reduced neuropil with increased cell-packing density (no neuronal loss), **hypofrontality** (reduced dorsolateral

prefrontal cortex metabolism at rest and on executive/working-memory tasks), and reduced expression of *GAD1* (GABA-synthesising enzyme) in prefrontal interneurons.

- **Genetics:** large GWAS show hundreds of small-effect risk loci plus rare large-effect copy-number variants; pathways involve **immunity, inflammation and cell signalling**. The strongest signal lies at the **complement component 4 (C4)** locus — increased C4A expression is hypothesised to drive **excessive synaptic pruning by microglia**, supporting a neurodevelopmental/neurodegenerative model.

Differential diagnosis

- **Primary psychiatric:** mood disorder (depressive/bipolar) with psychotic or catatonic features, schizoaffective disorder, delusional disorder, brief psychotic disorder, schizotypal personality disorder.
- **Substance-induced:** chronic amphetamine/cocaine/stimulant psychosis (formication, stereotypy), phencyclidine, cannabis; and prescription drugs (anti-parkinsonian agents, clonidine, quinacrine, procaine derivatives) — *rule out drug causes in any new-onset psychosis*.
- **Organic/medical:** thyroid, adrenal and pituitary disease, temporal-lobe (complex partial) seizures, CNS tumour/encephalitis/haemorrhage, metabolic derangements, heavy-metal/industrial toxicity. A full medical work-up with **CT/MRI brain** is advised at first episode of psychosis.

Management

- **Antipsychotics are the cornerstone** of acute and maintenance treatment. ~**70% of first-episode** patients respond; improvement begins within days but full remission needs **6–8 weeks**. Therapeutic doses produce **>80% D2 occupancy** (e.g. haloperidol 4–6 mg/d, olanzapine 10–15 mg/d, risperidone 4–6 mg/d); higher doses add toxicity, not efficacy.

Class	Examples	Key features
First-generation (typical)	Low-potency: chlorpromazine, thioridazine; mid: perphenazine, loxapine; high: **haloperidol**, fluphenazine, thiothixene	High-potency → more **EPS**; low-potency → more anticholinergic/orthostatic/sedative effects
Second-generation (atypical)	**Clozapine**, risperidone, **olanzapine**, quetiapine, ziprasidone, aripiprazole, paliperidone, lurasidone, asenapine, cariprazine, lumateperone	Higher 5-HT2:D2 ratio; better for **negative/cognitive** symptoms; metabolic risk (weight gain, dyslipidaemia, type-2 DM)
Novel mechanism (2024)	**Xanomeline/trospium** (M1/M4 muscarinic agonist)	First agent acting *without* D2/5-HT2 blockade → no EPS or metabolic complications

- **Clozapine** — drug of choice for **treatment-resistant schizophrenia** (~30% of non-responders improve) and uniquely **reduces suicidality**; needs a 6–9-month trial. Risks: **agranulocytosis (~1%, mandatory WBC monitoring)**, dose-related seizures (~10% at high dose), weight gain, drooling, hyperthermia; does **not** raise prolactin.

- **Long-acting injectables (LAI)** — risperidone, paliperidone, olanzapine, aripiprazole, haloperidol/fluphenazine decanoate — for **non-adherence**; reduce relapse. If medication is fully stopped, relapse rate is **~60% within 6 months**.
- **Adverse effects:** EPS (acute dystonia, akathisia, parkinsonism) → benztropine 1–2 mg bid or trihexyphenidyl 2 mg bid; akathisia → beta-blocker. **Tardive dyskinesia** (incidence 2–4%/yr, prevalence ~20%; *buccolinguo-masticatory triad*) → treat with the VMAT2 inhibitor **valbenazine**. **Neuroleptic malignant syndrome** — hyperthermia, autonomic instability, rigidity, raised CPK (a medical emergency). Hyperprolactinaemia, QT prolongation, metabolic syndrome — monitor glucose/lipids/ECG. The **CATIE** trial showed high real-world discontinuation; olanzapine had the lowest discontinuation but most metabolic effect, and perphenazine performed comparably to newer agents.
- **Psychosocial/non-pharmacological:** family psychoeducation, assertive community treatment, social-cognition and skills training, cognitive remediation; **ECT** for catatonia and treatment-resistant cases. Lorazepam 1–2 mg rapidly relieves catatonia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Dopaminergic pathways in schizophrenia** — midbrain origins (VTA, substantia nigra) projecting along four tracts, labelled: *Mesolimbic (VTA → nucleus accumbens) — positive symptoms (hyperactive)*; *Mesocortical (VTA → prefrontal cortex) — negative/cognitive symptoms (hypoactive)*; *Nigrostriatal (SN → striatum) — EPS on blockade*; *Tuberoinfundibular (hypothalamus → pituitary) — hyperprolactinaemia on blockade*.
- **Positive vs negative symptoms schematic** — two columns: *Positive* (Delusions, Hallucinations, Disorganised speech, Catatonia) and *Negative* (Affective flattening, Avolition, Anhedonia, Alogia, Asociality), with *Cognitive deficits* bridging both.

Clinical / Diagnostic significance

- Diagnosis is **clinical and longitudinal** — repeated observation improves reliability; reconsider the diagnosis (often → bipolar disorder) if the course is atypical.
- First episode mandates a **full medical work-up + neuroimaging** and a urine drug screen to exclude organic/substance causes.
- Patients have **reduced life expectancy** from suicide and from antipsychotic-associated **metabolic syndrome and cardiovascular disease** — metabolic monitoring is integral to care.
- Treatment failure is most often due to **inadequate dosing or non-adherence**; LAIs and clozapine are the structured responses to each.

High-yield exam pointers

- DSM-5-TR: **≥2 Criterion A symptoms ≥1 month + ≥6 months total**, with ≥1 of delusions/hallucinations/disorganised speech.
- Positive = mesolimbic **hyper**dopaminergia; negative = mesocortical **hypo**dopaminergia.
- Genetics: MZ concordance **50%**, DZ **10%**; both parents affected → **~40%**.
- Strongest molecular signal = **C4 complement → excess synaptic pruning** (microglia); imaging = **ventriculomegaly + hypofrontality**.

- **Clozapine** = treatment-resistant disease and anti-suicidality; watch **agranulocytosis (1%)** with WBC monitoring; no prolactin rise.
- **Tardive dyskinesia** → valbenazine (VMAT2 inhibitor); **NMS** = hyperthermia + rigidity + autonomic instability + ↑CPK.
- DSM-5 **dropped classical subtypes**; **xanomeline/trospium (M1/M4 agonist, 2024)** is the first non-dopaminergic antipsychotic.
- **Auditory** hallucinations favour schizophrenia; **visual** hallucinations favour an organic/toxic cause.
- **~10% die by suicide**; anosognosia is the chief driver of non-adherence and relapse.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Psychiatric Disorders" (Schizophrenia: clinical manifestations, epidemiology, differential diagnosis, antipsychotic pharmacology, CATIE, tardive dyskinesia, NMS) and "Biology of Psychiatric Disorders" (structural imaging, hypofrontality, GAD1, C4 complement and synaptic pruning).
- **DSM-5-TR** — "Schizophrenia Spectrum and Other Psychotic Disorders" (diagnostic criteria, course, prognosis, suicide risk, spectrum definitions).
- **Kaplan & Sadock's Comprehensive Textbook of Psychiatry** — dopaminergic pathway/neurochemistry and Schneiderian first-rank symptom framing.
- **CMDT 2026** — "Psychiatric Disorders" (classification, mesolimbic vs mesocortical D2 correlation, current drug regimens/doses, LAIs, xanomeline/trospium, ECT).

Coverage note: Schneiderian first-rank symptoms and Bleuler's "4 A's"/Kraepelin (dementia praecox) are given as universally-accepted standard psychiatry; the corpus references "schneiderian first-rank symptoms" but does not enumerate them, and the nigrostriatal/tuberoinfundibular limbs of the four-pathway model are standard pharmacology stated to frame Harrison's EPS/hyperprolactinaemia data.

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Toxic epidermal necrolysis

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Toxic epidermal necrolysis (TEN), originally described by *Lyell* (1956), is the most extensive form of a single severe mucocutaneous reaction spectrum, **Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN)**, characterised by widespread blistering and **full-thickness epidermal necrosis** with detachment of skin and erosion of two or more mucosal surfaces. It is almost always **drug-induced** (a culprit drug is identified in ~85% of cases), is mediated by drug-specific cytotoxic CD8+ T cells, and is a dermatological emergency with mortality reaching ~30% in TEN. Cases are classified by **maximal body-surface-area (BSA) detachment**: SJS <10%, SJS/TEN overlap 10–30%, and **TEN >30%**.

Nomenclature, spectrum and epidemiology

- **SJS** = epidermal detachment <10% BSA with widespread purpuric macules / flat atypical targets; **SJS/TEN overlap** = 10–30%; **TEN with spots** = >30% with purpuric macules/targets; **TEN without spots** = >30% with loss of large epidermal sheets, no discrete lesions.
- SJS and TEN are now regarded as one entity separated from **erythema multiforme (EM) major**, which is HSV-driven, has true/raised *typical targets* on the extremities, and is rarely drug-related.
- Incidence ~**1–2 cases per million per year**; occurs at all ages (rises in the elderly); female:male ~**2:1**; increased risk in **HIV** infection.

Pathogenesis and genetic predisposition

- A **delayed (type IV) hypersensitivity** reaction: **MHC class I–restricted** presentation of a drug/metabolite-altered antigen by keratinocytes/APCs drives clonal expansion of **CD8+ cytotoxic T lymphocytes (CTLs)** that infiltrate the skin.
- Keratinocyte apoptosis/necroptosis is effected by soluble mediators — **granulysin** (secretory 15-kDa form; the *key* mediator, high in blister fluid), **soluble Fas ligand (Fas–FasL)**, **perforin/granzyme B**, TNF-α, IFN-γ and inducible nitric oxide synthase. **Annexin A1 acting via formyl-peptide receptor 1** and overexpressed **RIP kinase 3 (RIP3)** implicate *necroptosis*.
- Mechanistic models of drug–HLA–TCR interaction: **hapten/pro-hapten** (covalent binding), **p-i (pharmacologic interaction)** concept (non-covalent binding to HLA/TCR), and **altered peptide repertoire** (classically *abacavir* in HLA-B*57:01).
- **Pharmacogenetic HLA associations** (drug- and phenotype-specific):

HLA allele	Drug	Population/notes
HLA-B*15:02	Carbamazepine (SJS/TEN, not DRESS)	Han Chinese, Thai, Malaysian
HLA-B*58:01	Allopurinol (SJS/TEN & DRESS)	Han Chinese; ACR advises pre-screening
HLA-B*57:01	Abacavir hypersensitivity	100% NPV; screening abolishes AHS
HLA-A*32:01	Vancomycin (DRESS)	—
HLA-B*13:01	Dapsone / sulfonamide	cost-effective screening in leprosy

- Non-MHC factors also matter, e.g. slow-metaboliser **CYP2C9*3** raises risk of phenytoin-induced SJS/TEN.

Causative drugs

- A short list accounts for ~half of all cases. **High-risk culprits (Rook's Box 118.3): allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam NSAIDs, phenobarbital, phenytoin, sulfamethoxazole/other sulfa antibiotics, and sulfasalazine**.
- Harrison additionally emphasises **trimethoprim-sulfamethoxazole, β-lactam antibiotics** and other antiepileptics.
- Typical **latency** from drug start to onset is **7–10 days (range 5–28 days)**. Paracetamol/aspirin/ibuprofen/corticosteroid are often confounders (used to treat the prodrome). In a minority (especially children) **Mycoplasma pneumoniae** is the trigger and no drug is found.

Clinical features

- **Prodrome:** malaise, fever, sore throat and upper-respiratory symptoms for a few days, often with conjunctivitis.
- **Skin:** fever >39°C then acute painful, **dusky atypical targets / purpuric macules** beginning on the face and upper trunk, spreading to involve trunk and limbs (palms/soles often prominent); lesions coalesce, blister and lead to confluent dusky erythema and **sheet-like epidermal detachment** over 5–10 days. Marked **skin pain** is characteristic.
- **Nikolsky sign positive** — gentle lateral pressure slides lesional epidermis off the dermis (detachable epidermis); not specific (also positive in pemphigus). Asboe-Hansen (bulla-spread) phenomenon may be present.
- **Mucosal involvement (≥2 sites, near-universal):** painful haemorrhagic erosive **stomatitis/cheilitis** with crusted lips; **ocular** chemosis, conjunctivitis, pseudomembranes, corneal/conjunctival epithelial defects; **urogenital** erosions; and **respiratory** tract sloughing (cough, dyspnoea, haemoptysis) in up to 25%.

Histopathology and investigations

- **Skin biopsy (lesional, adjacent to a blister):** full-thickness/confluent epidermal necrosis with **apoptotic keratinocytes (Civatte bodies)**, basal vacuolar degeneration and **subepidermal split**, with only a sparse perivascular lymphocytic dermal infiltrate. **Frozen-section biopsy** allows rapid diagnosis.
- A second **peri-lesional biopsy for direct immunofluorescence** (negative) excludes autoimmune bullous disease.
- **Bloods at presentation:** FBC (anaemia, leukopenia), urea & electrolytes, glucose, **bicarbonate**, LFTs, amylase, CRP/ESR, coagulation, **Mycoplasma serology**, ANA/ENA, complement, indirect immunofluorescence. Skin swabs for bacteriology, and a **chest X-ray** are mandatory. A **body map** records redness and detachment separately.

Prognosis — SCORTEN

- Overall SJS/TEN mortality ~22% (SJS <10%, TEN ~30%); death is usually from **septicaemia-induced multiorgan failure**.

- **SCORTEN** (*Bastuji-Garin, 2000*) is the validated severity score, calculated on **admission and again within day 1–5**; **one point each** for seven independent parameters:

SCORTEN parameter (1 point each)
Age **>40 years**
Presence of **malignancy**
Heart rate >120/min
Epidermal detachment >10% BSA at admission
Serum urea >10 mmol/L (BUN >28 mg/dL)
Serum glucose >14 mmol/L (>252 mg/dL)
Bicarbonate <20 mmol/L

- Predicted in-hospital mortality rises steeply with score (classically ~3% at 0–1 points, ~12% at 2, ~35% at 3, ~58% at 4, and **>90% at ≥5**). The newer **ABCD-10** score is an alternative (CMDT).

Management

- **Immediate withdrawal of the culprit drug** is the single most important intervention — early stoppage (before/at blistering) is a strong predictor of survival; delay increases mortality. Continue essential non-suspect medicines. **ALDEN** (Algorithm of Drug causality in Epidermal Necrolysis) aids *retrospective* culprit attribution.
- **Care setting:** detachment >10% BSA → transfer to an **ICU or burns unit**; barrier-nurse on a pressure-relieving mattress at ambient **25–28°C**, managed by an MDT (dermatology/burns, intensive care, **ophthalmology**, skin-care nursing, etc.).
- **Supportive care (the proven cornerstone):**
  - *Fluids:* crystalloid at **~2 mL/kg/%BSA detached** (less than for thermal burns), titrated to urine output; avoid over-resuscitation.
  - *Nutrition:* early **enteral/NG feeding** (20–25 kcal/kg/day catabolic phase, rising to 25–30 kcal/kg/day).
  - *Skin:* atraumatic handling (avoid BP cuffs/adhesive leads/wrist tags); emollient (50/50 white-soft/liquid paraffin); leave detached epidermis as a biological dressing or use non-adherent **silicone dressings**; topical antibiotic only on infected/crusted areas.
  - *Mucosae:* daily **ophthalmology review**, 2-hourly ocular lubricant, lysis of conjunctival adhesions, topical steroid drops ± **amniotic membrane transplantation** for severe ocular surface loss; mouth care and **urinary catheterisation** to prevent strictures.
  - *Other:* opioid **analgesia** (± ketamine for procedures), **PPI** stress-ulcer prophylaxis, **LMWH** thromboprophylaxis, vigilant **sepsis** surveillance (commence antibiotics only on clinical signs — *S. aureus* early, then *Pseudomonas*/Gram-negatives), and **macrolide** if Mycoplasma-triggered.
- **Immunomodulatory (adjunctive, unproven — no therapy has unequivocal RCT benefit):**
  - **Ciclosporin** 3–5 mg/kg/day for ~7–10 days then taper — most favoured in current practice; cohort data suggest faster re-epithelialisation and below-SCORTEN-predicted mortality.

- **Systemic corticosteroids** — early high-dose (prednisone 1–2 mg/kg/day, or pulsed IV dexamethasone/methylprednisolone); benefit conflicting, risk of sepsis/impaired healing.
- **IVIG** 0.5–1 g/kg/day for 3–4 days (total ~3–4 g/kg) — anti-Fas rationale; meta-analysis showed **no clear mortality benefit** in adults.
- **Etanercept** (TNF-α inhibitor) — treatment of choice in some centres; faster healing in uncontrolled studies.
- **Thalidomide is contraindicated** — the only RCT was stopped early for *excess deaths*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **SJS/TEN classification spectrum bar:** a horizontal axis of % BSA detachment with three zones labelled — **"SJS <10%"**, **"SJS/TEN overlap 10–30%"**, **"TEN >30%"**; annotate "atypical targets / purpuric macules" and "sheet-like epidermal detachment, Nikolsky +".
- **Pathogenesis schematic:** *Drug/metabolite* → **HLA class I + altered peptide** on keratinocyte → recognised by **CD8+ CTL (TCR)** → release of **granulysin, Fas–FasL, perforin/granzyme B, TNF-α** → **keratinocyte apoptosis/necroptosis** → full-thickness epidermal necrosis & detachment.

Clinical / Diagnostic significance

- Recognise the **red-flag features** (skin pain, dusky/target lesions, blisters, positive Nikolsky, mucosal erosions, fever) early — they distinguish SJS/TEN from benign morbilliform eruptions and mandate urgent specialist referral.
- A frozen-section/biopsy confirms full-thickness necrosis and excludes **staphylococcal scalded skin syndrome** (subcorneal split, no mucosal involvement), pemphigus, bullous pemphigoid, paraneoplastic pemphigus, bullous lupus, linear IgA disease and generalised bullous fixed drug eruption.
- **HLA pharmacogenetic screening** (e.g. HLA-B*15:02 before carbamazepine in South-East/East-Asian patients, HLA-B*58:01 before allopurinol, HLA-B*57:01 before abacavir) prevents cases.
- **Long-term sequelae** drive morbidity: chronic **ocular** disease (dry eye, symblepharon, entropion/trichiasis, corneal scarring, blindness — the most disabling), **bronchiolitis obliterans**, oesophageal/vaginal strictures, dyspigmentation, **onychomadesis**, telogen effluvium, and PTSD. Issue a **MedicAlert card/bracelet** naming the culprit drug; lifelong avoidance of it and cross-reacting congeners (e.g. aromatic antiepileptics).

High-yield exam pointers

- **TEN = >30% BSA detachment; SJS <10%; overlap 10–30%** — *Lyell syndrome*.
- Culprits mnemonic — **allopurinol, anticonvulsants (carbamazepine, lamotrigine, phenytoin, phenobarbital), sulfonamides, oxicam NSAIDs, nevirapine**; latency **5–28 days**.
- **Granulysin** is the *key* cytotoxic mediator; effector cells are **CD8+ CTLs** (MHC-I restricted).
- **HLA-B*15:02 → carbamazepine; HLA-B*58:01 → allopurinol; HLA-B*57:01 → abacavir.**
- **Nikolsky sign positive**; biopsy = **full-thickness epidermal necrosis, subepidermal split**.
- **SCORTEN** = 7 parameters; ≥5 predicts **>90% mortality**.

- **Stop the drug + ICU/burns-unit supportive care** are the only measures with clear survival benefit; **ciclosporin** is the most favoured adjunct; **thalidomide is harmful**.
- Commonest cause of death = **sepsis → multiorgan failure**; commonest disabling sequela = **chronic ocular scarring**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Cutaneous Drug Reactions" (SJS/TEN spectrum, immunopathogenesis, HLA pharmacogenetics, culprit drugs, ALDEN); "Immunologically Mediated Skin Diseases" (blistering differential).
- **Rook's Textbook of Dermatology, 10e** — "Severe Cutaneous Adverse Reactions to Drugs" (definition/nomenclature, classification, histopathology, SCORTEN parameters, investigations, detailed supportive and active-therapy management ladder, complications/prognosis).
- **CMDT 2026** — "Erythema Multiforme / Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis" (BSA criteria, current drug doses — corticosteroids, IVIG, ciclosporin, etanercept; ABCD-10/SCORTEN).

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Psoriasis vulgaris — treatment and complications

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Psoriasis vulgaris (chronic plaque psoriasis) is a common, immune-mediated, genetically determined inflammatory disease affecting up to **2%** of the population, characterised by sharply demarcated, erythematous plaques bearing **silvery micaceous scale**, typically over extensor surfaces (elbows, knees), scalp and the gluteal cleft. It is driven by IL-23/Th17-axis cytokines causing keratinocyte hyperproliferation; trauma reproduces lesions (**Koebner/isomorphic phenomenon**). It is no longer regarded as a skin-limited disorder but a *systemic inflammatory disease* with major cardiometabolic, articular and psychological comorbidity. Treatment is selected by **disease severity, extent (BSA), site and comorbidity**.

Assessment of severity (governs treatment choice)

- **PASI (Psoriasis Area and Severity Index)** — the standard trial and clinical tool. Erythema, scaling (infiltration/thickness) and induration are each graded **0–4**, multiplied by an **area score 0–6**, across four regions — head & neck, trunk, upper limbs, lower limbs — weighted **×0.1, ×0.2, ×0.3, ×0.4** respectively; total range **0–72**. Response is reported as **PASI-75/90/100** (% improvement).
- **BSA** estimated by patient's palm ≈ 1%. **DLQI** (Dermatology Life Quality Index, 0–30) measures quality-of-life impact; score >10 = very large effect.
- **Severe disease** variously defined as **PASI >10–12, or DLQI ≥10, or BSA >10%**, or involvement of high-impact sites (face, palms/soles, genitalia, nails). Practically, patients split into **candidates for topical therapy** vs **candidates for systemic therapy** (BSA ≥10%, high-impact site, or topical failure).

- General measures: emollients/adequate hydration, avoid skin drying and irritation, treat streptococcal triggers, and **avoid known aggravators — lithium, beta-blockers, antimalarials, NSAIDs, statins, and systemic glucocorticoid withdrawal**.

Topical therapy (mild/limited disease, BSA <10%)

- **Topical corticosteroids** — potent/very-potent agents are first-line for limited plaque, trunk and limb disease; mild–moderate potency for face, flexures and genitalia. Limitations: cutaneous **atrophy, striae, tachyphylaxis and rebound flare**; do not induce lasting remission.
- **Vitamin D analogues** — *calcipotriol* (50 µg/g, restrict to <100 g/week to avoid hypercalcaemia/hypercalciuria), *calcitriol* (3 µg/g), *tacalcitol*. The **calcipotriol + betamethasone dipropionate** fixed combination (ointment/gel/foam) is the most effective short-term topical strategy and is excellent for scalp disease.
- **Coal tar** (Goeckerman regimen with UVB) and **dithranol/anthralin** (Ingram regimen, Lassar's paste 0.05–4%) — older keratolytic/antiproliferative agents giving long remissions but messy/staining; largely replaced.
- **Topical calcineurin inhibitors** (tacrolimus 0.1%/0.03%, pimecrolimus) — preferred for **face, flexures and genitalia** (no atrophy).
- **Salicylic acid** keratolytic for thick scalp/plaque; newer non-steroidals **tapinarof 1%** (aryl-hydrocarbon-receptor agonist) and **roflumilast 0.3%** (topical PDE4 inhibitor).

Phototherapy (moderate disease, ~10–30% BSA)

- **Narrowband UVB (NB-UVB, 311–313 nm)** — first-line phototherapy, given **thrice weekly**, MED-based dosing; clearance >90%, non-immunosuppressive and safe in pregnancy. Treatment of choice for widespread **guttate** psoriasis. **Avoid in patients on ciclosporin** (carcinogenesis risk).
- **PUVA** (oral/topical **8-methoxypsoralen 0.6 mg/kg** + UVA) — highly effective; cumulative dose causes **non-melanoma skin cancer (SCC > BCC)**, hence lifetime limit ~**200 treatments**; *Re-PUVA* (with acitretin) is dose-sparing and synergistic.

Systemic (non-biologic) therapy (moderate-to-severe / BSA >30% / topical & phototherapy failure)

Agent	Class / mechanism	Dose	Key toxicity to monitor
Methotrexate	Antimetabolite (DHFR)	≤25 mg once weekly + folic acid 1–2 mg/d	Hepatic fibrosis (cumulative 3.5–4 g → hepatology/PIIINP/elastography), pancytopenia, pneumonitis, mucositis, **teratogenic**
Ciclosporin	Calcineurin inhibitor	≤5 mg/kg/day	**Nephrotoxicity, hypertension**, hyperkalaemia/uricaemia, gum hyperplasia; for **induction only**, rebound on stopping

Agent	Class / mechanism	Dose	Key toxicity to monitor
Acitretin	Oral retinoid	0.5–0.75 mg/kg/day	**Teratogenic (avoid pregnancy 3 yr)**, mucocutaneous dryness, hyperlipidaemia, hepatitis, hyperostosis; non-immunosuppressive — useful in **pustular** psoriasis & HIV
Fumaric acid esters (dimethyl fumarate)	Immunomodulator	up to 240 mg tds	GI upset, flushing, **lymphopenia (→ rare PML)**, proteinuria
Apremilast	Oral PDE4 inhibitor	30 mg BD	Diarrhoea, weight loss, **depression**; minimal immunosuppression, no lab monitoring
Deucravacitinib	Oral **TYK2** inhibitor	6 mg daily	URTI, raised CPK, herpes reactivation, folliculitis

- **Oral glucocorticoids must NOT be used** for plaque psoriasis — withdrawal precipitates life-threatening **generalised pustular** or erythrodermic flares.

Biologic therapy (severe disease, inadequate response/intolerance to standard systemics)

- **TNF-α inhibitors** — *etanercept, adalimumab, infliximab, certolizumab* (and *golimumab* for PsA). **Infliximab** (5 mg/kg IV, weeks 0, 2, 6 then q8w) gives the most rapid response — preferred for **erythrodermic and pustular flares**. TNFi can **worsen heart failure** and paradoxically induce psoriasis.
- **IL-12/23 p40 inhibitor** — *ustekinumab* (45 mg if <100 kg, 90 mg if >100 kg; weeks 0, 4, then q12w). Response is enhanced in **HLA-C*06:02-positive** patients.
- **IL-17 inhibitors** — *secukinumab, ixekizumab* (anti-IL-17A), *brodalumab* (anti-IL-17RA), *bimekizumab* (anti-IL-17A/F). Very rapid, high PASI-90/100 rates; risks: **mucocutaneous candidiasis**, may unmask/worsen **inflammatory bowel disease**; *brodalumab* carries a **suicidality black-box warning**.
- **IL-23 p19 inhibitors** — *guselkumab, risankizumab, tildrakizumab*. Highest sustained efficacy, infrequent dosing, and no signal for candidiasis or IBD.
- **Spesolimab** (anti-IL-36 receptor) — approved specifically for **generalised pustular psoriasis** (linked to *IL36RN* mutations).
- **Biologic safety rules**: screen for **latent TB (IGRA/CXR), hepatitis B/C and HIV** before starting; do not start with active severe infection; serious-infection rate ~**1.4–1.8 per 100 patient-years**; rare reports of demyelination, drug-induced lupus and PML.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **PASI scoring schematic** — body divided into 4 regions with weighting factors: *Head & neck ×0.1, Upper limbs ×0.2, Trunk ×0.3, Lower limbs ×0.4*; annotate each region with *Erythema (0–4) + Induration (0–4) + Scaling (0–4) × Area (0–6)*; final box *PASI = A + B + C + D (range 0–72)*.
- **Treatment pyramid / IL-23–Th17 target map** — base *General measures + Topicals (steroid, vitamin D analogue, calcineurin inhibitor)* → *Phototherapy (NB-UVB, PUVA)* → *Conventional systemics (MTX, ciclosporin, acitretin)* → apex *Biologics*; side ladder showing cytokine targets: *TNF-α, IL-12/23p40, IL-17A/F, IL-23p19, IL-36R* with the drug at each node.

Clinical / Diagnostic significance

- **Complications of the disease itself**: progression to **erythrodermic psoriasis** (>90% BSA — impaired thermoregulation, high-output cardiac failure, fluid/protein/electrolyte loss, sepsis, rare ARDS) and **generalised pustular psoriasis** (fever 39–40°C, sterile pustules, systemic upset, life-threatening).
- **Psoriatic arthritis** in up to **30%** (onset 30–50 yr) — five patterns: **symmetric (~50%), asymmetric (~35%), distal interphalangeal (classic, ~5%), spondylitic (~5%), arthritis mutilans (<5%)**; "sausage digits" (dactylitis), nail dystrophy. Joint damage is erosive and deforming — early recognition is mark-worthy.
- **Systemic comorbidity** (screen actively): **metabolic syndrome** (obesity, hyperlipidaemia, hypertension, diabetes); **cardiovascular disease** with increased MI/stroke/peripheral-vascular/atrial fibrillation/VTE risk and excess mortality; **NAFLD**; other immune-mediated diseases (**Crohn's, ulcerative colitis, coeliac disease, uveitis**); **anxiety, depression and suicidality**; increased non-melanoma skin cancer and lymphoma; gout and (rarely) secondary amyloidosis. **Ocular**: blepharitis, conjunctivitis, uveitis.
- **Complications of therapy** are exam-critical: topical-steroid atrophy/tachyphylaxis/rebound; vitamin-D-analogue hypercalcaemia; MTX hepatic/marrow/pulmonary toxicity and teratogenicity; ciclosporin nephrotoxicity, hypertension and malignancy; acitretin teratogenicity and hyperlipidaemia; PUVA-induced SCC/melanoma; biologic-associated serious infection, **TB and hepatitis B reactivation**, IL-17-related candidiasis and IBD.
- Investigations: usually clinical; **skin biopsy** (acanthosis with regular elongation of rete ridges, parakeratosis, Munro microabscesses, dilated dermal papillary vessels) when atypical. Baseline screen before systemics: FBC, LFTs, U&E, lipids/glucose, hepatitis & HIV serology, IGRA/CXR, pregnancy test.

High-yield exam pointers

- **PASI 0–72**, four regions weighted 0.1/0.2/0.3/0.4; treatment endpoints **PASI-75/90/100**; severe = PASI >10–12 or DLQI ≥10 or BSA >10%.
- **First-line by extent**: topical steroid ± vitamin D analogue (limited) → NB-UVB (moderate/guttate) → MTX/ciclosporin/acitretin or biologic (severe).

- **Never give systemic steroids** for plaque psoriasis — rebound pustular/erythrodermic flare on withdrawal.
- **Acitretin** = drug of choice in **pustular** psoriasis and when immunosuppression must be avoided; **teratogenic for 3 years**.
- **Infliximab** = fastest-acting biologic, best for **erythrodermic/pustular** flares; **spesolimab** (anti-IL-36R) specifically for GPP.
- Screen **TB, HBV/HCV, HIV** before any biologic/immunosuppressant; **IL-17 inhibitors → candidiasis & IBD**; **brodalumab → suicidality warning**.
- **HLA-C*06:02** predicts good ustekinumab response; *IL36RN* mutation underlies generalised pustular psoriasis.
- Treat psoriasis as a **systemic disease** — screen for psoriatic arthritis, metabolic syndrome, cardiovascular risk and depression; address weight and smoking.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders" (clinical types, FDA-approved systemic agents and biologics tables, PsA subtypes).
- **Rook's Textbook of Dermatology, 10e** — "Psoriasis and Related Disorders" (PASI methodology, severity classification, comorbidity Box, full topical/phototherapy/systemic/biologic pharmacology, generalised pustular psoriasis and *IL36RN*).
- **CMDT 2026** — "Dermatologic Disorders: Psoriasis" (current treatment ladder by BSA, drug doses and monitoring, spesolimab for GPP).

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