
R G U H S · M O D E L A N S W E R B A N K

RGUHS MD General Medicine — Paper I



B A S I C S C I E N C E S

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

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Textbook of Critical Care 8e — critical care
CMDT 2026 — diagnosis & management



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Contents

Environment & poisonings.....	5
Carbon monoxide poisoning.....	5
Scorpion envenomation.....	9
Organophosphorus poisoning.....	13
Paracetamol poisoning.....	18
Ethylene glycol poisoning.....	23
Poisonous snake bite.....	27
Russell's viper envenomation.....	32
Venomous snake bite poisoning.....	37
Lead toxicity.....	42
Vitamins, minerals, nutrition & electrolytes.....	46
Beer potomania.....	46
Beriberi.....	50
Hyponatraemia.....	54
Parenteral nutrition therapy.....	59
Pellagra.....	63
Thiamine physiology and deficiency.....	67
Total parenteral nutrition.....	71
Refeeding syndrome.....	76
Miscellaneous.....	81
Anatomy of the spinal cord.....	81
Autophagy mechanism in health and disease.....	87
Autosomal inherited diseases.....	91
Biosimilar.....	96
Cell culture technique and application.....	100
Circle of Willis.....	104
Newer anticoagulants.....	107
Oral antifungal therapy.....	112
Bioavailability and protein binding.....	116
Cloning principle and methods.....	120
Complement pathway, functions and regulation.....	125
Cytochrome P450 enzyme system and drug metabolism.....	130
Cytokines, physiology and clinical implications.....	134
Smoking-related health hazards and nicotine de-addiction.....	139
Delayed hypersensitivity reaction.....	144
Nucleotide repeat expansion disorders.....	148
Problems of old age.....	152

Thermoregulation.....	156
DNA replication.....	161
Down's syndrome — genetics and clinical features.....	165
Effects of disease on drug concentration and response.....	169
ELISA — principle, methods and applications.....	174
Epigenetics.....	178
Extraocular muscles and superior orbital fissure syndrome.....	182
Fabry's disease.....	186
Factors affecting drug metabolism.....	190
Falls in the elderly.....	194
Gene therapy.....	199
Genetic counselling.....	204
HLA antigenic system in health and disease.....	209
Drug pharmacokinetics and prescribing in pregnancy.....	213
Preoperative cardiac risk assessment.....	218
Hypersensitivity reactions.....	224
Inherited mitochondrial disorders in adults.....	228
Limbic system.....	233
Monoclonal antibodies — clinical pharmacology.....	237
Neurotransmitters.....	242
Pharmacogenomics.....	246
Plasma enzymes in clinical medicine.....	251
Polymerase chain reaction — technique and applications.....	255
Pregnancy-induced hypertension.....	259
Pyrogenic cytokines in pathogenesis of fever.....	264
Recombinant DNA technology.....	268
Stem cell therapy.....	272
Evidence-based medicine.....	278
Internal capsule — structure and blood supply.....	282
Temperature regulation.....	286
Teratogenesis.....	290
Therapeutic index.....	296
Organ transplant rejection.....	300
Genetic testing in pregnancy.....	304
Complement system — pathways and effector actions.....	309
Polymerase chain reaction and DNA sequencing.....	313
Therapeutic drug monitoring.....	317
X-linked disorders.....	322

Environment & poisonings



Carbon monoxide poisoning

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

Definition / Introduction — Carbon monoxide (CO) is a colourless, odourless, non-irritant gas produced by incomplete combustion of carbon-containing fuels. It is a prototype "**asphyxiant**" (systemic chemical hypoxia) poison that binds haemoglobin with ~200–250 times the affinity of oxygen, forming **carboxyhaemoglobin (COHb)**, thereby reducing oxygen-carrying capacity, impairing oxygen delivery and disrupting cellular oxidative metabolism. It is one of the leading causes of poisoning death worldwide — in the United States alone it accounts for >50,000 emergency-department visits and ~2000 deaths per year — and is frequently lethal before the patient reaches hospital.

SOURCE & COVERAGE

- ▶ **Common sources:** automobile exhaust, smoke inhalation in house/structural fires, improperly vented or defective domestic gas heaters/geysers, generators and industrial appliances, and degradation of some anaesthetic gases by CO₂ adsorbents.
- ▶ **Intent:** about half of non-lethal exposures are deliberate (self-harm); the **motor vehicle is the commonest source of intentional poisoning**. Accidental poisoning clusters in **cold weather** when faulty heating systems are used in poorly ventilated rooms.
- ▶ It is the **third leading cause of death from poisoning** overall, but is under-represented in hospital statistics because victims are often found dead and referred directly to medical examiners.
- ▶ The **fetus and newborn are especially susceptible** because fetal haemoglobin has a high affinity for CO.

Pathophysiology — mechanisms of toxicity

CO produces injury by several overlapping mechanisms, not by hypoxaemia alone:

Mechanism	Consequence
Binds Hb → carboxyhaemoglobin (affinity ~200–250× O ₂)	Reduced oxygen-carrying capacity → anaemic-type (histotoxic) hypoxia
COHb shifts the oxy-Hb dissociation curve to the LEFT	O ₂ unloaded only at very low tissue tensions → worsened tissue hypoxia
Binds myoglobin	Impaired O ₂ storage/use in cardiac and skeletal muscle
Binds cytochrome a/a3 (cytochrome c oxidase)	Blockade of mitochondrial electron transport / oxidative metabolism → lactic acidosis
Lipid peroxidation in brain, leukocyte adherence to endothelium, oxidative stress	Delayed neuronal injury and neuropsychiatric sequelae

- ▶ The **brain and heart** are the most sensitive target organs (high blood flow, high O₂ demand, poor tolerance of hypoxia).
- ▶ CO is also a low-affinity **anaesthetic agent** and an endogenous gaseous neurotransmitter linked to nitric oxide metabolism.

Clinical features (correlate with COHb saturation)

COHb saturation	Typical clinical features
10–20%	Headache, dizziness, nausea, abdominal pain, lethargy, poor concentration
20–40% (higher)	Confusion, impaired short-term memory, dyspnoea on exertion, syncope, visual disturbance, irritability
>50–60%	Hypotension, seizures, coma , cardiac ischaemia/arrhythmia, sudden collapse, death

- ▶ Symptoms are **non-specific and "flu-like"**, so the diagnosis is easily missed; suspect CO in any patient with severe headache or acutely altered mental status, **especially during cold weather** or when multiple household members are simultaneously ill.
- ▶ *Classic "cherry-red" skin* is the traditionally described sign but is **unreliable and usually a late/post-mortem finding**; importantly, CO does NOT produce true cyanosis — carboxyhaemoglobinaemia is listed as a cause of skin discolouration that is *not true cyanosis*.
- ▶ Other features: myocardial ischaemia (even in young patients), rhabdomyolysis, non-cardiogenic pulmonary oedema, and (with concurrent fire exposure) **co-existent cyanide poisoning and thermal airway injury**.

Diagnosis and investigations

- ▶ Diagnosis rests on direct measurement of arterial or venous COHb saturation by CO-oximetry. A normal smoker may have 5–10%; non-smokers <2–3%.
- ▶ **Pitfalls:** routine **pulse oximetry (SpO₂) is falsely normal/elevated** — it cannot distinguish COHb from oxyhaemoglobin; **arterial blood gas PaO₂ is also falsely normal** because dissolved O₂ is unaffected. Calculated O₂ saturation is normal but measured (co-oximetry) saturation is low — a *discordant* picture characteristic of asphyxiants. Specialised pulse CO-oximeters can estimate COHb with variable accuracy.
- ▶ **Admission COHb level confirms exposure but does NOT reliably reflect severity or prognosis**, and falls rapidly once high-flow oxygen is started.
- ▶ Supporting tests: ABG showing **elevated anion-gap (lactic) metabolic acidosis**; ECG and troponin for myocardial ischaemia; serum lactate; CK for rhabdomyolysis; and in selected cases neuroimaging (CT/MRI may show **basal ganglia / globus pallidus** changes — a standard radiological association).

Management

A. Emergency and supportive measures

- ▶ **Remove the patient from the source of exposure immediately.**

- ▶ Secure airway, assist ventilation; treat coma, seizures and hypotension along standard poisoning lines.
- ▶ If smoke inhalation/fire is involved, anticipate and treat **concurrent cyanide poisoning** (IV hydroxocobalamin ± sodium nitrite/sodium thiosulfate) and thermal airway injury.

B. Specific treatment — OXYGEN is the antidote

- ▶ The elimination half-life of COHb is ~4–5 h (≈5.5 h) **breathing room air**, falling to ~60–90 min (~71 min) **on 100% oxygen at 1 ATA**, and to ~20 min (~21 min) **on oxygen at 2.0 ATA**.
- ▶ Give **100% oxygen** by tight-fitting high-flow non-rebreather reservoir mask or via endotracheal tube; continue until the patient is asymptomatic and COHb is near-normal.

C. Hyperbaric oxygen (HBO) therapy

- ▶ HBO delivers 100% O₂ at supra-atmospheric pressure, dramatically shortening COHb half-life and (more importantly) is thought to reduce **delayed neuropsychiatric sequelae** via mechanisms beyond reversal of hypoxia — displacing CO from cytochromes, upregulating antioxidant defences, reducing leukocyte adherence and lipid peroxidation.
- ▶ CO poisoning is a **recognised primary indication** for HBO (Undersea & Hyperbaric Medical Society list), including poisoning **complicated by cyanide**.
- ▶ **Commonly recommended indications for HBO** (criteria differ between sources — RCTs disagree on benefit):

Source	Indications / risk markers for HBO referral
CMDT 2026	History of loss of consciousness; COHb >25%; metabolic acidosis; age >50 years ; cerebellar findings on examination
Harrison (Hyperbaric & Diving Medicine)	Moderate–severe poisoning; age >35 years ; metabolic acidosis on ABG; lengthy exposure (>24 h); history of unconsciousness; pregnancy is also a widely accepted indication

- ▶ **Evidence:** the most rigorous RCT (Weaver et al.) showed cognitive sequelae at 6 weeks in **25% with HBO vs 46% with normobaric oxygen** ($p = .007$, NNT = 5) and a persisting benefit at 12 months (18% vs 32%, NNT = 7). A Cochrane review found insufficient pooled evidence, so HBO use remains individualised and time-sensitive (ideally first sessions within 24 h).

Delayed neuropsychiatric syndrome and prognosis

- ▶ Survivors of severe poisoning may develop **persistent or delayed neuropsychiatric deficits** — characteristically after an interval of *days to weeks* of apparent recovery.
- ▶ Reported features: cognitive impairment/dementia, short-term memory loss, **parkinsonism and other movement disorders**, peripheral neuropathy, hearing loss, vestibular dysfunction, personality change and psychosis.
- ▶ **Risk factors for poor outcome:** age >35 years, exposure >24 h, metabolic acidosis, and loss of consciousness.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Oxygen–haemoglobin dissociation curve:** plot SaO_2 (y-axis) vs Po_2 (x-axis); show the normal sigmoid curve and a left-shifted curve in CO poisoning. Label: *normal curve, left shift due to COHb, P50 reduced, O₂ unloaded only at low tissue Po_2 → tissue hypoxia.*
- ▶ **Pathophysiology flow diagram:** *Inhaled CO → binds Hb (200–250× O₂ affinity) → ↓O₂-carrying capacity + LEFT shift of ODC; binds myoglobin; inhibits cytochrome c oxidase → impaired oxidative phosphorylation → lactic acidosis + brain/heart hypoxia → coma, seizures, delayed neuropsychiatric sequelae.*

Clinical / Diagnostic significance

- ▶ Never rely on SpO_2 or PaO_2 to exclude CO poisoning — both are falsely reassuring; demand a CO-oximetry COHb level.
- ▶ Consider CO in clusters of simultaneously ill household members, in winter, and in all fire/smoke-inhalation victims (screen for cyanide too).
- ▶ An unexplained **high-anion-gap lactic acidosis** with normal PaO_2 should trigger consideration of asphyxiant poisoning (CO, cyanide, H₂S).
- ▶ Pregnant patients warrant lower thresholds for 100% O₂ and HBO because of fetal vulnerability.
- ▶ Counsel survivors and arrange neuropsychological follow-up given the risk of the delayed syndrome.

High-yield exam pointers

- ▶ CO affinity for Hb = ~200–250× that of O₂; forms **carboxyhaemoglobin** and shifts the oxy-Hb curve to the LEFT.
- ▶ Diagnosis = CO-oximetry; pulse oximetry & PaO_2 are falsely normal; admission COHb does not predict severity/prognosis.
- ▶ COHb half-life: ~5 h (air) → ~71 min (100% O₂, 1 ATA) → ~21 min (O₂ at 2 ATA).
- ▶ **Antidote = oxygen**; 100% O₂ by non-rebreather is first-line; HBO for severe/high-risk cases.
- ▶ HBO indications (CMDT): LOC, COHb >25%, metabolic acidosis, age >50, cerebellar signs; (Harrison risk markers): age >35, acidosis, prolonged exposure, LOC, pregnancy.
- ▶ Toxicity is multi-mechanistic: Hb + **myoglobin** + **cytochrome c oxidase** binding → lactic acidosis; brain and heart are most vulnerable.
- ▶ **CO does not cause true cyanosis**; "cherry-red" skin is classic but unreliable/late.
- ▶ Beware **concurrent cyanide toxicity and airway burns** in fire victims.
- ▶ **Delayed neuropsychiatric syndrome** (parkinsonism, cognitive/memory deficits) can appear days–weeks after recovery; basal ganglia (globus pallidus) lesions on imaging.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Poisoning and Drug Overdose" (asphyxiant toxic syndromes, oxygen/antidotal therapy); "Hyperbaric and Diving Medicine" (dedicated Carbon Monoxide Poisoning section — epidemiology, mechanisms, COHb half-lives, HBO indications and Weaver RCT data); "Hypoxia and Cyanosis" (CO intoxication, left-shift of dissociation curve, carboxyhaemoglobinaemia is not true cyanosis).
- ▶ **CMDT 2026** — "Poisoning" (Carbon Monoxide: clinical findings by COHb level, diagnosis by CO-oximetry, HBO indication criteria) and "Pulmonary Disorders — Smoke Inhalation" (combined CO/cyanide injury).
- ▶ *Coverage note:* The corpus does not present a formal staging or a discrete table of cherry-red-skin/retinal signs for CO; the "cherry-red skin" and basal-ganglia/parkinsonism associations included are universally accepted standard internal medicine and are stated with appropriate caveats. HBO benefit is genuinely debated across the cited sources, reflected faithfully above.



Scorpion envenomation

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

Definition / Introduction — Scorpion envenomation (scorpionism) is systemic poisoning following the sting of an arachnid of the order Scorpiones, which injects peptide-rich venom from the **aculeus** (**stinger**) at the tip of the tail (telson). Of ~1000–1500 known species, only about 30 (almost all of the family *Buthidae*) are dangerous to humans, together causing several thousand deaths annually. The clinical hallmark is an **"autonomic storm"** — a massive, biphasic outpouring of acetylcholine and catecholamines — so that systemic and especially **cardiorespiratory** features are grossly out of proportion to the trivial local sting. In India the lethal species is the *Indian red scorpion* (*Mesobuthus / Hottentotta tamulus*), against which the α 1-blocker **prazosin** is the pharmacological cornerstone of treatment.

Epidemiology & medically important species

- ▶ Worldwide an estimated **>1.2 million serious stings** and **~3250 deaths** per year; children and the elderly suffer the most severe envenomation and highest mortality.
- ▶ Scorpions are nocturnal, hiding by day under rocks, bark, woodpiles or inside shoes, clothing and bedding; they sting only when threatened.
- ▶ The dangerous species belong almost exclusively to the family **Buthidae**.

Region	Important species	Distinguishing toxicity
India / South Asia	<i>Mesobuthus (Hottentotta) tamulus</i> — Indian red scorpion	Catecholamine storm, myocarditis , pulmonary oedema

Region	Important species	Distinguishing toxicity
Middle East / N. Africa	<i>Leiurus quinquestriatus</i> , <i>Androctonus</i> spp.	Catecholamine excess, hypertensive crisis, arrhythmias
Brazil	<i>Tityus serrulatus</i> (<i>tityustoxin</i>)	Childhood deaths; <i>T. trinitatis</i> (Trinidad) → pancreatitis
Iran / Iraq	<i>Hemiscorpius lepturus</i>	Cytotoxic — haemolysis, haemoglobinuria, AKI, skin necrosis
South Africa	<i>Parabuthus</i> , <i>Buthotus</i> spp.	CNS toxicity
SW USA (Arizona)	<i>Centruroides sculpturatus</i> / <i>exilicauda</i> — bark scorpion	Neuromuscular & cranial-nerve dysfunction

Venom & pathophysiology — the "autonomic storm"

- ▶ Venom contains low-molecular-weight **peptide neurotoxins** plus 5-hydroxytryptamine, histamine and kinins.
- ▶ Neurotoxins act on **voltage-gated sodium channels**, holding them **open** (prolonged depolarisation), and **block potassium channels** → repetitive, uncontrolled firing of autonomic and somatic nerves.
- ▶ This drives **massive release of acetylcholine and endogenous catecholamines** at autonomic ganglia, adrenal medulla and neuromuscular junctions, producing the characteristic **biphasic response**:
 - *Early transient parasympathetic (cholinergic) phase* — vomiting, profuse salivation, lacrimation, sweating, bronchorrhoea, bradycardia, hypotension, priapism.
 - *Sustained sympathetic (adrenergic) phase* — hypertension, tachycardia, cool clammy peripheries, mydriasis, myocardial injury and pulmonary oedema.
- ▶ *Tityustoxin* binds Na^+/K^+ channels causing sialorrhoea, lacrimation and rhinorrhoea; *Hemiscorpius* venom (**hemicalcin**) acts on **ryanodine-sensitive calcium channels** and is cytotoxic/haemolytic.

Clinical features

- ▶ **Local** — immediate, severe **burning pain** and **hyperaesthesia**; swelling, erythema and ecchymosis are usually minimal and *out of proportion* to symptoms. Pain is accentuated by gently tapping the site (positive "**tap test**"). Pain may persist for days to weeks.
- ▶ **Autonomic** — restlessness, profuse sweating, hypersalivation, lacrimation, rhinorrhoea, nausea/vomiting; cool extremities, alternating hypotension/hypertension, brady- then tachy-arrhythmia, priapism.
- ▶ **Neuromuscular / cranial nerve** — muscle twitching, jerking and fasciculation (may be **mistaken for seizures**), blurred vision, roving/abnormal eye movements, slurred speech and difficulty handling secretions.
- ▶ **Course** — systemic features progress to maximal severity by ~5 h and usually subside within 1–2 days, though pain and paraesthesia may last weeks. **Appearance of gastrointestinal/autonomic features within the first few hours signals progression to severe envenomation.**

- ▶ Children and the elderly deteriorate fastest; **fatal respiratory arrest** is the dominant mode of death in these groups.

Complications

- ▶ **Cardiovascular** — *scorpion-sting myocarditis* / catecholamine (stress) cardiomyopathy, tachy- and brady-arrhythmias, hypertensive crisis, and **cardiogenic shock**.
- ▶ **Respiratory** — acute **pulmonary oedema** (both cardiogenic from LV dysfunction and capillary-leak/non-cardiogenic) and **respiratory failure/arrest** — the leading cause of death.
- ▶ **Acute pancreatitis** — notably with *Tityus* stings.
- ▶ **Renal / haematological** — **rhabdomyolysis**, intravascular **haemolysis**, haemoglobinuria and **acute kidney injury** (especially *Hemiscorpius lepturus*).
- ▶ **Metabolic** — hyperthermia, lactic acidosis.
- ▶ **Local** (cytotoxic species) — purpura, bullae, tissue necrosis and ulceration.
- ▶ Allergic reactions to venom (rarely anaphylaxis); secondary bacterial infection.

Management

- ▶ **First aid** — reassure and **keep the patient calm and immobile**; apply a **cold pack / pressure dressing** to the site to slow venom absorption; **infiltrate local anaesthetic without a vasoconstrictor** for pain; clean the wound and give **tetanus prophylaxis**. Avoid incision and tourniquets.
- ▶ **Triage** — most stings (non-lethal species) need only ice packs, analgesics or antihistamines and can be observed at home, returning if cranial-nerve or neuromuscular signs appear.

Problem	Drug / intervention
Agitation, involuntary movements	Continuous IV midazolam infusion (monitor for respiratory depression)
Hypertension & pulmonary oedema	Prazosin (drug of choice), nifedipine, hydralazine, sodium nitroprusside
Bradycardia	IV atropine
Severe / systemic envenomation	Species-specific antivenom (e.g. FDA-approved equine <i>Centruroides</i> IgG F(ab') ₂)
Cardiogenic pulmonary oedema / shock	Oxygen, vasodilators/afterload reduction, inotropes, ventilatory support, ICU care

- ▶ **Prazosin** — the **pharmacological antidote of choice for the Indian red scorpion autonomic storm**: this α_1 -adrenergic blocker abolishes catecholamine-driven vasoconstriction, reduces preload and afterload, and **reverses/prevents pulmonary oedema**, giving accelerated recovery with preserved myocardial function. (Conventional Indian teaching: oral $\sim 30 \mu\text{g/kg}$, repeated ~ 3 -hourly until peripheries are warm, dry and the patient stabilises — see Coverage note.)
- ▶ **Antivenom** — available in endemic regions and, with supportive care, reduces morbidity and mortality from severe envenomation; IV administration rapidly reverses cranial-nerve and neuromuscular dysfunction. (Its role relative to prazosin in *M. tamulus* envenomation is debated; prazosin remains the Indian mainstay.)

- ▶ **Supportive/ICU** — close cardiorespiratory monitoring, oxygen and mechanical ventilation for pulmonary oedema/respiratory failure, fluid and electrolyte correction, and treatment of rhabdomyolysis/AKI and pancreatitis as they arise.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Scorpion external morphology (labelled)**: pedipalps/pincers (chela), cephalothorax (prosoma), four pairs of legs, mesosoma (abdomen), metasoma (segmented "tail"), and telson bearing the aculeus (stinger) with venom gland.
- ▶ **"Autonomic storm" flow diagram**: *Venom neurotoxin* → *Na⁺ channel held open + K⁺ channel block* → *repetitive nerve firing* → *massive ACh + catecholamine release* → *biphasic response* — label the **parasympathetic/cholinergic (early)** limb (vomiting, salivation, lacrimation, sweating, bradycardia) and the **sympathetic/adrenergic (late)** limb (hypertension, tachycardia, myocarditis, pulmonary oedema); show **prazosin blocking the α_1 receptor**.

Clinical / Diagnostic significance

- ▶ Diagnosis is **clinical** (history of sting + autonomic storm); **identifying the species** guides prognosis and the need for antivenom.
- ▶ Suspect **myocarditis/cardiomyopathy** in any stung child with tachypnoea, gallop or pulmonary oedema — obtain ECG (ST-T changes, arrhythmia), **echocardiography** (global LV hypokinesia), and cardiac biomarkers.
- ▶ Monitor for **rhabdomyolysis and AKI** (CK, urine myoglobin, creatinine), and consider **serum amylase/lipase** where *Tityus*-type pancreatitis is plausible.
- ▶ The combination of **minimal local signs with florid systemic/cranial-nerve toxicity** is the key clue distinguishing dangerous scorpionism from a trivial sting.

High-yield exam pointers

- ▶ Lethal species belong to family **Buthidae**; India = *Mesobuthus (Hottentotta) tamulus* (Indian red scorpion).
- ▶ Mechanism = neurotoxin keeps **Na⁺ channels open** + blocks **K⁺ channels** → **autonomic storm** (cholinergic then adrenergic).
- ▶ Local signs are **out of proportion** to severe pain; **positive tap test**.
- ▶ **Pulmonary oedema, myocarditis and respiratory arrest** are the chief killers; children/elderly worst affected.
- ▶ **Prazosin** is the drug of choice for the Indian red scorpion (reverses autonomic storm, preserves myocardium).
- ▶ **IV midazolam** for agitation/involuntary movements; **atropine** for bradydysrhythmia; **nifedipine/nitroprusside/hydralazine** for hypertensive pulmonary oedema.
- ▶ Species-specific **antivenom** (equine *Centruroides* F(ab')₂ is FDA-approved) reverses cranial-nerve/neuromuscular signs.
- ▶ Remember **pancreatitis** (*Tityus*) and **haemolysis + AKI + skin necrosis** (*Hemiscorpius lepturus*).

- First aid = reassurance, immobilisation, cold pack/pressure dressing, local anaesthetic **without** vasoconstrictor, tetanus prophylaxis; **avoid incision/tourniquet**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Ectoparasite Infestations and Arthropod Injuries" (Scorpion Stings section: species, sodium-channel mechanism, catecholamine release, complications, and treatment including midazolam, prazosin, nifedipine, nitroprusside, atropine and antivenom).
- **Bologna, Dermatology, 5e** — "Bites and Stings" (clinically important scorpion species table; symptoms out of proportion to cutaneous signs; cardiorespiratory deaths in children <10 y; pancreatitis; **prazosin reverses the autonomic storm of *Hottentotta tamulus***).
- **Rook's Textbook of Dermatology, 10e** — "Arthropods" (Buthidae, venom components, epidemiology ~1.2 million serious stings/~3250 deaths, tityustoxin and hemicalcin mechanisms, biphasic clinical features, antivenom/supportive management).
- **CMDT 2026** — "Poisoning: Spider Bites & Scorpion Stings" (*Centruroides* features; FDA-approved species-specific antivenom; analgesia).

Coverage note: The corpus covers scorpion envenomation only moderately and from a largely non-Indian standpoint. It confirms *Mesobuthus tamulus* as the Indian species and **prazosin** as the antidote for its autonomic storm, but does **not** state the prazosin dose or any formal severity grading; the dose given (~30 µg/kg orally, ~3-hourly) and the biphasic cholinergic→adrenergic framing reflect standard, widely accepted Indian internal-medicine teaching (Bawaskar protocol) and should be applied per local guidelines rather than as verbatim corpus content.



Organophosphorus poisoning

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

Definition / Introduction — Organophosphorus (OP) compounds are organic esters of phosphoric/phosphorothioic acid used as insecticides (diazinon, malathion, parathion, chlorpyrifos, acephate) and as chemical-warfare nerve agents (tabun [GA], sarin [GB], soman [GD], VX). They produce poisoning by **irreversibly inhibiting acetylcholinesterase**, causing accumulation of acetylcholine and an overwhelming **cholinergic crisis** at muscarinic, nicotinic and CNS receptors. OP poisoning — most often **deliberate self-poisoning** in agrarian Asia — accounts for the bulk of the >150,000 pesticide-poisoning deaths each year worldwide and is a leading cause of acute-poisoning ICU admission in India.

Pathophysiology — cholinesterase inhibition and "aging"

- **Two cholinesterases are inhibited:**
 - *Acetylcholinesterase (AChE; "true" or RBC cholinesterase)* — in erythrocyte membranes, nervous tissue and skeletal muscle; the better index of synaptic enzyme inhibition.
 - *Plasma butyrylcholinesterase (BuChE; pseudocholinesterase)* — in serum, liver, pancreas, heart and brain; easier to assay, falls first, but is less specific.

- ▶ OP compounds **phosphorylate** the active (esteratic) site of AChE, inactivating it. Acetylcholine is therefore not hydrolysed and accumulates at synapses → initial **overstimulation** of cholinergic receptors, followed by **depolarising blockade/paralysis** of transmission in the CNS, autonomic ganglia, parasympathetic and selected sympathetic (sweat-gland) endings, and at the neuromuscular junction.
- ▶ "**Aging**" = loss of an alkyl group from the phosphorylated enzyme, making the OP–enzyme bond *permanent and irreversible*. Time to aging is agent-specific (minutes for **soman**, up to >24–48 h for others). **Oximes can only reactivate the enzyme before aging occurs** — hence the urgency of antidote therapy. Once aged, recovery requires **resynthesis of new enzyme over weeks**.
- ▶ Many formulations contain an **aromatic hydrocarbon solvent (xylene)** and surfactants — these add aspiration (lipoid) pneumonitis and CNS depression, and OP is **well absorbed transdermally**, by inhalation, transconjunctivally and by ingestion.
- ▶ *Carbamates* (carbaryl, aldicarb, propoxur) inhibit the same enzyme but the carbamylated bond is **reversible and does not age**, giving a shorter, generally more benign illness.

Clinical features — cholinergic toxidrome

Most patients are symptomatic within **8 h** of ingestion and nearly all by **24 h**; onset is fastest with inhalation, slowest transdermally. Three receptor groups produce overlapping signs.

Receptor group	Mechanism	Clinical effects (mnemonic)
Muscarinic	Post-ganglionic parasympathetic + sweat glands	DUMBELS — Defecation, Urination, Miosis, Bradycardia/Bronchorrhoea/Bronchospasm ("Killer Bs"), Emesis, Lacrimation, Salivation. Also SLUDGE (Salivation, Lacrimation, Urination, Defecation, GI cramps, Emesis), sweating
Nicotinic	Autonomic ganglia, adrenal medulla, NMJ	Muscle fasciculations , cramps, weakness → paralysis (incl. diaphragm); mydriasis, pallor, tachycardia, hypertension
CNS	Central cholinergic receptors	Anxiety, restlessness, tremor, headache, confusion, delirium, seizures, coma

- ▶ *Either picture may dominate* — parasympathetic effects usually predominate, but severe poisoning may present with **nicotinic features first** (tachycardia, hypertension). Classic severe triad: **pinpoint pupils + excessive secretions/sweating + difficulty breathing**, often with a **garlic/hydrocarbon odour**.
- ▶ **Death is due to respiratory failure** — combination of bronchorrhoea, bronchospasm, respiratory-muscle paralysis and central respiratory depression; aspiration of gastric contents/hydrocarbon worsens it. Myocardial ischaemia and pancreatitis may occur.

Four recognised clinical syndromes (high-yield):

- ▶ **1. Acute cholinergic crisis** — minutes to hours; the muscarinic/nicotinic/CNS toxidrome above.
- ▶ **2. Intermediate syndrome** — 1–5 days after exposure (up to ~40% of ingestions); proximal limb, **neck-flexor**, cranial-nerve and **respiratory-muscle weakness** *without* cholinergic features; may need ventilation; usually resolves within ~7 days. **Not reported with nerve-gas poisoning**.

- ▶ **3. OP-induced delayed neuropathy (OPIDN)** — a distal, symmetrical sensorimotor axonopathy appearing ~1–3 weeks later (classically attributed to inhibition of *neuropathy target esterase, NTE*); leg cramps → weakness/paralysis mimicking **Guillain–Barré syndrome**; *not* reversed by atropine/oximes.
- ▶ **4. Chronic toxicity / neuropsychiatric sequelae** — with low-grade repeated exposure: cognitive/memory impairment, mood change, autonomic dysfunction, extrapyramidal signs.

Diagnosis / Investigations

- ▶ **Clinical** — diagnosis rests on history + the cholinergic toxidrome; **do not delay antidote** awaiting enzyme assays.
- ▶ **Cholinesterase assays** —
 - *Plasma BuChE* falls first; in poisoning, plasma/RBC cholinesterase is **<50% of normal**; BuChE normalises in **28–42 days** (if no oxime given).
 - *RBC AChE* is the better marker: reduced to **10–20%** of normal in moderate, **<10%** in severe poisoning; full recovery needs RBC turnover (up to **120 days**).
- ▶ **Cautions:** BuChE is low in liver disease, malnutrition, pregnancy, genetic variants and with certain drugs; RBC AChE is factitiously low with haemoglobinopathy, pernicious anaemia and antimalarials.
- ▶ **Ancillary:** ECG — sinus brady/tachycardia, **prolonged QT, ST/T changes, AV block**, torsades/VT; CXR — pulmonary oedema/aspiration; bloods — hyper-/hypoglycaemia, leucocytosis, amylase (pancreatitis); ABG. EMG can demonstrate NMJ dysfunction/intermediate syndrome.

Management

General principles: secure airway and ventilation, decontaminate, **adequate atropinisation**, and **early oxime** before aging — with intensive supportive care. Therapy must **not** be withheld pending cholinesterase results.

Step	Detail
Resuscitation	Airway, 100% O ₂ , suction secretions; intubate for coma/seizures/respiratory failure/bronchorrhoea. Use a non-depolarising relaxant if paralysis needed — avoid succinylcholine (prolonged apnoea, as it is hydrolysed by BuChE). IV crystalloid for hypotension.
Decontamination	Staff wear nitrile/neoprene gloves, gown, face shield (latex is inadequate); remove all clothing as hazardous waste; wash skin/hair/nails with soap & water ; dilute 1:10 hypochlorite (bleach) decontaminates equipment. Gastric lavage only within 1 h of large ingestion after airway protection; activated charcoal, lavage and haemodialysis are of no proven benefit.

Step	Detail
Atropine (<i>physiological antidote — muscarinic only</i>)	Bolus 1.2–3 mg IV (CMDT: 2 mg); double the dose every 5 min until atropinised — <i>clear chest on auscultation, HR >80/min, SBP >80 mmHg</i> . Tens—hundreds of mg may be needed. Then infusion at 10–20%/h of the total atropinising dose (~0.4–4 mg/h), titrated; watch for toxicity (absent bowel sounds, hyperthermia, delirium). Tachycardia and mydriasis are NOT contraindications/endpoints . <i>Glycopyrrolate</i> is an alternative without CNS effects.
Pralidoxime (2-PAM) (<i>enzyme reactivator — nicotinic + muscarinic; reverses muscle weakness if given before aging</i>)	WHO regimen: 30 mg/kg IV bolus over 5–10 min, then 8 mg/kg/h infusion for 24–48 h. (CMDT: 1–2 g IV load, then 200–500 mg/h.) Give as early as possible ; still worthwhile even 24–48 h post-exposure. Continue while signs of acetylcholine excess persist. Not for asymptomatic or pure-carbamate (carbaryl) poisoning.
Seizures	Benzodiazepines (IV); atropine may abort early cholinergic seizures.
Adjuncts (unproven)	Magnesium sulfate and calcium-channel blockers show some benefit but are not routine .

Organophosphate vs Carbamate — key contrasts

Feature	Organophosphate	Carbamate
Enzyme bond	Phosphorylation — irreversible, ages	Carbamylation — reversible, no aging
Duration	Prolonged (weeks for enzyme resynthesis)	Short — recovers in hours (spontaneous, usually <24 h)
CNS penetration / seizures	Yes (adults)	Poor in adults (less CNS toxicity, no seizures)
Pralidoxime	Indicated, early	Usually not needed ; avoid in single-agent carbaryl
Atropine	Yes	Yes — mainstay

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Cholinergic synapse / mechanism schematic** — label: *presynaptic neuron, acetylcholine (ACh) vesicles, synaptic cleft, acetylcholinesterase (AChE), postsynaptic muscarinic & nicotinic receptors, OP compound phosphorylating AChE ("aging"), pralidoxime reactivating AChE, atropine blocking muscarinic receptor*.
- **"DUMBELS / SLUDGE + nicotinic + CNS" toxidrome figure** — a body silhouette labelled: *miosis (pinpoint pupils), lacrimation, salivation, bronchorrhoea, bronchospasm, bradycardia, vomiting, diarrhoea, urination, sweating (muscarinic); fasciculations, weakness, mydriasis, tachycardia, hypertension (nicotinic); seizures/coma (CNS)*.

Clinical / Diagnostic significance

- **Bedside diagnostic clue:** pinpoint pupils + secretions + bradycardia + garlicky breath in a patient who may have agricultural access ⇒ treat empirically.

- ▶ **Atropine titration is the therapeutic art** — dose to the chest and haemodynamics, not the pupils; under-atropinisation kills via bronchorrhoea.
- ▶ **Watch for the intermediate syndrome** at days 1–5: recurrent respiratory failure after apparent recovery — keep ICU/ventilatory vigilance.
- ▶ **Fat-soluble agents** (fenthion, dimethoate) cause prolonged/relapsing illness needing days–weeks of atropine ± oxime infusion.
- ▶ Avoid **succinylcholine, ester local anaesthetics and β -blockers**, which may worsen toxicity.

High-yield exam pointers

- ▶ OP = **irreversible** AChE inhibitor; **aging** makes oximes ineffective — *soman ages in minutes*.
- ▶ RBC AChE more specific; **plasma BuChE** falls first/easier to measure; activity <50% **normal** in poisoning.
- ▶ Muscarinic = DUMBELS/SLUDGE + Killer Bs (bradycardia, bronchorrhoea, bronchospasm); Nicotinic = fasciculations, weakness, mydriasis, tachycardia, hypertension; CNS = seizures/coma.
- ▶ **Death = respiratory failure** (bronchorrhoea + respiratory-muscle paralysis + central depression).
- ▶ **Atropine** endpoints: clear chest, HR >80, SBP >80; **pralidoxime (2-PAM)** WHO dose **30 mg/kg bolus + 8 mg/kg/h**.
- ▶ **Atropine treats muscarinic effects only; pralidoxime reverses nicotinic (muscle) weakness** — give both.
- ▶ **Four syndromes**: acute crisis → intermediate syndrome (1–5 d, respiratory/proximal weakness) → OPIDN (~1–3 wk, distal neuropathy, NTE) → chronic neuropsychiatric.
- ▶ **Carbamate** poisoning: reversible, no aging, shorter course, pralidoxime usually unnecessary (avoid in carbaryl).
- ▶ Nerve agents (sarin, soman, tabun, VX) are OP compounds; **do not** cause the intermediate syndrome.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Poisoning and Drug Overdose" (cholinergic/acetylcholinesterase-inhibitor toxidrome and antidote table).
- ▶ **Tintinalli's Emergency Medicine** — "Pesticides" (organophosphate pathophysiology, aging, four clinical syndromes, cholinesterase assays, atropine and pralidoxime regimens, carbamate contrasts) — principal depth source.
- ▶ **CMDT 2026** — "Poisoning: Pesticides — Cholinesterase Inhibitors" (atropine and pralidoxime dosing, decontamination).

Coverage note: The neuropathy-target-esterase (NTE) mechanism and classic 1–3-week timing of OPIDN, and the term "intermediate syndrome," are universally accepted toxicology teaching; the corpus (Tintinalli) describes these syndromes in detail but frames the delayed/chronic neuropathies with slightly different labels — the standard timing/mechanism is presented here for exam completeness.



Paracetamol poisoning

Asked in: Paper IV Jul 2021 · Paper IV Nov 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Paracetamol (acetaminophen, *N*-acetyl-*p*-aminophenol, APAP) is the most widely used over-the-counter analgesic–antipyretic and, in overdose, the commonest cause of drug-induced acute liver failure in the Western world (accounting for nearly half of all acute liver failure cases). Toxicity is a **dose-dependent direct hepatotoxicity** caused by the reactive metabolite ***N*-acetyl-*p*-benzoquinone-imine (NAPQI)**, which, once hepatic glutathione is depleted, binds covalently to hepatocyte macromolecules producing **centrilobular (zone 3) hepatic necrosis**. It is eminently treatable: the antidote *N*-acetylcysteine (NAC), if given early, is nearly 100% protective, making early recognition and the Rumack–Matthew nomogram central to management.

Pharmacology, metabolism and the basis of toxicity

- ▶ **Pharmacokinetics:** rapid GI absorption; peak therapeutic level at 30 min–2 h (≈ within 2 h after overdose, later with extended-release or anticholinergic/opioid co-ingestants); ~100% bioavailability, ~20% protein-bound, $V_d \approx 0.85 \text{ L/kg}$, elimination half-life ≈ 2.5 h.
- ▶ **Normal (therapeutic) metabolism:** mainly **glucuronidation (40–67%)** and **sulfation (20–46%)** to non-toxic conjugates; <5% excreted unchanged; only 5–15% **oxidised by CYP450 (chiefly CYP2E1)** to the reactive electrophile **NAPQI**, which is immediately conjugated by **glutathione** to harmless mercapturic acid and renally excreted.
- ▶ **In overdose:** glucuronidation and sulfation pathways are **saturated**, diverting more drug through CYP2E1, so excess NAPQI is generated. When hepatic **glutathione falls below ~30% of normal**, unconjugated NAPQI **binds covalently to nucleophilic hepatocyte proteins** ("APAP–protein adducts"), causing **centrilobular hepatic necrosis** and hepatocyte death (lysis typically on day 2, releasing transaminases).

- **Massive ingestion** (>500 mg/kg, peak level >750 µg/mL [>5000 µmol/L]) can cause **early metabolic acidosis with raised lactate and altered sensorium** even before liver failure — due to glutathione-depletion-related 5-oxoproline accumulation and inhibition of mitochondrial respiration.

Toxic dose and risk factors

- **Toxic exposure** (≥6 yr): a single ingestion of >150–200 mg/kg or >10 g; a single dose of 10–15 g (occasionally less) may produce liver injury; **fatal fulminant disease usually with ≥25 g**.
- **Repeated supratherapeutic ("staggered") ingestion**: >6 g/day or 150 mg/kg/24 h; ~8 g/day (twice the recommended maximum) over several days can readily cause liver failure, especially with opioid–acetaminophen combinations.
- **Factors increasing risk (low glutathione / induced CYP2E1)**:

Mechanism	Examples
Glutathione depletion	Chronic alcohol use, malnutrition/starvation, prolonged fasting in febrile illness, AIDS
CYP2E1 / mixed-oxidase induction	Chronic alcohol, isoniazid, anti-tubercular & anticonvulsant drugs, rifampicin, phenobarbital
Underlying liver vulnerability	Hepatitis C co-infection

- In **chronic alcoholics**, the toxic threshold may fall to as low as 2 g; the FDA-recommended maximum daily dose has been reduced from 4 g to 3 g (lower still in heavy alcohol users), and the acetaminophen content of prescription opioid-combination tablets capped at 325 mg/tablet.

Clinical features — the four stages

Stage	Timing	Clinical features	Laboratory
1	First 24 h	Often asymptomatic; anorexia, nausea, vomiting, malaise, pallor, diaphoresis	Usually normal
2	Days 2–3	GI symptoms improve; right-upper-quadrant pain & hepatic tenderness	Rising AST/ALT; raised bilirubin & prolonged PT if severe
3	Days 3–4	Peak hepatotoxicity — recurrent vomiting, jaundice, encephalopathy, fulminant hepatic failure , metabolic acidosis, coagulopathy, AKI/anuria, ± pancreatitis	AST/ALT may exceed 10,000 IU/L (far higher than viral hepatitis); raised INR, lactate, creatinine; hypoglycaemia
4	After day 5	Recovery (clinical improvement over 7–8 days; complete hepatic regeneration in 1–3 months) or deterioration to multi-organ failure and death	Resolving vs worsening

- **Diagnostic biochemical signature**: strikingly **high aminotransferases with relatively low bilirubin** in a "hyperacute" picture should raise suspicion of paracetamol even without a clear history.
- **Acute kidney injury** occurs in up to ~75% of severe cases but is usually self-limited; rare extrahepatic effects include myocardial injury and pancreatitis.

Diagnosis and the Rumack–Matthew nomogram

- ▶ Measure a serum acetaminophen concentration in every patient with intentional overdose (history is unreliable; toxicity is delayed and treatable). Also send AST/ALT, bilirubin, PT/INR, creatinine, glucose, ABG/lactate, and a co-ingestant screen (salicylate level).
- ▶ Rumack–Matthew nomogram plots serum level against time since ingestion to predict hepatotoxicity. The **treatment line corresponds to a 4-hour level of 150 µg/mL (1000 µmol/L)** (lowered from the original 200 µg/mL line to widen the safety margin); levels **above the line** warrant NAC.
- ▶ Risk by 4-hour level: >200 µg/mL (>1300 µmol/L) ≈ 60% hepatotoxicity, ~5% mortality; >300 µg/mL (>2000 µmol/L) ≈ 90% hepatotoxicity; <150 µg/mL suggests injury is highly unlikely.
- ▶ Nomogram limitations — **does NOT apply to:** levels drawn <4 h or >24 h after ingestion, unknown time of ingestion, chronic/staggered ingestion, extended-release preparations, or IV acetaminophen overdose. In these settings, treat empirically guided by detectable level (>10 µg/mL [>66 µmol/L]) and/or rising transaminases.

Treatment

- ▶ **Resuscitation & supportive care:** secure airway/breathing/circulation; correct hypoglycaemia, electrolytes, acidosis and coagulopathy; manage cerebral oedema in fulminant failure.
- ▶ **GI decontamination:** a single dose of **activated charcoal** if presenting within 1–2 h of ingestion (charcoal's minor interference with oral NAC absorption is not clinically significant). Lavage/whole-bowel irrigation are generally unnecessary given rapid absorption.
- ▶ **N-acetylcysteine (NAC) — the antidote:**
 - **Mechanism:** acts as a **glutathione precursor/substitute and sulfate precursor**, and can **directly reduce NAPQI** back to acetaminophen; in established toxicity it is also **antioxidant**, improves microcirculatory flow and oxygen delivery, and reduces neutrophil-mediated injury.
 - **Timing:** nearly **100% effective if started within 8 h** of ingestion; efficacy declines with delay but NAC still benefits even when given up to 24 h (and is used in established hepatotoxicity/late presentation).
 - **IV regimen (standard 21-hour):** 150 mg/kg over 1 h → 50 mg/kg over 4 h → 100 mg/kg over 16 h. The IV route is preferred for vomiting, hepatic failure or pregnancy.
 - **Oral regimen (72-hour):** loading 140 mg/kg, then 70 mg/kg every 4 h for 17 doses (with an antiemetic such as ondansetron for the disagreeable taste/nausea).
 - **Adverse effects:** **anaphylactoid reactions** in 4–17% of IV NAC (mostly in the first 2 h, more in asthmatics); manage by **slowing/temporarily stopping the infusion** and giving diphenhydramine, then resume at a slower rate.
 - **Massive overdose** (>30 g or level >2× the nomogram line): consider enhanced dosing (e.g., higher third-bag dose) and contact a poison centre.
- ▶ **Extracorporeal removal:** haemodialysis is **rarely indicated** — reserved for massive overdose with altered mental status, metabolic acidosis and very high levels; NAC is dialysable, so the dose is increased during dialysis.

- ▶ Liver transplantation referral if fulminant failure evolves despite NAC.

King's College Criteria for liver transplantation (paracetamol-induced acute liver failure)

- ▶ Arterial pH <7.30 (after fluid resuscitation), OR
- ▶ All three of: PT >100 s (INR >6.5) + serum creatinine >3.3 mg/dL (>292 µmol/L) + grade III/IV hepatic encephalopathy.
- ▶ Adjunct poor-prognosis markers: arterial lactate >3.5 mmol/L (Harrison) after resuscitation, hypoglycaemia, and rising serum phosphate.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acetaminophen metabolism pathway:** Acetaminophen → branch to Glucuronidation (40–67%), Sulfation (20–46%), Renal excretion of unchanged drug (<5%), and CYP2E1 (5–15%) → NAPQI. From NAPQI draw two arrows: (a) + Glutathione → mercapturic acid (APAP-mercaptopate) → renal excretion (non-toxic); (b) when glutathione <30% normal → covalent binding to hepatocyte proteins → centrilobular hepatic necrosis / cell death. Label: NAPQI, glutathione, CYP2E1, centrilobular (zone 3) necrosis.
- ▶ **Rumack–Matthew nomogram:** Y-axis = plasma acetaminophen (µg/mL and µmol/L, log scale), X-axis = hours after ingestion (4–24 h). Draw the **treatment line** through 150 µg/mL at 4 h (sloping down to ~37.5 µg/mL at 12 h); label zones "Treatment recommended (above line)" and "Toxicity unlikely (below line)"; mark "take level ≥4 h after ingestion."

Clinical / Diagnostic significance

- ▶ A near-asymptomatic stage 1 with a potentially lethal stage 3 means **management is dictated by the level/nomogram and time, not by early symptoms** — never reassure on a "well-looking" patient.
- ▶ The APAP level **must be drawn at ≥4 h** post-ingestion; if the result will not be available within the 8-h window, start NAC **empirically** and reassess once the level returns.
- ▶ **Pregnancy:** treat exactly as in non-pregnant patients — NAC is safe and effective and crosses the placenta; delay in treatment is associated with fetal loss.
- ▶ Suspect paracetamol in any **acute liver failure with very high transaminases and low bilirubin**, and in unexplained early high-anion-gap metabolic acidosis after massive ingestion.
- ▶ All intentional-overdose patients need a **psychiatric evaluation**; report cases to the regional poison-control centre.

High-yield exam pointers

- ▶ Toxic metabolite = NAPQI, generated by CYP2E1; detoxified by **glutathione**; toxicity when glutathione <30% → **centrilobular (zone 3) necrosis**.
- ▶ **Toxic dose ≥150 mg/kg or >10 g**; fatal usually ≥25 g; alcoholic threshold may be as low as 2 g.
- ▶ **Four stages:** (1) <24 h GI/asymptomatic, (2) days 2–3 RUQ pain + rising LFTs, (3) days 3–4 fulminant hepatic failure, (4) after day 5 recovery or death.

- ▶ **Rumack–Matthew nomogram** treatment line = **150 µg/mL at 4 h**; not valid <4 h, >24 h, staggered, or extended-release ingestions.
- ▶ **NAC is ~100% effective if given within 8 h**; benefit up to 24 h and in established hepatotoxicity.
- ▶ **IV NAC**: 150 mg/kg/1 h → 50 mg/kg/4 h → 100 mg/kg/16 h (21-h protocol); **oral**: 140 then 70 mg/kg × 17 doses (72 h).
- ▶ **NAC anaphylactoid reactions 4–17%** — slow/stop infusion + antihistamine.
- ▶ **King's College Criteria**: pH <7.30 or (PT >100 s + creatinine >3.3 mg/dL + grade III/IV encephalopathy) → transplant referral.
- ▶ **Activated charcoal** only useful early (within 1–2 h); **haemodialysis** rarely needed (massive overdose).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Toxic and Drug-Induced Hepatitis" (acetaminophen mechanism, NAPQI/glutathione, toxic dose, stages, nomogram thresholds, NAC, lactate prognosis) and "Poisoning and Drug Overdose."
- ▶ **Tintinalli's Emergency Medicine** — "Acetaminophen" (pharmacokinetics, metabolism figure, four-stage table, Rumack–Matthew nomogram, IV/oral NAC regimens and dosing table, anaphylactoid reactions, King's College Criteria, massive/IV/extended-release overdose).
- ▶ **CMDT 2026** — "Poisoning" (current management, activated charcoal timing, FDA-approved 21-hour IV acetylcysteine regimen, fomepizole as investigational adjunct, high-risk thresholds).



Ethylene glycol poisoning

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

Definition / Introduction — Ethylene glycol (EG) is a colourless, sweet-tasting toxic alcohol used in antifreeze, brake fluid and windshield washer/de-icer fluids; poisoning follows accidental, suicidal or substitute-alcohol ingestion. EG itself is relatively non-toxic and produces only an ethanol-like inebriation, but its sequential oxidation by **alcohol dehydrogenase (ADH)** generates organic-acid metabolites (glycolate, oxalate) that cause a life-threatening **high-anion-gap metabolic acidosis (AGMA)** with damage to the CNS, heart, lungs and kidneys. The combination of a **high anion gap plus a high osmolar gap** is the diagnostic signature, and rational therapy (fomepizole, hemodialysis, cofactors) is built around blocking and removing the toxic metabolites.

SOURCE & COVERAGE

- ▶ **Sources:** antifreeze, brake fluid, windshield washer/de-icer fluids. EG is a low-molecular-weight solute, so it raises serum osmolality and the **osmolal gap** while the parent compound predominates.
- ▶ **Parent vs metabolite toxicity:** EG is one of the agents whose *metabolites are more toxic than the parent compound* (alongside acetaminophen and methanol) — hence early high blood levels mandate antidote/dialysis even before symptoms peak.
- ▶ **Metabolic cascade (rate-limiting step = ADH):** EG → (ADH) → glycoaldehyde → (aldehyde dehydrogenase) → **glycolic acid (glycolate)** → glyoxylic acid → **oxalic acid (oxalate)**.
- ▶ **Mechanisms of injury (Harrison Ch 470):**
 - EG causes **CNS depression** and **increased serum osmolality**.
 - Metabolites — *primarily glycolic acid* — cause the **AGMA, CNS depression and renal failure**.
 - Lactic acid (l-lactate) production rises because metabolites inhibit the **tricarboxylic acid cycle** and alter the intracellular redox state, adding to the anion gap.
 - **Oxalic acid** precipitates as **calcium oxalate** in tissues and urine → **hypocalcaemia**, tissue oedema and **crystalluria**; acute tubular injury is caused *initially by glycolate* and *later amplified by tubular obstruction from oxalate crystals*.

Clinical features — the evolving stages

EG poisoning classically evolves through overlapping phases; the parent alcohol intoxicates early, while delayed metabolite toxicity drives the acidosis, cardiopulmonary collapse and renal failure.

Phase	Dominant mediator	Clinical features
Neurological (early)	Parent EG	"Ethanol-like" intoxication <i>without the smell of alcohol</i> , nausea, vomiting, increased osmolar gap , early calcium-oxalate crystalluria; severe cases → coma, seizures
Cardiopulmonary	Glycolate / organic acids	Tachypnoea (Kussmaul breathing), hypotension , cardiac dysfunction, ARDS in severe cases

Phase	Dominant mediator	Clinical features
Renal (delayed)	Oxalate / glycolate	Delayed AGMA, flank/back pain, oliguria and acute renal failure (ATN), hypocalcaemia (± tetany)

Biochemical hallmarks — the dual "gap"

- ▶ **High anion-gap metabolic acidosis:** EG is a leading toxic cause of severe AGMA (with methanol and salicylates). The unmeasured anions are **glycolate and oxalate**, so the measured **anion gap exceeds the lactate level** (a clue that the acidosis is *not* primarily lactic).
- ▶ **Osmolal gap:** difference of **>10 mmol/L** between **measured osmolality** (by freezing-point depression) and **calculated osmolality** = $2[\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8$. EG (a low-MW glycol) widens this gap.
- ▶ **Temporal dissociation of the two gaps:** the **osmolar gap rises early** (parent EG present) and **falls as it is metabolised**, while the **anion gap rises later** as glycolate/oxalate accumulate — so a *normal osmolar gap does not exclude EG late after ingestion*, and a high AG may appear once the osmolar gap has fallen.
- ▶ The combination of **high AG + high osmolar gap** is *highly suspicious for EG or methanol* and should be taken as **evidence of EG toxicity before confirmatory EG levels return** — **do not delay treatment** awaiting the level.

Diagnosis and investigations

- ▶ **History** of antifreeze/solvent ingestion or unexplained inebriation with severe acidosis.
- ▶ **ABG + electrolytes:** severe metabolic acidosis with a **high anion gap**; calculate the AG.
- ▶ **Serum osmolality** (measured, freezing-point depression) vs **calculated** → **osmolal gap**.
- ▶ **Quantitative EG level** — useful but treatment is not deferred for it; levels guide antidote/dialysis thresholds.
- ▶ **Serum calcium** — **hypocalcaemia** (also seen in fluoride and oxalate poisoning); check ECG for QT prolongation.
- ▶ **Renal function / urinalysis** — rising creatinine, ATN; **calcium-oxalate crystalluria** (envelope-shaped / needle crystals).
- ▶ **Lactate** — may be mildly elevated; the AG typically *exceeds* measured lactate.
- ▶ Some EG products fluoresce under **Wood's lamp** (fluorescein additive) — supportive, *standard toxicology, not in the provided chapters*.

Management

Therapy targets three goals: **block ADH** (stop metabolite formation), **correct acidaemia and divert metabolism with cofactors**, and **remove EG/metabolites by dialysis**. (Harrison Ch 58 treatment box + Ch 470 table.)

Intervention	Detail / indication
Supportive	IV isotonic fluids; airway protection/ventilation for CNS depression, seizures; treat shock

Intervention	Detail / indication
Correct acidaemia	IV sodium bicarbonate for severe acidaemia
ADH blockade — antidote of choice	Fomepizole (4-methylpyrazole): 15 mg/kg IV over 30 min loading dose, then 10 mg/kg every 12 h for four doses. Predictable fall in EG level without the obtundation seen with ethanol. Continue until blood pH normal or osmolar gap <10 mOsm/kg H ₂ O
Ethanol (alternative)	Of <i>historic interest</i> ; competes with EG for ADH; used only if fomepizole is unavailable
Antidote thresholds	Start ethanol/fomepizole for AGMA, crystalluria/renal dysfunction, EG level >3 mmol/L (20 mg/dL), or ethanol-like intoxication / raised osmolal gap when the level is not readily obtainable
Cofactors (divert metabolism)	Thiamine, high-dose pyridoxine, magnesium and folinic acid — push glyoxylate toward non-toxic glycine/α-hydroxy-β-ketoadipate rather than oxalate
Hemodialysis	Indicated when arterial pH <7.3, persistent high-AG acidosis, osmolar gap >20 mOsm/kg H ₂ O, or end-organ damage (CNS, renal failure); also enhances EG elimination and shortens treatment when EG level >8 mmol/L (50 mg/dL)

- ▶ Fomepizole and ethanol both act by **competing with EG for alcohol dehydrogenase**; fomepizole is preferred (no CNS depression, no level monitoring, predictable kinetics).
- ▶ Hemodialysis removes both the parent EG and the dialysable metabolites/anions and corrects the acidosis simultaneously.

Toxic alcohols compared

Feature	Ethylene glycol	Methanol	Isopropyl alcohol
Key enzyme	Alcohol dehydrogenase	Alcohol dehydrogenase	Alcohol dehydrogenase
Toxic metabolite	Glycolate, oxalate	Formic acid	Acetone (parent toxic)
Anion gap	High AGMA	High AGMA	No high AG (unless shock)
Osmolar gap	Raised	Raised	Raised
Target organ	CNS, heart, lungs, kidney	Optic nerve / retina , CNS	CNS; haemorrhagic gastritis
Specific cofactor	Thiamine, pyridoxine , Mg, folinic acid	Folinic acid / folate	(none; supportive)
Antidote / dialysis	Fomepizole + HD	Fomepizole + HD	Supportive + HD if level >400 mg/dL

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Metabolic pathway with antidote block (label exactly):** *Ethylene glycol* → [Alcohol dehydrogenase (ADH)] → *Glycoaldehyde* → [Aldehyde dehydrogenase] → *Glycolic acid (glycolate)* → *Glyoxylic acid* → *Oxalic acid (oxalate)* → *Calcium oxalate crystals*. Mark *Fomepizole / Ethanol* = ADH inhibition (block) at the first step; show *Thiamine and Pyridoxine* diverting *Glyoxylate* to non-toxic α -hydroxy- β -ketoadipate / *Glycine*. Annotate metabolite effects: AGMA, renal failure, hypocalcaemia.
- ▶ **Time-course graph of the two gaps:** x-axis = *time after ingestion (hours)*; two curves — *Osmolar gap* (peaks early, then declines) and *Anion gap* (rises later); shade overlap labelled *high osmolar gap + high anion gap = window of EG toxicity*.

Clinical / Diagnostic significance

- ▶ A patient with severe high-AG metabolic acidosis + high osmolar gap + calcium-oxalate crystalluria + hypocalcaemia is EG poisoning until proven otherwise.
- ▶ Empirical fomepizole + bicarbonate must not be delayed for confirmatory EG levels — early ADH blockade prevents metabolite-driven renal failure and death.
- ▶ The osmolar gap normalises before the anion gap, so timing of presentation changes which gap is abnormal; rely on the clinical picture, not a single gap.
- ▶ Hemodialysis is both detoxifying (removes EG + anions) and corrective (treats acidosis/renal failure) — a key therapeutic decision point.
- ▶ EG is a "toxic time-bomb": an apparently well, inebriated patient can deteriorate hours later as metabolites accumulate — observe and re-check gaps.

High-yield exam pointers

- ▶ Source = antifreeze; ADH converts EG to glycolate (acidosis) and oxalate (renal failure + hypocalcaemia).
- ▶ Diagnostic dyad = high anion gap + high osmolar gap; calcium-oxalate crystalluria is the urinary clue.
- ▶ Calculated osmolality = $2\text{Na}^+ + \text{glucose}/18 + \text{BUN}/2.8$; osmolal gap >10 mmol/L is significant (measured by freezing-point depression).
- ▶ Fomepizole 15 mg/kg load, then 10 mg/kg q12h $\times 4$ doses — antidote of choice; continue until pH normal or osmolar gap <10 .
- ▶ Hemodialysis if pH <7.3 , osmolar gap >20 , end-organ damage, or EG level >8 mmol/L (50 mg/dL); antidote threshold EG >3 mmol/L (20 mg/dL).
- ▶ Cofactors: thiamine, pyridoxine, magnesium, folinic acid; alkali with NaHCO_3 .
- ▶ Ethanol is now second-line, used only when fomepizole is unavailable.
- ▶ Distinguish from methanol (formate $\rightarrow$ blindness, folinic acid) and isopropanol (acetone, no high AG).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 470 "Poisoning and Drug Overdose" (EG mechanism/clinical/treatment table, osmolal-gap and AGMA discussion) and Ch 58 "Acidosis and Alkalosis" (toxic-alcohol section, osmolar-gap calculation, fomepizole dosing and hemodialysis criteria). *Coverage note:* the precise phase **timing windows** (hours), Wood's-lamp fluorescence, urinary crystal morphology, and the named intermediates *glycoaldehyde/glyoxylic acid* are standard textbook toxicology not spelled out in the provided chapters (the chapters explicitly name ADH, glycolate, oxalate); they are accurate, universally accepted additions for completeness.

**Poisonous snake bite**

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

Definition / Introduction — Snake envenomation is the injection of venom — a complex mixture of enzymes, polypeptides, glycoproteins and other constituents — through hollow or grooved maxillary fangs, producing **local tissue necrosis, coagulopathy, organ dysfunction and/or neuromuscular-junction paralysis**. Globally there are an estimated 1.2–5.5 million snakebites/year with 421,000–1,200,000 envenomations, and the WHO aims to halve snakebite deaths by 2030. Notably, ~20–25% of pit-viper bites (and up to 75% of sea-snake bites) are "**dry**" bites with no venom delivered, so management is driven by *evidence of envenomation*, not the fact of the bite alone. The cornerstone of treatment is rapid transport to a facility with airway support and **species-appropriate antivenom**, which is the only specific antidote.

Venomous snakes & clinical syndromes (orientation)

- ▶ **Viperids** (pit vipers, Russell's viper *Daboia russelii*, saw-scaled viper): triangular head, elliptical pupils, long mobile fangs, loreal heat-pits — predominantly **cytotoxic + haemotoxic** (local swelling/necrosis, coagulopathy, bleeding).
- ▶ **Elapids** (cobras *Naja*, kraits *Bungarus*, coral snakes *Micrurus*): fixed small erect fangs (fewer puncture marks), predominantly **neurotoxic** — descending paralysis.
- ▶ **Sea snakes**: predominantly **myotoxic** — myalgia, trismus, rhabdomyolysis, flaccid paralysis (often delayed hours).

Syndrome	Key features (source-grounded)
Local (cytotoxic)	Pain, soft-tissue swelling, ecchymosis, haemorrhagic/serum-filled vesicles & bullae, tissue loss/necrosis
Haemotoxic	Spontaneous bleeding, haemolysis, venom-induced consumptive coagulopathy, thrombocytopenia
Neurotoxic	Nausea/headache/paraesthesia → cranial-nerve signs (<i>ptosis</i> , dysphagia) → peripheral weakness → diaphragmatic paralysis & respiratory failure

Syndrome	Key features (source-grounded)
Systemic	Fatigue, vomiting, taste change, mouth numbness, tachy-/bradycardia, hypotension, fasciculations, pulmonary oedema, renal dysfunction, rhabdomyolysis

First-aid / Field management (pre-hospital)

- ▶ **Rapid transport** to a medical facility equipped to provide airway/breathing/circulation support and antivenom is the single most important step; discourage delay with traditional healers.
- ▶ **Reassure and immobilise:** remove jewellery/tight clothing (anticipated swelling), clean wound with soap and running water, cover with a sterile dressing — but *wound care must not delay transport*.
- ▶ **Splint** the bitten extremity to limit movement; keep it in a neutral position of comfort at approximately heart level.
- ▶ Do **not** attempt to capture the snake — take digital photographs from a safe distance to aid identification.
- ▶ **Abandon harmful traditional measures:** do NOT incise or apply suction (worsens tissue damage, infection, ineffective); do NOT apply tourniquets or lympho-occlusive bandages ("venom sequestration devices") — they intensify local necrosis and risk ischaemia/loss of function.
- ▶ **Pressure-immobilisation bandage:** reserved ONLY for bites by a *reliably identified, primarily neurotoxic elapid* with no local tissue effect — wrap the entire limb and immobilise to restrict lymphatic spread; **never for viperid bites**. Wrap pressure 40–70 mmHg (upper limb), 55–70 mmHg (lower limb) — snug but loose enough to slip a finger under; the victim must be *carried* (walking pumps venom systemically).

Hospital management — resuscitation, monitoring & investigations

- ▶ **ABC first:** bites to face/neck may need **early endotracheal intubation** before swelling occludes the airway. Monitor vitals, cardiac rhythm, SpO₂ and urine output.
- ▶ Establish **two large-bore IV lines in unaffected limbs**; because of coagulopathy, minimise venipunctures and avoid non-compressible sites (e.g. subclavian).
- ▶ **Hypotension:** early shock is due to bradykinin-potentiating factors (vasodilation, splanchnic/pulmonary pooling), systemic bleeding, haemolysis and third-spacing → give isotonic crystalloid (**normal saline or Ringer's lactate 20–40 mL/kg IV**). Add a **vasopressor (noradrenaline/adrenaline)** only if shock persists after volume + antivenom (consider concurrent anaphylaxis).
- ▶ Remove any field bandages **cautiously** (sudden release of stagnant acidotic venom-laden blood can cause hypotension/dysrhythmia).
- ▶ **Mark and measure:** outline the leading edge of swelling/ecchymosis/tenderness and measure limb circumference at three points **every 15 min until stable**, then 1–2 hourly; keep the limb above heart level. Watch neurotoxic victims for *ptosis* heralding airway compromise.
- ▶ **Investigations:** CBC (haemorrhage/haemolysis/thrombocytopenia), blood group & cross-match, renal & hepatic panel, PT/INR, **fibrinogen**, FDP/D-dimer, CK (rhabdomyolysis), urine for

blood/myoglobin; ECG and chest X-ray in severe cases. In resource-limited settings the **20-minute whole-blood clotting test (20WBCT)** detects coagulopathy: 1–2 mL venous blood in a clean dry glass tube left undisturbed 20 min — *failure to clot = coagulopathy*. Recheck labs every 6 h after antivenom.

Antivenom therapy (the mainstay)

- ▶ **Principle:** antivenoms are antibodies (or Fab/F(ab')₂ fragments) raised in horses or sheep that bind and neutralise *circulating, unbound* venom before it reaches target tissue. They may be **monospecific** or **polyspecific**; selection must match the offending species (no cross-protection unless venoms are homologous).
- ▶ **Key limitation:** antivenom reverses only *active* venom toxicity — it does **not** reverse established effects such as established paralysis or renal failure (these need time + supportive care).
- ▶ **Indications —**
 - *Viperid / cytotoxic bites:* progressive local findings (rapidly spreading swelling, swelling >½ the limb, extensive blistering/bruising, severe pain) **or** any systemic envenomation (systemic symptoms or laboratory abnormality).
 - *Neurotoxic elapid bites:* give at the **first sign of neurotoxicity** (cranial-nerve dysfunction, peripheral neuropathy).
 - Isolated mild pain/swelling after an unidentified bite may be from a harmless species — antivenom is then useless and potentially harmful.
- ▶ **Administration:** **IV only**, started *slowly* with the clinician at the bedside, then titrated up to deliver the full starting dose over ~1 h; redose if the patient worsens or venom effects recur. Antivenom should generally continue for viperid bites until definite improvement (reduced pain, stable vitals, restored coagulation).

Severity (US grading)	Findings	Antivenom approach
None	Fang marks only ("dry" bite)	None; observe
Mild	Local findings only, non-progressive	Usually none; observe
Moderate	Progressing swelling, systemic symptoms/signs, lab abnormality	Antivenom (e.g. CroFab 4–6 vials)
Severe	Neurologic dysfunction, respiratory distress, CV instability/shock	Antivenom (e.g. CroFab 6 vials); ICU

Antivenom reactions & their treatment

- ▶ **Early (anaphylactic / anaphylactoid):** tachycardia, rigors, vomiting, urticaria, dyspnoea, laryngeal oedema, bronchospasm, hypotension. **Skin testing is neither sensitive nor specific and is not recommended;** prophylactic antihistamines/glucocorticoids are *not* proven beneficial (limited Sri Lankan data support low-dose SC adrenaline pretreatment 0.25 mg of 1:1000). Adrenaline and airway equipment must always be ready.
- ▶ **Treatment of acute reaction:** STOP the infusion → **IM adrenaline 0.01 mg/kg (max 0.5 mg) + IV antihistamine** (diphenhydramine 1 mg/kg, max 50 mg) + **IV glucocorticoid** (hydrocortisone 2

mg/kg, max 100 mg). Once controlled, **restart antivenom at 5–10 mL/h** and titrate up; for refractory hypotension run a concomitant IV adrenaline infusion in a monitored (ED/ICU) setting.

- **Late (serum sickness):** 1–2 weeks later — myalgia, arthralgia, fever, chills, urticaria, lymphadenopathy, renal/neurologic dysfunction. Treat with **oral prednisone 1–2 mg/kg/day** until resolution, then taper over 1–2 weeks, plus antihistamines/analgesics.

Management of complications & supportive care

- **Coagulopathy / bleeding:** blood products are *rarely* needed and factors rebound after adequate antivenom — give FFP/platelets **only after adequate antivenom** (otherwise they fuel ongoing consumption).
- **Neurotoxicity:** for **post-synaptic** neurotoxin bites (e.g. cobra) give a trial of an **acetylcholinesterase inhibitor** — pretreat with **atropine 0.6 mg IV**, then **edrophonium 10 mg IV** (or **neostigmine 0.02 mg/kg IV/IM**); if objective improvement at 30 min, continue **neostigmine 0.5 mg IV/IM/SC hourly**. These are *adjuncts*, not substitutes for intubation/antivenom; intubate and ventilate established paralysis (may need days–weeks).
- **Rhabdomyolysis / AKI:** IV fluids and urine-output monitoring; AKI (usually reversible acute tubular necrosis) may need **haemodialysis/peritoneal dialysis**; bilateral cortical necrosis carries a poorer renal prognosis.
- **Compartment syndrome** (deep IM venom; pain, weakness, altered sensation, cyanosis, apparent pulselessness): measure intracompartmental pressure — **>30–40 mmHg → give more antivenom and elevate the limb**. Fasciotomy is NOT recommended for North-American crotalids (no benefit, increased morbidity) and is a last resort even where Asian-species data allow it; true compartment syndrome requiring fasciotomy occurs in <1%.
- **Wound care & adjuncts:** clean with soap/water, sterile dressing, splint with padding between digits, elevate after antivenom started; **tetanus immunisation**; analgesia with **paracetamol or opioids** — **avoid salicylates/NSAIDs** (impair clotting). Prophylactic antibiotics are usually unnecessary after North-American bites but warranted where secondary infection is common or if first-aid included incision/suction. Debride frank necrosis only after coagulopathy reverses; leave intact blebs alone; start **physiotherapy** early.
- **Observation/disposition:** observe any envenomed patient ≥24 h; an apparently "dry" viperid bite ≥8–12 h (delayed toxicity); observe ≥24 h after coral-snake (*Micrurus*), hump-nosed pit viper (*Hypnale*) and sea-snake bites (delayed onset). ICU for progressive findings despite antivenom, head/neck bites or antivenom hypersensitivity. **At discharge** warn about wound infection, serum sickness, recurrent coagulopathy and long-term sequelae such as **pituitary insufficiency after Russell's viper (*Daboia russelii*) envenomation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Algorithm box ("Management of snakebite")** with labelled arrows: *Bite* → *Reassure/immobilise/splint, remove constrictions* → *Transport (avoid incision/suction/tourniquet)* → *ABC + 2 IV lines + crystalloid* → *Assess envenomation (local progression / 20WBCT / labs)* → *Antivenom if local-progressive or systemic/neurotoxic* → *Treat reactions (adrenaline)* → *Manage complications (intubation, ACh-esterase inhibitor, dialysis, blood products)* → *Observe ≥24 h* → *Discharge advice*.
- ▶ **Labelled snake-head identification figure:** labels — *Viperid: triangular head, elliptical pupil, long mobile fang, loreal pit; Elapid: rounded head, round pupil, short fixed fang; mark fang/puncture marks and local swelling/ecchymosis at bite site.*

Clinical / Diagnostic significance

- ▶ The decision to give antivenom rests on **objective evidence of envenomation** (progressive local signs, systemic features, abnormal 20WBCT/coagulation, neurotoxic signs) — not on the bite alone, since dry bites are common.
- ▶ The **20WBCT** is a cheap, bedside, resource-independent test that confirms venom-induced consumptive coagulopathy and guides antivenom in district/rural settings.
- ▶ *Ptosis* and bulbar weakness are early warnings of impending respiratory failure — secure the airway **before** decompensation.
- ▶ Antivenom both treats and *causes* anaphylaxis; readiness with adrenaline at the bedside is mandatory before every infusion.

High-yield exam pointers

- ▶ **Antivenom is the only specific treatment** and acts only on circulating (unbound) venom — give early; useless for established paralysis/renal failure.
- ▶ **Never** incise, suck, or apply a tourniquet/tight bandage; pressure-immobilisation is only for *neurotoxic elapid* bites, never viperid.
- ▶ Crystalloid 20–40 mL/kg for hypotension; vasopressors only after volume + antivenom.
- ▶ Acute antivenom reaction → stop infusion, **IM adrenaline 0.01 mg/kg (max 0.5 mg)** + antihistamine + steroid, restart at 5–10 mL/h.
- ▶ **Serum sickness** at 1–2 weeks → oral prednisone 1–2 mg/kg/day with taper.
- ▶ Neostigmine (with atropine) helps **post-synaptic** neurotoxic (cobra-type) bites; not a substitute for ventilation/antivenom.
- ▶ Snakebite coagulopathy → give blood products **only after** adequate antivenom; avoid NSAIDs/aspirin.
- ▶ Fasciotomy is rarely needed (<1%); rising compartment pressure → **more antivenom**, not the knife.
- ▶ Observe ≥24 h (≥8–12 h for "dry" viperid bites); beware delayed toxicity from kraits, coral snakes, hump-nosed viper and sea snakes; warn of late Russell's-viper hypopituitarism.

SOURCE & COVERAGE

Harrison 22e — Ch 471 "Disorders Caused by Venomous Snakebites and Marine Animal Exposures" (incl. Tables 471-1 and 471-2). **Coverage note:** Harrison's management protocol and named antivenoms (CroFab/Anavip, *Micrurus* antivenin) are US/Canada-specific and, as the text states, should not be transposed to other regions. India-specific standards relevant to RGUHS — the "**Big Four**" (Russell's viper, common krait, Indian cobra, saw-scaled viper) and **Indian polyvalent anti-snake venom** dosing — are universally-accepted Indian internal medicine but are not detailed in this US-focused chapter; only *Daboia russelii*, kraits (*Bungarus*) and cobras (*Naja*) are explicitly named in the source. Indian polyvalent ASV vial regimens and WHO/national snakebite protocols fall outside the provided text and should be confirmed against a national guideline.



Russell's viper envenomation

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

Definition / Introduction — Russell's viper envenomation is systemic and local poisoning after bite by *Daboia russelii*, an Old World viperid of major importance in South Asia. The dominant syndrome is **viperid cytotoxic-hemotoxic envenomation** with painful swelling, tissue injury, venom-induced consumptive coagulopathy, spontaneous bleeding, shock, and acute kidney injury; certain Indian Russell's vipers may also cause neurotoxicity. It is an emergency because antivenom reverses circulating venom best before fixed renal failure, established paralysis, and tissue necrosis have developed.

Epidemiology and species importance

- ▶ Russell's viper is a medically important Indian viperid and a classic rural/agricultural hazard; Brenner notes that snake bite in the Indian subcontinent commonly occurs when people work barefoot in fields.
- ▶ Harrison lists **Russell's vipers (*Daboia russelii*)** among snakes responsible for large numbers of deaths outside North America, together with cobras, saw-scaled/carpet vipers, large African vipers, lancehead pit vipers, and tropical rattlesnakes.
- ▶ In the Indian subcontinent, **AKI develops after viper-family bites**, especially Russell's viper, saw-scaled viper (*Echis carinatus*), and pit vipers.
- ▶ Brenner gives the incidence of AKI after Russell's viper or *E. carinatus* bites in India as **13-32%**; a Sri Lankan series of unidentified viper bites reported AKI in **27%**.
- ▶ Risk of severe disease rises with large venom load, bite on a vascular area or head/neck, delayed transport, traditional treatment before hospital care, lack of appropriate antivenom, shock, coagulopathy, and established renal injury.

Venom pathophysiology

- ▶ Snake venom is a variable mixture of **enzymes, polypeptides, glycoproteins, and other constituents**; venom composition varies by species, snake age, diet, and geography, so local protocols matter.
- ▶ **Local cytotoxic/vascular injury**: venom increases vascular permeability and damages tissues, causing pain, edema, ecchymosis, bullae, hemorrhagic blebs, necrosis, and later functional loss.
- ▶ **Hemotoxic/procoagulant effect**: viper venom activates and consumes clotting factors, fibrinogen, and platelets, producing **venom-induced consumptive coagulopathy** or a DIC-like state with prolonged clotting times, low fibrinogen, thrombocytopenia, high FDP/D-dimer, and bleeding.
- ▶ **Shock mechanisms**: early hypotension may reflect bradykinin-potentiating vasodilatation, systemic bleeding, hemolysis, and intravascular volume loss into swollen tissues.
- ▶ **Renal injury**: AKI is multifactorial: bleeding, hypotension, circulatory collapse, intravascular hemolysis, hemoglobinuria, DIC/microangiopathic hemolysis, myoglobinuria when present, and direct venom nephrotoxicity.
- ▶ **Renal pathology**: acute tubular necrosis is the predominant lesion in snakebite-associated AKI; cortical necrosis may occur and carries much poorer renal recovery.
- ▶ **Neurotoxicity**: Harrison specifically notes that certain Indian Russell's vipers can cause neurologic dysfunction with ptosis, dysphagia, peripheral weakness, diaphragmatic paralysis, aspiration, and respiratory failure.

Clinical features and severity

- ▶ **Local features**: fang marks, early severe pain, rapidly progressive swelling, tenderness, regional lymphadenopathy, ecchymosis, serum-filled or hemorrhagic bullae, cellulitis-like inflammation, and full-thickness necrosis in severe bites.
- ▶ Swelling may involve the whole limb; hand, forearm, and anterior leg bites require vigilance for compartment pressure, although true fasciotomy-requiring compartment syndrome is uncommon.
- ▶ **Bleeding/coagulopathy**: persistent oozing from fang marks or venipuncture sites, gum bleeding, epistaxis, hematuria, hematemesis, melena, hemoptysis, ecchymoses, muscle/fascial compartment bleeding, serous cavity bleeding, and rarely subarachnoid hemorrhage.
- ▶ **Systemic features**: nausea, vomiting, altered/metallic taste, mouth numbness or perioral tingling, generalized weakness, tachycardia or bradycardia, hypotension/shock, pulmonary edema, spontaneous hemorrhage, and altered sensorium in severe envenomation.
- ▶ **Renal features**: oliguria commonly develops within the first **24 h**, but may be delayed **2-3 days**; anuria or non-oliguric AKI may occur. Clues include gross or microscopic hematuria, hemoglobinuria, jaundice from intravascular hemolysis, and renal-angle pain preceding oliguria.
- ▶ **Neurologic features**: headache, paresthesias, ptosis, diplopia, dysphagia, bulbar weakness, peripheral motor weakness, respiratory muscle paralysis, and aspiration risk.
- ▶ Practical grading:

Grade	Definition
Dry / none	Fang marks only; no progressive swelling, systemic symptoms, or laboratory abnormality after observation
Mild	Local pain, ecchymosis, and nonprogressive swelling only
Moderate	Progressive swelling, systemic symptoms, or laboratory abnormality such as thrombocytopenia/prolonged clotting
Severe	Shock, major bleeding, severe coagulopathy, neurotoxicity, respiratory distress, AKI, pulmonary edema, or extensive local necrosis

Diagnosis and monitoring

- ▶ Diagnosis is clinical: compatible bite history plus local injury, hematologic abnormality, systemic toxicity, or renal/neurotoxic features. Do not wait for snake identification before treating a compatible syndrome.
- ▶ **Bedside assessment:** ABC, vital signs, mental status, respiratory effort, bulbar function, distal pulses, capillary refill, sensory-motor status, and urine output.
- ▶ Mark the leading edge of swelling/ecchymosis/tenderness; measure limb circumference at the bite site and at joints proximal/distal every **15 min** until stable, then every **1-2 h**.
- ▶ **Core investigations:** CBC with platelets, blood group and cross-match, PT/INR/aPTT, fibrinogen, FDP or D-dimer, renal function, electrolytes, liver tests, glucose, creatine kinase, urinalysis for blood/myoglobin, ECG, and chest radiograph/ABG when severe or respiratory compromise is suspected.
- ▶ **20-min whole-blood clotting test (20WBCT):** place **1-2 mL venous blood** in a clean, dry glass tube, leave undisturbed for **20 min**, then invert. Persistent liquid blood/no clot indicates clinically important coagulopathy when formal coagulation tests are unavailable.
- ▶ Repeat CBC/coagulation studies every **4 h** if initial tests are normal but envenomation remains possible; after antivenom, repeat about every **6 h** until swelling, vital signs, and coagulation are stable.
- ▶ Watch for recurrent coagulopathy because venom antigens may outlast antivenom; late bleeding can appear after apparent improvement.

Management: first aid, antivenom and ICU care

- ▶ **First aid:** move away from the snake, reassure, keep the patient still, remove rings/bangles/tight clothing, splint the bitten limb in a neutral position, and transport rapidly to a facility with antivenom, airway support, and laboratory testing.
- ▶ Clean with soap and water and cover with a sterile dressing if this does not delay transport. Do **not** incise, suck, apply electric shock, ice, alcohol, stimulants, tight tourniquets, or massage. Pressure-immobilization is not recommended for viperid/cytotoxic bites because it may worsen local tissue injury.
- ▶ **Initial hospital care:** secure airway and breathing; intubate early for face/neck swelling, bulbar weakness, falling ventilation, or respiratory insufficiency. Monitor ECG, oxygen saturation, blood pressure, urine output, and mental status.

- ▶ Establish two large-bore IV lines in unaffected limbs; minimize venipuncture and avoid noncompressible sites because coagulopathy may be profound.
- ▶ Treat shock with isotonic crystalloid **20-40 mL/kg IV**; if shock persists after fluids and antivenom, use vasopressors such as norepinephrine or epinephrine and reassess for venom or antivenom anaphylaxis.
- ▶ **Antivenom is the mainstay.** Use geographically appropriate antivenom that covers Russell's viper venom; in India this generally means locally supplied polyvalent anti-snake venom according to product and institutional protocol.
- ▶ Indications for antivenom: rapidly progressive swelling; swelling involving more than half the limb; severe pain, bruising, blistering, or necrosis; any systemic toxicity; positive 20WBCT or abnormal PT/INR/aPTT/fibrinogen; thrombocytopenia; active bleeding; shock; neurotoxicity; rhabdomyolysis; AKI; or pulmonary edema.
- ▶ Give antivenom **IV only**, start slowly with clinician at bedside, and increase if no reaction; skin testing is neither sensitive nor specific. Keep epinephrine and airway equipment ready.
- ▶ If acute antivenom reaction occurs, stop temporarily and treat with **IM epinephrine 0.01 mg/kg up to 0.5 mg**, IV antihistamine such as diphenhydramine **1 mg/kg up to 50 mg**, and hydrocortisone **2 mg/kg up to 100 mg**; restart slowly at **5-10 mL/h** if antivenom remains necessary.
- ▶ Blood products are reserved for life-threatening bleeding or dangerously low platelets and should be given **after adequate antivenom**, because early replacement can fuel ongoing consumptive coagulopathy.
- ▶ AKI care: maintain perfusion, avoid nephrotoxins, monitor potassium/acidosis/fluid overload, and involve nephrology early; hemodialysis or peritoneal dialysis is used when indicated. ATN is often reversible; cortical necrosis has a poor renal prognosis.

Complications, disposition and follow-up

- ▶ Major complications: shock, DIC-like coagulopathy, intracranial or gastrointestinal bleeding, pulmonary edema, neuromy paralysis, aspiration, AKI, hyperkalemia/acidosis, local necrosis, compartment syndrome, secondary infection, serum sickness, recurrent coagulopathy, chronic limb disability, and late pituitary insufficiency.
- ▶ Suspect compartment syndrome when severe compartment-localized pain is opioid-resistant with weakness, sensory change, cyanosis, or tense swelling. Measure pressure; if **>30-40 mmHg**, give additional antivenom and elevate. Fasciotomy is last resort after antivenom failure and surgical consultation.
- ▶ Provide wound care, tetanus prophylaxis, acetaminophen or opioids for pain, and avoid NSAIDs/salicylates. Routine prophylactic antibiotics are not required unless there is infection, incision, mouth suction, necrosis, or local protocol supports use.
- ▶ Debride necrotic tissue only after coagulopathy is corrected; intact blebs should usually be left undisturbed, ruptured blebs debrided aseptically, and physiotherapy started early after swelling stabilizes.

- ▶ Admit all envenomated patients for at least **24 h**; ICU is indicated for shock, respiratory/neurotoxic signs, severe coagulopathy/bleeding, AKI, pulmonary edema, head/neck bite, progressive findings despite antivenom, or antivenom anaphylaxis.
- ▶ At discharge, warn about recurrent bleeding/coagulopathy over **2-3 weeks**, serum sickness at **1-2 weeks**, wound infection, chronic functional loss, and symptoms of adrenal/pituitary insufficiency after Russell's viper bite. Arrange repeat CBC, PT/INR, and fibrinogen if coagulopathy occurred.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Russell's viper envenomation flowchart:** bite -> first aid/immobilization -> ABC -> local/systemic/renal/neuro assessment -> 20WBCT + labs -> antivenom indications -> IV antivenom -> monitor coagulation, urine output, swelling, respiration -> complications/follow-up.
- ▶ **Pathophysiology diagram:** *Daboia venom* -> local vascular injury/tissue necrosis; procoagulant VICC/DIC -> bleeding; capillary leak/hemolysis/shock -> AKI; neurotoxicity -> ptosis/bulbar weakness/respiratory failure; late pituitary insufficiency.

Clinical / Diagnostic significance

- ▶ A **positive 20WBCT is a treatment-triggering bedside sign** of viperid coagulopathy when formal PT/fibrinogen are delayed.
- ▶ **Oliguria after Russell's viper bite is renal failure until proved otherwise**; check creatinine, potassium, urine blood/myoglobin, acid-base status, and involve nephrology early.
- ▶ **Ptosis or dysphagia after a viper bite is dangerous**, because certain Indian Russell's vipers can cause neurotoxicity; monitor ventilation and intubate before respiratory arrest.
- ▶ **Antivenom neutralizes circulating venom**, not established ATN/cortical necrosis, fixed paralysis, or necrotic tissue; delay is the key preventable cause of poor outcome.
- ▶ **Blood products before antivenom are a common error** unless resuscitation is life-saving; replace components after venom neutralization when bleeding demands it.

High-yield exam pointers

- ▶ Russell's viper = **painful swelling + coagulopathy/bleeding + shock + AKI**; add neurotoxicity for certain Indian bites.
- ▶ Mention Indian renal data: AKI after Russell's viper/*Echis* bites **13-32%**; oliguria often within **24 h**, sometimes **2-3 days**.
- ▶ Must write **20WBCT**: 1-2 mL blood, clean dry glass tube, 20 min, no clot = coagulopathy.
- ▶ Antivenom indications: progressive local swelling, bleeding/coagulopathy, shock, neurotoxicity, rhabdomyolysis, AKI, pulmonary edema.
- ▶ Antivenom is **IV only**; no skin testing; keep epinephrine ready and restart slowly after treated reaction if still indicated.
- ▶ First aid: immobilize, remove constrictors, rapid transport; **no incision, suction, tourniquet, ice, alcohol, massage, or pressure-immobilization for viperid bites**.

- ▶ Blood products only after adequate antivenom except life-saving resuscitation; avoid NSAIDs and salicylates.
- ▶ Compartment syndrome is treated first with antivenom and pressure monitoring; fasciotomy is last resort.
- ▶ Follow up for **recurrent coagulopathy for 2-3 weeks**, serum sickness, renal recovery, limb function, and late pituitary insufficiency.

SOURCE & COVERAGE

Harrison 22e — "Disorders Caused by Venomous Snakebites and Marine Animal Exposures"; Tintinalli's Emergency Medicine — "Snakebite"; Brenner & Rector's The Kidney — "Indian Subcontinent"; CMDT 2026 — "Poisoning". Coverage note: the corpus is strong for syndrome, AKI, monitoring, and general antivenom principles, but does not provide India-specific Russell's viper ASV dosing; dosing should follow local antivenom product and institutional protocol.



Venomous snake bite poisoning

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

Definition / Introduction — Venomous snake bite poisoning is local and/or systemic envenomation following injection of snake venom through fangs. It is a medical emergency because venom may cause progressive tissue necrosis, coagulopathy, shock, acute kidney injury, rhabdomyolysis, neuromuscular paralysis, and death from respiratory failure. Snakebite envenoming is the deadliest neglected tropical disease; Harrison estimates 1.2-5.5 million bites and 421,000-1,200,000 envenomations worldwide each year. In India, an exam answer should think syndromically: **viperid/cytotoxic-hemotoxic bite** versus **elapid/neuroparalytic bite**.

Epidemiology and important snakes

- ▶ Medically important venomous snakes belong mainly to **Viperidae** (Old World vipers and pit vipers) and **Elapidae** (cobras, kraits, coral snakes, sea snakes, Australian elapids); less common families include Lamprophiidae and venomous colubrids.
- ▶ Indian high-yield clinical pattern: **cobra/krait** bites usually suggest neuroparalysis; **Russell's viper** and **saw-scaled viper** bites suggest local swelling, bleeding/coagulopathy, shock, and renal injury.
- ▶ Harrison lists **cobras, carpet/saw-scaled vipers, Russell's vipers, large African vipers, lancehead pit vipers, and tropical rattlesnakes** among snakes causing large numbers of deaths globally.
- ▶ **Dry bite** means fang marks without venom effect. About **20-25% of pit viper bites** are dry; dry bites may be even more frequent with some snakes, including sea snakes.
- ▶ Risk of death rises with delayed transport, traditional treatment before hospital care, lack of correct antivenom, bites on head/neck, children, pregnancy, shock, respiratory paralysis, and established renal failure.
- ▶ Do not overdepend on colour or popular identification rules; a **safe photograph** may help, but attempted capture increases repeat bite risk.

Venom pathophysiology

- ▶ Snake venoms are complex mixtures of **enzymes, polypeptides, glycoproteins, and other constituents**; composition varies with species, age, diet, geography, and even within the same species.
- ▶ Major mechanisms:

Venom effect	Pathophysiology	Typical clinical result
Cytotoxic / local	Vascular permeability, tissue digestion, local necrosis	Pain, edema, ecchymosis, bullae, tissue loss
Hemotoxic / procoagulant	Fibrinogen and platelet consumption, fibrinolysis, endothelial injury	Bleeding, prolonged PT/INR/aPTT, low fibrinogen, DIC-like state
Neurotoxic	Pre- or postsynaptic neuromuscular blockade	Ptosis, ophthalmoplegia, dysphagia, respiratory paralysis
Myotoxic	Myolysis and rhabdomyolysis	Myalgia, myoglobinuria, hyperkalemia, AKI
Systemic vascular	Vasodilation, capillary leak, hemolysis, bleeding	Hypotension, shock, pulmonary edema

- ▶ Renal failure may follow hypotension, myoglobinuria, coagulopathy, hemolysis, or direct nephrotoxicity; it is often acute tubular necrosis but cortical necrosis is possible.
- ▶ Established presynaptic paralysis, renal failure, and rhabdomyolysis may not be reversed by antivenom; hence early recognition and early antivenom are crucial.

Clinical manifestations and severity

- ▶ **Local envenomation:** fang marks, immediate or delayed pain, progressive swelling, tenderness, ecchymosis, hemorrhagic or serum-filled vesicles/bullae, regional lymphadenopathy, cellulitis-like appearance, necrosis. Swelling may threaten airway after face/neck bites and function after hand/forearm bites.
- ▶ **Systemic viperid/cytotoxic syndrome:** nausea, vomiting, metallic or altered taste, perioral tingling, weakness, tachycardia or bradycardia, hypotension, spontaneous bleeding, thrombocytopenia, coagulopathy, hemolysis, pulmonary edema, AKI.
- ▶ **Neuromuscular syndrome:** nausea/headache/paresthesias may precede cranial nerve signs; ptosis, diplopia, dysarthria, dysphagia, loss of facial expression, salivation, descending flaccid weakness, diaphragmatic paralysis, aspiration, and respiratory arrest. Symptoms may be delayed for 12 h or more after some elapid bites.
- ▶ **Myotoxic/sea-snake-like syndrome:** variable local pain, generalized myalgia, trismus, rhabdomyolysis, myoglobinuria, hyperkalemia, and progressive flaccid paralysis.
- ▶ Severity grading useful at bedside:

Grade	Practical definition
None / dry bite	Fang marks only; no local progression, systemic features, or laboratory abnormality
Mild	Local pain/ecchymosis/nonprogressive swelling only

Grade	Practical definition
Moderate	Clearly progressive swelling, systemic symptoms/signs, and/or laboratory abnormality
Severe	Neurologic dysfunction, respiratory distress, cardiovascular instability, or shock

First aid and prehospital care

- ▶ Move the patient away from the snake; keep calm and still; **immobilize the bitten limb** in a neutral position and arrange rapid transport to a facility with airway support, laboratory testing, and antivenom.
- ▶ Remove rings, bangles, anklets, footwear, and tight clothing before swelling progresses. Clean with soap and running water if this does not delay transport; cover with a sterile dressing and splint.
- ▶ **Avoid** incision, suction, electric shock, ice, alcohol, stimulants, tight tourniquets, massage, and attempts to capture the snake.
- ▶ Pressure-immobilization may delay systemic absorption in a reliably identified **primarily neurotoxic elapid bite without significant local cytotoxicity**; it is **not recommended for viperid/cytotoxic bites** because it may worsen local injury.
- ▶ If pressure-immobilization is used by a trained rescuer, Harrison gives approximate wrap pressures of **40-70 mmHg for upper limb** and **55-70 mmHg for lower limb**, with complete limb immobilization and carriage to hospital.

Hospital assessment and investigations

- ▶ Start with **ABC**: early endotracheal intubation for face/neck swelling, bulbar weakness, falling vital capacity, difficulty swallowing, or respiratory insufficiency.
- ▶ Monitor vital signs, cardiac rhythm, oxygen saturation, mental status, and **urine output**. Establish two large-bore IV lines in unaffected limbs; minimize venipuncture and avoid noncompressible sites because coagulopathy may develop.
- ▶ Record time of bite, first-aid methods used, progression of symptoms, comorbidities, drugs, pregnancy, and snake identification if safely available.
- ▶ Mark the leading edge of swelling/ecchymosis/tenderness; measure limb circumference at three points every **15 min** until stable, then every **1-2 h**.
- ▶ Laboratory work-up: CBC with platelets, blood group and cross-match, PT/INR/aPTT, fibrinogen, FDP or D-dimer, renal and hepatic function, electrolytes, glucose, creatine kinase, urinalysis for blood/myoglobin; ECG/chest radiograph in severe envenomation or major comorbidity; ABG if respiratory compromise.
- ▶ **20-min whole-blood clotting test (20WBCT)**: place **1-2 mL venous blood** in a clean dry glass tube, leave undisturbed for **20 min**, then invert. Persistent liquid blood/no clot indicates coagulopathy when laboratory coagulation tests are unavailable.
- ▶ If initial labs are normal, repeat CBC and coagulation tests every **4 h** until systemic envenomation is excluded; after antivenom, recheck about every **6 h** until clinical stability.

Treatment: antivenom and supportive care

- ▶ **Specific antivenom is the mainstay** for significant envenomation. Use the geographically appropriate monovalent or polyvalent antivenom; in India this means locally available polyvalent anti-snake venom as per institutional protocol and manufacturer instructions.
- ▶ Indications for antivenom:
 - progressive local injury: rapidly spreading swelling, swelling involving more than half the limb, extensive bruising/blistering, or severe pain;
 - any systemic feature: hypotension, shock, vomiting not controlled, bleeding, neurotoxicity, rhabdomyolysis, AKI, cardiac collapse;
 - any significant laboratory abnormality: thrombocytopenia, prolonged clotting times, low fibrinogen, positive 20WBCT, rising CK, renal injury.
- ▶ Give antivenom **IV only**; do not inject IM or into a digit. Start slowly with the clinician at bedside, then increase if no reaction. Skin testing is not sensitive or specific and is not useful.
- ▶ Treat acute antivenom reaction by stopping the infusion temporarily and giving **IM epinephrine 0.01 mg/kg up to 0.5 mg**, IV antihistamine such as **diphenhydramine 1 mg/kg up to 50 mg**, and glucocorticoid such as **hydrocortisone 2 mg/kg up to 100 mg**; restart slowly at 5-10 mL/h if antivenom remains necessary.
- ▶ Resuscitate shock with isotonic crystalloid **20-40 mL/kg IV**; if shock persists after fluids and antivenom, use vasopressors such as norepinephrine or epinephrine.
- ▶ Neurotoxic paralysis: secure airway early; ventilatory support may be needed for days to weeks. In objective postsynaptic neurotoxicity, a trial of acetylcholinesterase inhibitor may be used: atropine **0.6 mg IV**, then neostigmine **0.02 mg/kg IV/IM**; if objective improvement occurs, neostigmine **0.5 mg** every 1 h as needed with atropine cover. This never replaces intubation or antivenom.
- ▶ Blood products are rarely needed and, if essential for life-threatening bleeding or dangerously low platelets, should be given **after adequate antivenom** to avoid fueling consumptive coagulopathy.
- ▶ Wound care: soap-water cleansing, sterile dressing, splintage with padding between digits, tetanus prophylaxis, acetaminophen/opioids for pain, avoid salicylates/NSAIDs, and avoid routine prophylactic antibiotics unless infection, incision, or mouth suction occurred.

Complications, disposition and follow-up

- ▶ Important complications: shock, airway edema, aspiration, respiratory paralysis, DIC-like coagulopathy, recurrent coagulopathy, AKI, rhabdomyolysis, hyperkalemia, tissue necrosis, compartment syndrome, secondary infection, serum sickness, and chronic disability.
- ▶ Suspect compartment syndrome with severe compartment-localized pain resistant to opioids, weakness, sensory change, cyanosis, or apparent pulselessness. Measure pressure; **>30-40 mmHg** indicates additional antivenom and elevation. Fasciotomy is a last resort after antivenom, because fasciotomy is needed in **<1%** of cases in modern series and may increase morbidity.
- ▶ Observe any envenomated patient in hospital for at least **24 h**. An apparently dry viperid bite needs **8-12 h** observation; coral snake/other elapid/sea snake bites need at least **24 h** because systemic toxicity may be delayed.

- ▶ ICU admission: head/neck bite, progressive findings despite initial antivenom, respiratory or cardiovascular instability, severe neurotoxicity, severe coagulopathy/bleeding, renal failure, or acute hypersensitivity to antivenom.
- ▶ Discharge only when swelling is improving, coagulopathy is corrected, pain is controlled, and the patient is ambulatory. Warn about recurrence of bleeding/coagulopathy over **2-3 weeks**, serum sickness at **1-2 weeks**, wound infection, and need for repeat CBC/PT/fibrinogen if coagulopathy occurred.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flowchart: snakebite management** — Bite -> ABC and immobilization -> classify dry/mild/moderate/severe -> labs including 20WBCT -> antivenom indications -> IV antivenom -> monitor swelling/coagulation/respiration -> complications and follow-up.
- ▶ **Limb monitoring diagram** — fang marks, leading edge of swelling, ecchymosis, bullae, three circumference measurement levels, distal pulse/capillary refill, sensory-motor status, compartment-pressure site.

Clinical / Diagnostic significance

- ▶ Ptosis after snakebite is respiratory failure until proved otherwise; do not wait for cyanosis before intubating or ventilating.
- ▶ 20WBCT is a bedside triage test, not a substitute for PT/INR/aPTT/fibrinogen where available; persistent liquid blood after 20 min is clinically significant.
- ▶ Antivenom reverses circulating venom, not established necrosis, renal failure, or fixed presynaptic paralysis; delay is the main preventable cause of poor outcome.
- ▶ Recurrent coagulopathy occurs because venom antigens may outlast antivenom; repeat labs and counsel against trauma/elective surgery for 2-3 weeks after acute coagulopathy.
- ▶ Routine antibiotics, routine fasciotomy, incision/suction, and tight tourniquets are common harmful errors in exam and practice.

High-yield exam pointers

- ▶ Write the two syndromes first: **hemotoxic/cytotoxic viper bite** and **neuroparalytic elapid bite**.
- ▶ First aid mantra: **reassure, immobilize, remove constrictors, rapid transport; no incision, suction, ice, alcohol, or tourniquet**.
- ▶ Must mention **ABC**, early intubation for bulbar/respiratory signs, and mechanical ventilation when needed.
- ▶ Must write investigations: CBC/platelet, PT/INR/aPTT, fibrinogen, FDP/D-dimer, renal function, CK, urine myoglobin, and **20WBCT**.
- ▶ Antivenom indications: progressive swelling, systemic toxicity, neurotoxicity, coagulopathy, rhabdomyolysis, renal failure, shock.
- ▶ Antivenom is **IV only**; manage anaphylaxis with epinephrine and restart slowly if benefit outweighs risk.
- ▶ Blood products only after adequate antivenom; NSAIDs and salicylates are avoided.

- ▶ Compartment syndrome is diagnosed by pressure and treated first with antivenom; fasciotomy is last resort.
- ▶ Observe dry bite 8-12 h, envenomation at least 24 h, and warn about serum sickness and recurrent coagulopathy.

SOURCE & COVERAGE

Harrison 22e — "Disorders Caused by Venomous Snakebites and Marine Animal Exposures"; Tintinalli's Emergency Medicine — "Snakebite"; CMDT 2026 — "Poisoning".



Lead toxicity

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

Definition / Introduction — Lead (Pb) is a *xenobiotic* heavy metal with **no physiological role and no safe threshold of exposure** — it is theoretically toxic at any level. Toxicity (*plumbism* / *saturnism*) usually results from **chronic, repeated low-level exposure** rather than a single ingestion, and predominantly injures the **nervous system, haematopoietic system, gastrointestinal tract and kidneys**. Because absorbed lead is ~95–99% sequestered in red cells and bone (bone half-life >20 years), it accumulates silently and causes both acute encephalopathic crises and insidious chronic organ damage.

Risk factors and sources of exposure

- ▶ **Occupational (the dominant adult risk):** manufacture and recycling of automobile/storage batteries, smelting, soldering, plumbing, **demolition or sanding of lead-painted houses and bridges**, stained-glass making, ceramic/pottery glazing, radiator repair, and **firing ranges (inhalation of bullet dust)**.
- ▶ **Environmental / domestic:** ingestion of **paint chips and house dust in homes built before ~1975**, lead-contaminated soil, drinking water from **lead pipes and plumbing/solder**, food or drink from **improperly glazed ceramics or lead-contaminated cookware**, and historic combustion of **leaded gasoline** (now globally phased out) plus electronic-waste recycling.
- ▶ **Ingested / cultural sources:** contaminated **spices, traditional herbal and folk remedies** (Ayurvedic medicines, Latino *azarcon/greta*), contaminated candies, and **retained lead bullet fragments lodged in or near a joint** (synovial fluid corrodes the metal → chronic toxicity).
- ▶ **Organic lead** (e.g., *tetraethyl lead* in older fuels) is additionally **absorbed dermally** and is highly neurotoxic.
- ▶ **Host susceptibility factors:** **young children** (hand-to-mouth/pica behaviour, higher fractional GI absorption, immature blood–brain barrier, developing CNS); **nutritional deficiency of iron, calcium and zinc** (enhances GI lead absorption); **pregnancy and lactation** (bone lead is mobilised into blood and crosses the placenta and into breast milk); and genetic polymorphisms (e.g., *ALAD* variants) modifying handling and effect.

Toxicokinetics and mechanism of toxicity

- ▶ **Absorption** via ingestion or inhalation (organic lead also dermally); in blood 95–99% is bound to red cells, so lead must be measured in **whole blood, not serum**.
- ▶ **Distribution**: soft-tissue half-life ~30 days; ~15% of a dose is deposited in **bone (half-life >20 years)**, the major cumulative reservoir reflected by *KXRF bone-lead* measurement. Excreted mainly in **urine**, also in breast milk.
- ▶ **Molecular toxicity**: interferes with **mitochondrial oxidative phosphorylation**, ATPases and **calcium-dependent second messengers**; binds **sulphydryl groups**; enhances oxidative stress and apoptosis; and substitutes for calcium/zinc in metalloproteins.
- ▶ **Haem-synthesis block (key for exam)**: lead **inhibits δ -aminolevulinic acid dehydratase (ALA-dehydratase, ALAD)** and **ferrochelatase** → accumulation of **ALA and coproporphyrin III** in urine and a rise in **free erythrocyte / zinc protoporphyrin (FEP/ZPP)**, with impaired haem formation causing anaemia. Lead intoxication is a recognised differential of *ALA-dehydratase-deficient porphyria*. Inhibition of **pyrimidine-5'-nucleotidase** leaves ribosomal RNA aggregates producing **basophilic stippling** of red cells.

Clinical features

System	Acute / high-level exposure	Chronic / subclinical exposure
CNS (children)	Lead encephalopathy — convulsions, coma, death (BPb >80–120 µg/dL); raised ICP	Impaired IQ, developmental & neurobehavioural delays, language/motor/balance/hearing/behaviour & school-performance deficits (BPb 25–60 µg/dL; <i>no safe threshold</i>)
CNS / PNS (adults)	Headache, irritability, lethargy; severe → encephalopathy	Demyelinating peripheral neuropathy , mainly motor → wrist drop (radial nerve), foot drop; slowed reaction time, impaired short-term memory, declining cognition, depression, loss of libido
GI	Lead colic — colicky abdominal pain, anorexia, constipation , nausea	Burton's line — bluish-grey lead line at the gingiva-tooth border
Haematological	Anaemia, impaired haematopoiesis	Anaemia with basophilic stippling ; microcytic in children, normocytic–normochromic in adults; elevated FEP/ZPP
Renal	Proximal tubular dysfunction → Fanconi syndrome , pyuria, azotaemia	Chronic interstitial nephritis and chronic renal failure; hyperuricaemia → saturnine gout
Other	—	Hypertension, ECG conduction delays, ↑cardiovascular morbidity/mortality, reduced sperm counts , spontaneous abortion

- ▶ **Blood-lead severity bands (CMDT/Harrison)**: *subclinical* neurodevelopmental effects even at 1–25 µg/dL; 25–60 µg/dL — headache, irritability, subclinical neuropathy, anaemia (children); 60–80 µg/dL — moderate toxicity, impaired neurotransmission; >80–100 µg/dL — severe poisoning/encephalopathy.

Diagnosis / Investigations

- ▶ **Venous whole-blood lead level (BPb)** is the *diagnostic gold standard*. The CDC blood-lead reference value is 3.5 µg/dL — exceeding it triggers source investigation; OSHA mandates worker removal at BPb >40 µg/dL (newer proposals: keep <10 µg/dL, remove >20 µg/dL).
- ▶ **Peripheral smear**: normocytic/normochromic (adults) or microcytic (children) anaemia with basophilic stippling.
- ▶ **Biochemical markers of haem-pathway block**: elevated **free erythrocyte / zinc protoporphyrin (FEP/ZPP)**, raised **urinary ALA and coproporphyrin III**.
- ▶ **Imaging**: long-bone x-rays show dense **metaphyseal "lead lines"** in children; abdominal radiograph may reveal radiopaque ingested lead (paint chips, fishing weight, retained bullet).
- ▶ **Bone-lead by KXRF** estimates cumulative body burden (research/specialist).
- ▶ **Screening**: CDC recommends screening US children when they begin to crawl (~6 months).

Treatment

- ▶ **First and most important step** — *identify and remove the source of exposure* (occupational hygiene, abatement of lead paint/water, report to public-health authority); **chelation is reserved for symptomatic and/or high-level toxicity**.
- ▶ **Decontamination**: for recent ingestion of a retained lead object (e.g., fishing weight) visible on x-ray, use **whole-bowel irrigation, endoscopy or surgical removal** (activated charcoal does **not** bind lead).
- ▶ **Supportive care**: secure airway, treat seizures and coma; manage raised ICP in encephalopathy.
- ▶ **Chelation agents** (consult a toxicologist / poison centre, 1-800-222-1222):

Severity	First-line chelation (per CMDT 2026)
Severe — encephalopathy or BPb >70–100 µg/dL	Edetate calcium disodium (CaEDTA) ~50 mg/kg/day (1500 mg/m ² /day) in 4–6 divided doses or continuous IV infusion, + dimercaprol (BAL) 4–5 mg/kg IM every 4 h × 5 days for encephalopathy
Moderate — symptomatic / BPb 45–69 µg/dL	CaEDTA (as above) or oral succimer (DMSA) 10 mg/kg every 8 h × 5 days, then every 12 h × 2 weeks
Mild–moderate, ambulatory	Oral succimer (DMSA) is preferred

- ▶ **Sequencing pearl**: in encephalopathy give **dimercaprol (BAL) first/with CaEDTA** — CaEDTA alone can redistribute lead into the CNS and *worsen encephalopathy*.
- ▶ **Adjuncts**: correct **iron, calcium, magnesium and zinc deficiency** to reduce further lead absorption; **calcium supplementation (1200 mg)** lowers blood lead and limits bone-lead mobilisation in pregnancy; vitamin C is only a weak natural chelator.
- ▶ **Evidence caveats**: a large RCT of chelation in **asymptomatic children (BPb 20–40 µg/dL)** showed **no improvement in IQ**; benefit of chelation for chronic adult cardiovascular outcomes remains unproven (TACT-2 negative).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Haem-synthesis pathway showing the two lead-blocked enzymes.** Labels: *Glycine + Succinyl-CoA* → **ALA synthase** → δ -ALA → **ALA-dehydratase (BLOCKED by lead)** → *Porphobilinogen* → ... → *Protoporphyrin IX* → **Ferrochelatase (BLOCKED by lead)** + Fe^{2+} → *Haem*; annotate "↑urinary ALA & coproporphyrin III", "↑FEP/ZPP", "anaemia".
- ▶ **Clinical signs schematic of plumbism.** Labels: *Burton's (gingival) lead line*, *basophilic stippling on smear*, *wrist drop (motor neuropathy)*, *lead colic / constipation*, *metaphyseal lead lines on x-ray*, *encephalopathy*.

Clinical / Diagnostic significance

- ▶ Suspect lead in any patient with **unexplained abdominal colic + anaemia + peripheral motor neuropathy**, or a child with developmental regression/encephalopathy and a relevant exposure history (old housing, occupation, folk remedies).
- ▶ **Basophilic stippling + microcytic anaemia + raised ZPP** strongly suggests plumbism and helps separate it from iron-deficiency and sideroblastic anaemia.
- ▶ Lead is a **reportable / notifiable** exposure in many jurisdictions; OSHA-style biological monitoring and medical removal protect occupational cohorts.
- ▶ Chronic low-level lead is now an established risk factor for **hypertension, resistant hypertension, chronic kidney disease and cardiovascular mortality** — relevant to the internist beyond overt poisoning.

High-yield exam pointers

- ▶ No safe blood-lead level; CDC reference value = 3.5 $\mu\text{g}/\text{dL}$. Measure lead in **whole blood, not serum**.
- ▶ Lead **inhibits ALA-dehydratase and ferrochelatase** → ↑urinary ALA/coproporphyrin, ↑FEP/ZPP, anaemia.
- ▶ **Basophilic stippling** (pyrimidine-5'-nucleotidase inhibition) is the classic smear clue.
- ▶ **Burton's line** = gingival lead line; **wrist drop** = motor (radial) neuropathy; **lead colic** = abdominal pain with constipation.
- ▶ **Children get metaphyseal "lead lines" on x-ray** and are most vulnerable (pica, ↑absorption, developing brain).
- ▶ Encephalopathy appears at BPb >80–120 $\mu\text{g}/\text{dL}$.
- ▶ **Treatment hierarchy**: remove source → supportive care → chelation. **Severe/encephalopathy** → CaEDTA + dimercaprol (BAL given first); **moderate/oral** → succimer (DMSA).
- ▶ Iron/calcium/zinc repletion reduces lead absorption; **calcium 1200 mg** curbs bone-lead mobilisation in pregnancy.
- ▶ **Saturnine gout** = lead nephropathy with hyperuricaemia/gout.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Heavy Metal Poisoning" (lead sources, toxicokinetics, blood-lead toxicity bands, diagnosis, chelation) and "The Porphyrrias" (lead inhibition of ALA-dehydratase; raised urinary ALA/coproporphyrin III); smear chapter on basophilic stippling in lead poisoning.
- ▶ **CMDT 2026** — "Poisoning" chapter, *Lead* section (clinical findings, blood-lead severity ranges, CaEDTA / dimercaprol / succimer regimens and doses, decontamination, source removal).

Coverage note: The spec lists no dedicated toxicology subspecialty textbook; grounding is from Harrison 22e + CMDT 2026, which cover this topic comprehensively. *Burton's line*, *saturnine gout*, ferrochelatase inhibition and the BAL-before-EDTA sequencing pearl are universally accepted standard internal medicine added for exam completeness; the corpus explicitly supports the gingival "lead line", ALA-dehydratase inhibition, raised protoporphyrin, and the chelation regimens.



Vitamins, minerals, nutrition & electrolytes



Beer potomania

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

Definition / Introduction — *Beer potomania* is a distinctive form of **hypotonic, dilutional hyponatremia** caused by **very low dietary solute intake** rather than by excess antidiuretic hormone (AVP/ADH). It classically occurs in chronic heavy beer drinkers whose near-sole calorie source is beer — a beverage rich in water and carbohydrate but almost devoid of protein and salt (only **1–2 mmol/L of Na⁺**). Because renal free-water excretion is *obligately coupled to urinary solute (osmole) excretion*, an extremely low solute load shrinks the maximum volume of water the kidney can clear, so that even a modest fluid (beer) load overwhelms it and dilutional hyponatremia ensues despite **maximally suppressed AVP and maximally dilute urine**. The same physiology underlies the "*tea-and-toast*" syndrome in malnourished, non-alcoholic patients on protein-poor diets.

Pathophysiology — why low solute intake causes hyponatremia

- ▶ **Free-water excretion is solute-limited.** The kidney can excrete free water only in proportion to the solute (mainly urea + electrolytes) delivered to and excreted by the distal nephron. Maximum urine output $\approx$ (daily solute excreted) $\div$ (minimum achievable urine osmolality).
- ▶ **Minimum urine osmolality** the human kidney can achieve with full AVP suppression is **~50 mOsm/kg**.
- ▶ *Quantitative illustration (CMDT):*

- A normal Western diet generates ~1000 mOsm of solute/day → at a minimum Uosm of 50 mOsm/kg the kidney can put out up to ~20 L of dilute urine/day, so ordinary water loads are easily cleared.
- A beer-only / "tea-and-toast" diet generates only ~200 mOsm/day → maximum urine output falls to ~4 L/day. Once daily fluid (beer) intake exceeds this ceiling, electrolyte-free water is retained and serum Na⁺ falls.
- ▶ **AVP is appropriately suppressed** (or rapidly suppressible) — this is an *ADH-independent* hyponatremia. The defect is inadequate substrate (solute) for water excretion, **not** inappropriate antidiuresis.
- ▶ Contributory factors in alcoholics: **poor protein/salt intake**, beer-induced **carbohydrate load** (further suppresses ureagenesis and lowers urinary solute), and often coexisting **GI losses**, **hypokalemia** and **malnutrition**.

Etiology and predisposing settings

- ▶ **Chronic heavy beer drinkers** whose only nutrient is beer — the eponymous setting (beer = high water + carbohydrate, minimal protein/Na⁺).
- ▶ **"Tea-and-toast" diet** — elderly, frail or non-alcoholic patients on very low-protein, low-salt diets.
- ▶ **Extreme/restricted diets** — e.g. extreme vegetarian or nutrient-restricted "fad" diets with high water intake.
- ▶ Common background of **malnutrition**, **thiamine deficiency**, **hypokalemia**, **hypomagnesemia** and **alcoholic liver disease**, all of which heighten the risk during correction.

Clinical and biochemical profile

Feature	Typical finding in beer potomania
Volume status	Clinically euvolemic (often mildly hypovolemic)
Serum osmolality	Low (hypotonic, <275–280 mOsm/kg)
Urine osmolality	Very low — <100 mOsm/kg to low 200s (dilute urine; suppressed AVP)
Urine Na ⁺	<20 mmol/L (often <10–20)
Serum AVP/ADH	Suppressed or rapidly suppressible with saline
Serum K ⁺	Frequently low (poor intake, GI losses)
Serum uric acid	Variable; not the hypouricemia typical of SIAD
Response to saline/diet	Hyponatremia corrects rapidly (often dangerously fast)

- ▶ **Symptoms** track the rate and depth of the fall in Na⁺: anorexia, nausea, headache, lethargy, gait unsteadiness/falls; with severe or acute drops — confusion, seizures, obtundation, coma (cerebral oedema).

- ▶ Many cases are **chronic** (>48 h), so the brain has osmotically adapted and the patient may be only mildly symptomatic despite $\text{Na}^+ < 120 \text{ mmol/L}$ — which is precisely what makes overcorrection dangerous.

Diagnostic approach and differential diagnosis

- ▶ **Step 1 — confirm true hypotonic hyponatremia:** measure serum osmolality to exclude *pseudohyponatremia* (hyperlipidemia/hyperproteinemia) and *hypertonic (translocational) hyponatremia* (hyperglycemia, mannitol).
- ▶ **Step 2 — measure urine osmolality:** $\text{Uosm} < 100 \text{ mOsm/kg}$ places the patient in the *ADH-independent* group (suppressed AVP) — the bracket that contains beer potomania, primary polydipsia and tea-and-toast diet. $\text{Uosm} > 100$ implies a continuing AVP effect (SIAD, hypovolemia, oedematous states).
- ▶ **Step 3 — measure urine Na^+ and assess volume/diet:** low Uosm + low urine Na^+ + a corroborating dietary history clinches low-solute hyponatremia.

Parameter	Beer potomania / low solute	Primary (psychogenic) polydipsia	SIAD
Mechanism	Low solute → low free-water clearance	Massive water intake > excretory capacity	Inappropriate AVP (water retention)
AVP	Suppressed	Suppressed	Inappropriately high
Urine osmolality	$< 100 \rightarrow$ low 200s	$< 100 \text{ mOsm/kg}$	> 100 (usually > 300) mOsm/kg
Urine Na^+	$< 20 \text{ mmol/L}$	Low	Usually $> 30\text{--}40 \text{ mmol/L}$
Serum uric acid	Not characteristically low	Normal	Low ($< 4 \text{ mg/dL}$)
Dietary clue	Beer-only / "tea & toast"	Polydipsia, psychiatric illness	None

Treatment and the critical danger of overcorrection

- ▶ **Mainstay:** simply resuming a normal diet $\pm$ isotonic (0.9%) saline restores urinary solute excretion and the kidney rapidly dumps the retained free water — so the Na^+ tends to **self-correct very quickly and unpredictably**.
- ▶ This is the central exam point: **patients with beer potomania carry a HIGH risk of osmotic demyelination syndrome (ODS / central pontine myelinolysis)** because they combine *every* major ODS risk factor — alcoholism, malnutrition, hypokalemia, severe chronic hyponatremia, and a strong tendency to overcorrect once solute is restored and AVP shuts off.
- ▶ **Correction-rate limits (chronic hyponatremia):** do not exceed $\sim 8 \text{ mmol/L}$ in 24 h (some texts 8–10 mmol/L/24 h , and $< 18 \text{ mmol/L/48 h}$). In high-risk patients (which beer potomania is), aim lower — 4–6 mmol/L/day ; this is a *limit*, not a *target*.
- ▶ **Anticipate and pre-empt the auto-correction:** monitor serum Na^+ frequently (every 1–2 h initially). If a brisk water diuresis begins, *re-lower* Na^+ with hypotonic fluid (D5W) and/or use a

DDAVP (desmopressin) "clamp" to stop the free-water diuresis and keep correction within limits.

- ▶ **Correct hypokalemia cautiously** — K^+ repletion itself raises serum Na^+ and can precipitate overcorrection.
- ▶ **Give thiamine** before/with any dextrose-containing fluids in alcoholics (prevent Wernicke encephalopathy).
- ▶ For genuinely *symptomatic/severe acute* hyponatremia, hypertonic 3% NaCl (e.g. 100 mL boluses over ~10 min, targeting a prompt 4–5 mmol/L rise) is used — but in chronic beer potomania the threat is usually too-rapid correction, not under-correction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flow diagram of solute-limited water excretion:** boxes/arrows — *Low dietary solute (beer: low protein, Na^+ 1–2 mmol/L) → Low urinary solute excretion (~200 mOsm/day) → Reduced maximum free-water clearance (max urine ~4 L/day at U_{osm} 50 mOsm/kg) → Beer (water) intake exceeds ceiling → Free-water retention → Dilutional hyponatremia (with AVP suppressed, $U_{osm} < 100$, $U_{Na} < 20$). Add a side note: "Normal diet ≈ 1000 mOsm/day → up to ~20 L/day."*
- ▶ **Hyponatremia work-up algorithm:** Serum osmolality (exclude pseudo/hypertonic) → if hypotonic, **Urine osmolality:** < 100 mOsm/kg branch → **ADH-independent** → label the three boxes *Primary polydipsia | Beer potomania | Tea-and-toast diet*; > 100 branch → assess volume status → hypovolemic / SIAD (euvoletic) / hypervolemic. Labels to include: S_{osm} , U_{osm} 50–100 mOsm/kg, $U_{Na} < 20$ mmol/L, suppressed AVP.

Clinical / Diagnostic significance

- ▶ A correctable, **diet-related** cause of hyponatremia that must be distinguished from SIAD — misclassifying it as SIAD and fluid-restricting/giving hypertonic saline can drive dangerous overcorrection.
- ▶ The triad **low U_{osm} + low urine Na^+ + suggestive dietary history** is diagnostic; serum uric acid and volume assessment help separate it from SIAD.
- ▶ Illustrates a key renal-physiology teaching point: **free-water clearance is rate-limited by solute delivery**, not by water intake alone.
- ▶ A *sentinel* condition for **ODS prophylaxis** — anticipate spontaneous overcorrection, monitor intensively, and be ready with DDAVP/D5W re-lowering.

High-yield exam pointers

- ▶ Beer potomania = **low-solute, ADH-INDEPENDENT hypotonic hyponatremia**; AVP is *suppressed*, urine is *maximally dilute*.
- ▶ Beer is essentially salt- and protein-free — only 1–2 mmol/L Na^+ ; high water + carbohydrate load.
- ▶ Biochemistry: $U_{osm} < 100$ (to low 200s) mOsm/kg, urine $Na^+ < 20$ mmol/L, low serum osmolality.

- ▶ Mechanism number to quote: normal diet ~1000 mOsm/day → up to ~20 L urine; beer diet ~200 mOsm/day → only ~4 L.
- ▶ Differential = **primary polydipsia** and "**tea-and-toast**" diet (other ADH-independent, low-Uosm causes).
- ▶ Treatment = **normal diet + isotonic saline** → corrects fast → **highest risk of ODS/central pontine myelinolysis**.
- ▶ Correction limit ~8 mmol/L/24 h (high-risk target 4–6 mmol/L/day); monitor Na⁺ 1–2 hourly; consider **DDAVP clamp** and D5W to prevent/treat overcorrection.
- ▶ Co-manage **hypokalemia, magnesium, and thiamine**; cautious K⁺ replacement (raises Na⁺).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Fluid and Electrolyte Disturbances" (hyponatremia: low solute intake / beer potomania; SIAD; osmotic demyelination syndrome and correction limits).
- ▶ **CMDT 2026** — "Electrolyte & Acid-Base Disorders" (hypotonic hyponatremia diagnostic algorithm; ADH-independent low-solute causes — beer potomania and tea-and-toast diet; solute-dependent maximum urine volume; Furst ratio; correction rate, ODS risk factors, and DDAVP clamp).



Beriberi

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

Definition / Introduction — *Beriberi* is the clinical syndrome of **thiamine (vitamin B1) deficiency**. Because thiamine pyrophosphate is the coenzyme that drives oxidative decarboxylation and the pentose-phosphate transketolase reaction, its lack cripples aerobic energy generation in the most metabolically active tissues — heart, peripheral nerve and brain. Prolonged deficiency therefore produces a high-output cardiac failure (**wet beriberi**), a symmetric sensorimotor polyneuropathy (**dry beriberi**) and a central neuropsychiatric disorder (**Wernicke-Korsakoff syndrome**), with considerable clinical overlap between these forms.

Thiamine: biochemistry and why deficiency causes disease

- ▶ **Vitamin B1** was the *first vitamin to be identified*; it is a water-soluble vitamin with small body stores that deplete within **weeks** of a deficient diet (unlike B12/vitamin A, which last ≥1 year).
- ▶ Active cofactor = **thiamine pyrophosphate (TPP)**. Functions:
 - Coenzyme for **decarboxylation of α-keto acids** (pyruvate, α-ketoglutarate) and branched-chain amino acids → essential for ATP/energy generation.
 - Coenzyme for the **transketolase** reaction, interconverting hexose and pentose phosphates (basis of the diagnostic enzyme assay).
 - Postulated role in **peripheral nerve conduction**.

- ▶ **Food sources:** yeast, organ meat, pork, legumes, beef, whole grains, nuts. *Milled/polished rice and processed grains contain very little thiamine* — hence endemic beriberi in rice-eating populations. Food processing removes it and high-heat/prolonged cooking destroys it.
- ▶ **Anti-thiamine factors:** heat-labile **thiaminases** (raw fish, shellfish) destroy the vitamin; heat-stable **polyhydroxyphenols/tannins** (coffee, tea, Brussels sprouts, betel nut) inactivate it.
- ▶ Overt deficiency develops at a dietary level $<0.3 \text{ mg}/1000 \text{ kcal}$.

Aetiology and at-risk groups

- ▶ **Developing world / classic beriberi:** disproportionate reliance on **polished rice** and highly processed staples; famine, refugee and displaced populations.
- ▶ **Western world (commonest causes):** **chronic alcohol use disorder** and chronic illness (e.g., cancer). Alcohol *directly impairs intestinal thiamine absorption, blocks TPP synthesis and increases urinary excretion*.
- ▶ **Refeeding/carbohydrate load:** giving a large carbohydrate load (oral, enteral or **parenteral glucose**) to a thiamine-depleted patient can precipitate **acute thiamine deficiency with lactic acidosis** — thiamine must always be given *before/with* refeeding.
- ▶ **Other groups:** prolonged **hyperemesis gravidarum**, anorexia and eating disorders, post **bariatric/metabolic surgery** ("bariatric Wernicke"), dialysis, chronic **diuretic** therapy (increased urinary thiamine loss in heart failure/hypertension).
- ▶ **Drugs** that inhibit the intestinal thiamine transporter ThTR2 — **metformin, verapamil** — raise deficiency risk.
- ▶ **Maternal thiamine deficiency** → **infantile beriberi** in breast-fed babies.

Clinical types — Wet vs Dry beriberi

Feature	Wet (cardiovascular) beriberi	Dry (neurological) beriberi
Dominant system	Heart and circulation	Peripheral ($\pm$ central) nervous system
Precipitating setting	Deficiency + severe physical exertion + high carbohydrate intake	Deficiency + inactivity + low-calorie intake
Mechanism	Impaired myocardial energy metabolism + dysautonomia; marked peripheral vasodilatation	Energy failure in peripheral nerve → axonal degeneration
Onset	Can appear after ~3 months of deficient diet	Insidious
Cardiac features	High-output congestive heart failure , enlarged heart/cardiomegaly, tachycardia, pulmonary oedema, peripheral oedema with warm extremities (mimics cellulitis)	Usually absent
Neurological features	Peripheral neuritis may coexist	Symmetric motor + sensory polyneuropathy , pain/paraesthesia, diminished/absent reflexes , <i>legs affected more than arms</i> , difficulty rising from a squatting position

Feature	Wet (cardiovascular) beriberi	Dry (neurological) beriberi
Reference	High-output failure listed among nutritional (beriberi) causes	Distal, length-dependent neuropathy

- ▶ The two forms **overlap**; pain and paraesthesiae occur in either. An acute fulminant cardiovascular collapse with lactic acidosis (*acute pernicious* / "Shoshin" beriberi) is the most dramatic cardiac presentation — see Coverage note.

Wernicke-Korsakoff syndrome (central nervous beriberi)

- ▶ Seen especially in **alcoholic** patients with chronic thiamine deficiency; the brain counterpart of beriberi.
- ▶ Wernicke's encephalopathy — classic triad:
 - Ophthalmoplegia (weakness of one or more extraocular muscles) and **horizontal nystagmus**
 - Cerebellar / truncal ataxia
 - Global confusion / mental impairment
- ▶ When there is additional **memory loss with confabulatory psychosis** → Wernicke-Korsakoff syndrome (Korsakoff = amnesia, confabulation, impaired new learning).
- ▶ Despite the characteristic picture, the syndrome is frequently **underdiagnosed**; a high index of suspicion in any malnourished, alcoholic, post-bariatric or hyperemetic patient is essential.

Investigations / Diagnosis

- ▶ Largely **clinical**, supported by a **therapeutic response to empirical thiamine**.
- ▶ Erythrocyte transketolase activity measured *before and after* adding TPP: a **>25% stimulation** (activity coefficient ≥ 1.25) indicates deficiency.
- ▶ **Direct thiamine assay** — serum/whole-blood thiamine or its phosphate esters by HPLC; normal $\approx 70\text{--}180\text{ nmol/L}$.
- ▶ Urinary thiamine excretion is also used.
- ▶ Always assess **co-existing deficiencies** (other B vitamins, magnesium) and look for the underlying cause (alcohol, malabsorption, bariatric surgery, hyperemesis).

Treatment

- ▶ **Acute beriberi / Wernicke's (Harrison regimen):** thiamine 200 mg IV three times daily until there is no further improvement in acute signs, then **oral thiamine 10 mg/day** until recovery is complete. (CMDT: 50–100 mg/day IV initially, then oral 5–100 mg/day.)
- ▶ **Cardiovascular and ophthalmoplegic features improve within 24 hours**; neuropathy clears gradually; **Korsakoff psychosis may be permanent** or persist for months.
- ▶ **Give glucose only after/with thiamine** in at-risk patients to avoid precipitating acute deficiency and lactic acidosis.
- ▶ **Replete magnesium** — it is a required cofactor for thiamine activation; thiamine supplementation is ineffective if magnesium is depleted. Co-administer other water-soluble (B-complex) vitamins.

- ▶ Liberal **prophylactic thiamine** (e.g., 50–100 mg oral thiamine daily for ≥ 1 week in alcohol withdrawal; generous parenteral cover in the emergency setting) for all patients with alcohol use disorder.
- ▶ **Outcome:** roughly one-fourth recover immediately, one-fourth over days, and about half achieve only partial or no benefit — underscoring the value of *early* treatment.
- ▶ **Toxicity:** essentially none from food/supplements; rare hypersensitivity/anaphylaxis has followed high-dose IV thiamine.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two-circle "Wet vs Dry beriberi" overlap (Venn) diagram.** Labels — *Common stem:* "Thiamine (B1) deficiency $\rightarrow$ $\downarrow$ TPP $\rightarrow$ impaired oxidative decarboxylation/transketolase $\rightarrow$ energy failure"; *Wet circle:* "High-output cardiac failure, cardiomegaly, tachycardia, warm peripheral oedema, pulmonary oedema"; *Dry circle:* "Symmetric sensorimotor polyneuropathy, legs $>$ arms, absent ankle reflexes, foot/wrist drop"; *Overlap:* "pain, paraesthesia, peripheral neuritis"; *Central extension:* "Wernicke-Korsakoff syndrome".
- ▶ **Wernicke triad triangle.** Three vertices labelled **Ophthalmoplegia / nystagmus**, **Cerebellar (truncal) ataxia**, **Confusion (global)**; arrow to a fourth box "+ **amnesia & confabulation** = Korsakoff".

Clinical / Diagnostic significance

- ▶ Beriberi is a key **reversible cause of high-output heart failure** (alongside anaemia, thyrotoxicosis, AV shunts, Paget's disease, cirrhosis) — suspect it in dilated cardiomyopathy/CCF with warm extremities in a malnourished or alcoholic patient.
- ▶ Wet beriberi oedema with **warm, well-perfused extremities** is a clinical clue distinguishing it from low-output failure and from cellulitis.
- ▶ **Refeeding syndrome:** never load carbohydrate into a chronically malnourished or alcoholic patient without prior thiamine — iatrogenic Wernicke's and lactic acidosis are classic, examinable pitfalls.
- ▶ A **rapid response to IV thiamine** (ocular signs within 24 h) is both therapeutic and diagnostic.
- ▶ Post-**bariatric surgery** patients are a modern high-risk group; persistent vomiting in such a patient mandates parenteral thiamine.

High-yield exam pointers

- ▶ Thiamine = **vitamin B1**, the *first vitamin identified*; cofactor **TPP** for pyruvate/ α -ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase and **transketolase**.
- ▶ **Polished/milled rice** diets and **chronic alcoholism** are the prototypical causes; **thiaminases** (raw fish) and **tannins** (tea, betel nut) are dietary antagonists.
- ▶ **Wet** = **cardiac** (high-output failure, warm oedema); **Dry** = **neuropathy** (symmetric, legs $>$ arms, lost ankle jerks).
- ▶ **Wernicke triad** = **ophthalmoplegia/nystagmus** + **ataxia** + **confusion**; add **amnesia** + **confabulation** = **Korsakoff**.

- ▶ **Diagnosis:** erythrocyte transketolase activity with >25% TPP stimulation (coefficient ≥ 1.25); blood thiamine by HPLC (≈ 70 – 180 nmol/L).
- ▶ **Treatment:** high-dose **parenteral thiamine first, glucose later**; replete **magnesium**; ocular/cardiac signs reverse within 24 h, Korsakoff amnesia may be permanent.
- ▶ **Carbohydrate repletion without thiamine** $\rightarrow$ **acute deficiency + lactic acidosis** (refeeding Wernicke).
- ▶ **Infantile beriberi** results from maternal thiamine deficiency in breast-fed infants.
- ▶ Thiamine has **no significant toxicity**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Vitamin and Trace Mineral Deficiency and Excess*" (thiamine biochemistry, food sources, wet/dry beriberi, Wernicke-Korsakoff, transketolase diagnosis, treatment regimen); "*Alcohol and Alcohol Use Disorders*" (alcohol-related thiamine deficiency, prophylactic thiamine in withdrawal); "*Heart Failure*" chapter (beriberi as a cause of high-output cardiac failure).
- ▶ **CMDT 2026** — "*Nutrition, Nutritional Disorders, & Obesity*" (clinical features of wet vs dry beriberi, biochemical tests, normal thiamine 70 – 180 nmol/L, parenteral treatment doses, magnesium dependence, referral).
- ▶ *Coverage note:* The eponym "**Shoshin**" (**acute fulminant cardiac**) **beriberi** is standard internal-medicine terminology but is **not named in this corpus**; it is included only as universally accepted teaching. No dedicated subspecialty textbook was specified for this nutrition topic (specialty_books empty), so depth is drawn from Harrison + CMDT, which cover the topic adequately.



Hyponatraemia

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

Definition / Introduction — Hyponatremia is a plasma Na^+ concentration <135 mmol/L and is the commonest electrolyte abnormality in clinical practice, occurring in up to 22% of hospitalised patients. It is fundamentally a disorder of *water balance* — an **excess of body water relative to sodium** — and almost always reflects an increase in circulating arginine vasopressin (AVP/ADH) and/or increased renal sensitivity to AVP, combined with continued free-water intake. The serum Na^+ therefore says *nothing* about total-body sodium or volume status, both of which must be assessed independently. The key clinical danger is **cerebral oedema** (acute) and **osmotic demyelination from over-rapid correction** (chronic).

Pathophysiology of water homeostasis

- ▶ Serum osmolality is normally held at **285–295 mOsm/kg** by two effectors: **thirst** and **AVP** acting on renal V2 receptors (insertion of aquaporin-2 $\rightarrow$ free-water reabsorption).

- ▶ Hyponatremia develops when water intake exceeds the kidney's capacity to excrete electrolyte-free water — either because AVP is inappropriately high, renal diluting capacity is impaired, or solute delivery to the diluting segment is inadequate (low-solute states).
- ▶ **Non-osmotic AVP release** (hypovolemia, arterial underfilling in heart failure/cirrhosis, nausea, pain, stress, drugs) overrides osmotic suppression and is central to most hyponatremias.
- ▶ Estimated osmolality = $2[\text{Na}^+] + \text{glucose}(\text{mg/dL})/18 + \text{BUN}(\text{mg/dL})/2.8$. **Effective osmolality (tonicity)** subtracts urea (an ineffective osmole); true hypotonic hyponatremia has an effective osmolality $<275 \text{ mOsm/kg}$.

Classification — first by tonicity, then by volume status

Step	Category	Serum osmolality	Mechanism / examples
1	Pseudohyponatremia (isotonic)	Normal	Lab artifact in severe hyperlipidemia / hyperproteinemia ($\uparrow$ solid phase of plasma); excluded by measuring osmolality
1	Hypertonic (translocational)	High	Hyperglycemia , mannitol — osmotic water efflux from cells; Na^+ falls $\sim 1.6 \text{ mmol/L}$ per 100 mg/dL rise in glucose. <i>No cerebral oedema</i>
1	Hypotonic ("true")	Low (<275)	Genuine water excess — subclassified by volume status (Step 2)
2	Hypovolemic	Low	$\downarrow$ total body water, $\downarrow\downarrow$ total body Na^+
2	Euvolemic	Low	$\uparrow$ total body water, near-normal Na^+
2	Hypervolemic	Low	$\uparrow\uparrow$ total body water, $\uparrow \text{Na}^+$ (oedematous states)

Aetiology of hypotonic hyponatremia by volume status

Volume status	Urine Na^+	Causes
Hypovolemic	$<20 \text{ mmol/L}$ (extrarenal)	Vomiting, diarrhoea, GI/tube drainage, third-spacing (pancreatitis, burns, trauma), insensible/sweat loss with hypotonic replacement
Hypovolemic	$>20 \text{ mmol/L}$ (renal)	Thiazide diuretics , mineralocorticoid deficiency / primary adrenal insufficiency (Addison's $\rightarrow \uparrow \text{K}^+$), salt-losing nephropathy, osmotic diuresis (glycosuria, ketonuria), bicarbonaturia (RTA, vomiting), cerebral salt wasting
Euvolemic	$>20\text{--}30 \text{ mmol/L}$	SIAD (commonest), hypothyroidism , secondary (glucocorticoid) adrenal insufficiency , reset osmostat, drugs; beer potomania / low-solute (here $\text{UNa} <20$, $\text{U-osm} <100\text{--}200$)
Hypervolemic	$<10 \text{ mmol/L}$ (Na^+ -avid)	Congestive heart failure , cirrhosis , nephrotic syndrome
Hypervolemic	$>20 \text{ mmol/L}$	Acute & chronic renal failure

- ▶ **Cerebral salt wasting** — hyponatremia with *true hypovolemia* and inappropriate natriuresis in intracranial disease (subarachnoid haemorrhage, TBI, craniotomy, meningitis, encephalitis).

Distinction from SIAD is critical: it responds to **aggressive Na^+ - Cl^- repletion**, whereas SIAD requires water restriction.

Syndrome of Inappropriate Antidiuresis (SIAD/SIADH)

- ▶ **Commonest cause of euvolemic hyponatremia.** Patients are not strictly euvolemic but *subclinically volume-expanded* with "AVP escape" limiting further retention.
- ▶ **Bartter–Schwartz diagnostic criteria** (a diagnosis of exclusion): (1) hyponatremia with **hypo-osmolality** ($<280 \text{ mOsm/kg}$); (2) **inappropriately concentrated urine** ($\text{U-osm} >100$); (3) **urine Na^+ usually $>20\text{--}30 \text{ mmol/L}$** (euvolemic, normal salt intake); (4) **absence of cardiac, renal, hepatic, thyroid and adrenal disease**; (5) normal acid–base/potassium.
- ▶ Supportive: **low serum uric acid** ($<4 \text{ mg/dL}$) and **low BUN** ($<10 \text{ mg/dL}$) from dilution + enhanced clearance — distinguishes from hyperuricemic hypovolemic hyponatremia.
- ▶ **Causes (4 groups):** **Malignancy** — *small-cell lung carcinoma* (75% of malignancy-associated SIAD; $\sim 10\%$ have $\text{Na}^+ <130$ at presentation), head & neck, GI; **Pulmonary** — pneumonia, TB, abscess, positive-pressure ventilation; **CNS** — tumour, SAH, meningitis, encephalitis, head trauma; **Drugs** — SSRIs, tricyclics, **carbamazepine**, **chlorpropamide**, cyclophosphamide/ifosfamide, vincristine, NSAIDs, antipsychotics, MDMA ("Ecstasy"), desmopressin/oxytocin.

Clinical features

- ▶ Symptoms are predominantly **neurological** (cerebral oedema within the rigid skull) and depend on **severity and rate of fall**.
- ▶ **Acute ($<48 \text{ h}$) symptomatic hyponatremia** — a **medical emergency**: nausea, headache, vomiting → seizures, obtundation, **brainstem herniation**, coma, death; may cause **non-cardiogenic ("neurogenic") pulmonary oedema** with respiratory failure. **Premenopausal women** are at highest risk of encephalopathy. Settings: post-operative hypotonic fluids, TURP/hysteroscopy glycine irrigation, exercise (marathon) and MDMA-associated, psychogenic polydipsia.
- ▶ **Chronic ($>48 \text{ h}$):** brain adapts by extruding **organic osmolytes** (creatine, betaine, glutamate, myoinositol, taurine) — largely complete by 48 h — so patients are often paucisymptomatic, but show subtle gait/cognitive deficits, **falls**, and $\uparrow$ **fracture/osteoporosis** risk. This adaptation is the basis of ODS risk on correction.
- ▶ **Severity (CMDT):** mild 130–134, moderate 125–129, **severe $<125 \text{ mmol/L}$** .

Diagnostic approach

- ▶ **Step 1 — measure serum osmolality** to exclude pseudo- and hypertonic hyponatremia; calculate effective osmolality (<275 confirms hypotonic).
- ▶ **Step 2 — clinical volume status** (JVP, orthostatic vitals, oedema).
- ▶ **Step 3 — urine osmolality and urine Na^+ :** $\text{U-osm} <100 \text{ mOsm/kg}$ → primary polydipsia / low-solute; $\text{U-osm} >100$ → AVP active. $\text{UNa} <20\text{--}30$ → hypovolemic or Na^+ -avid (CHF/cirrhosis); $\text{UNa} >30$ → SIAD-type.

- ▶ **Step 4 — targeted tests:** serum glucose (correct for translocation), **uric acid** (low in SIAD), TSH, 0900 cortisol / **cosyntropin (ACTH-stimulation) test** for adrenal insufficiency; chest/CNS imaging (CT thorax in smokers for small-cell carcinoma).
- ▶ "Gold standard" for hypovolemic hyponatremia = correction of Na^+ after a normal-saline challenge.

Treatment

- ▶ **Three guiding principles:** symptom severity sets urgency; chronicity sets the *safe correction rate*; response to therapy is **unpredictable** → monitor Na^+ **every 1–4 h**.
- ▶ **Acute symptomatic (seizures/coma) — hypertonic 3% saline (513 mmol/L):** 100 mL bolus over 10 min, repeatable $\times 2$, aiming to raise Na^+ by 1–2 mmol/L/h for a total of only 4–6 mmol/L — enough to abort herniation; or infusion 0.5–2 mL/kg/h. Add O_2 /ventilatory support and IV loop diuretic if pulmonary oedema. Na^+ deficit = $0.6 \times \text{body weight} \times (\text{target} - \text{actual } \text{Na}^+)$.
- ▶ **Safe correction limits (avoid ODS):** <8–10 mmol/L in first 24 h and <18 mmol/L in 48 h; high-risk patients (alcoholics, malnourished, hypokalemic, $\text{K}^+ < 120$) target only 4–6 mmol/L/day. "Limit, not a goal."
- ▶ **Chronic / aetiology-specific:**
 - **Hypovolemic** → isotonic 0.9% saline (shuts off AVP — watch for *auto-correction* and overshoot).
 - **Hypervolemic (CHF/cirrhosis)** → fluid + Na^+ restriction, treat underlying disease, loop diuretics, ACE inhibition.
 - **Euvolemic/SIAD** → **fluid restriction** guided by the Furst / **urine-to-plasma electrolyte ratio** ($\text{UNa} + \text{UK}$)/ PNa : ratio >1 restrict <500 mL/d, ~1 restrict 500–700 mL/d, <1 restrict <1 L/d. Add **oral salt tablets + furosemide 20 mg BD, oral urea, SGLT2 inhibitors** (osmotic glycosuric diuresis), or **demeclocycline**.
 - **Vaptans (V2 antagonists) — tolvaptan (oral) and conivaptan (IV, mixed V1A/V2) —** aquaretics for SIAD and hypervolemic hyponatremia; **contraindicated in hypovolemic and acute hyponatremia**, avoid in cirrhosis, limit to ≤ 30 days (hepatotoxicity); start in hospital with liberalised fluids.
- ▶ **Overcorrection rescue / prophylaxis:** if Na^+ rises too fast, **re-lower** with **DDAVP (desmopressin)** $\pm$ D5W; a planned "**DDAVP clamp**" with concurrent hypertonic saline gives controlled correction in high-risk patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm box (Fig.):** Top — "Hyponatremia ($\text{Na}^+ < 135$)". Branch 1 *Serum osmolality* → Normal = pseudohyponatremia / High = hyperglycemia, mannitol / Low = true hypotonic. From "Low", branch on **volume status** → **Hypovolemia** ($\text{UNa} < 20$ extrarenal: GI loss, third-space; $\text{UNa} > 20$ renal: diuretics, Addison's, CSW), **Euvolemia** (SIAD, hypothyroidism, glucocorticoid deficiency), **Hypervolemia** (CHF, cirrhosis, nephrotic — $\text{UNa} < 10$; renal failure — $\text{UNa} > 20$). Label arrows $\text{UNa} < 20$ / $\text{UNa} > 20$.
- ▶ **Brain-cell osmolyte diagram:** ICF cell with arrows — *acute* water influx → swelling/cerebral oedema; *chronic* efflux of organic osmolytes (taurine, myoinositol, glutamate); on **over-rapid correction** → osmotic shrinkage → **osmotic demyelination (pons)**. Labels: "cerebral oedema", "osmolyte efflux (48 h)", "central pontine myelinolysis".

Clinical / Diagnostic significance

- ▶ **Osmotic demyelination syndrome (ODS):** occurs 2–6 days after over-rapid correction; **central pontine myelinolysis** → flaccid then spastic quadriparesis, dysarthria, dysphagia, diplopia, "locked-in syndrome"; **extrapontine** lesions (cerebellum, lateral geniculate, thalamus, putamen, cortex) → ataxia, parkinsonism, dystonia, mutism. Often **irreversible** — prevention by rate control is paramount.
- ▶ A **low uric acid + low BUN** in a euvolemic hyponatremic patient strongly favours SIAD; **hyperuricemia** favours volume depletion.
- ▶ Hyponatremia is an independent **adverse prognostic marker** in heart failure and cirrhosis (degree reflects neurohumoral activation).
- ▶ Always recheck for **thiazide effect** and **adrenal insufficiency** before labelling SIAD; defer SIAD diagnosis 1–2 weeks after stopping a thiazide.

High-yield exam pointers

- ▶ Hyponatremia = **water problem**, not a salt problem; Na^+ value reflects nothing about volume status.
- ▶ Three-step work-up: **serum osmolality** → **volume status** → **urine Na^+ /osmolality**.
- ▶ **Translocational Na^+ correction:** subtract ~1.6 mmol/L per 100 mg/dL glucose above normal.
- ▶ SIAD = Bartter–Schwartz criteria; uric acid < 4 mg/dL; commonest malignancy = **small-cell lung carcinoma**.
- ▶ **Acute symptomatic** → 3% saline 100 mL boluses, target rise only 4–6 mmol/L.
- ▶ **Correction ceiling:** < 8 – 10 mmol/L/24 h, $< 18/48$ h (high-risk 4–6/day) — exceeding this → ODS / central pontine myelinolysis.
- ▶ **Vaptans never in hypovolemic or acute hyponatremia;** isotonic saline corrects hypovolemic type.
- ▶ **Cerebral salt wasting** (hypovolemic, treat with salt) vs SIAD (euvolemic, restrict water) — opposite therapies.
- ▶ Overcorrection rescue = DDAVP + D5W; correct **hypokalemia** cautiously (it itself raises Na^+).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Fluid and Electrolyte Disturbances" (sodium disorders; SIAD; ODS; hypertonic saline and vaptan therapy).
- ▶ **CMDT 2026** — "Electrolyte & Acid-Base Disorders" (osmolality formula, severity grading, Bartter–Schwartz criteria, 3% saline boluses, Furst ratio, SGLT2 inhibitors/oral urea, DDAVP clamp) and "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (SIADH causes).

**Parenteral nutrition therapy**

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

Definition / Introduction — Parenteral nutrition (PN) is the delivery of a nutritionally complete mixture of crystalline amino acids, glucose (dextrose), lipid emulsion, electrolytes, minerals, vitamins and trace elements **directly into the bloodstream**, bypassing the gastrointestinal (GI) tract. It is one of three forms of *specialized nutritional support* (SNS) — the others being optimized voluntary nutrition and enteral nutrition (EN). PN is reserved for patients in whom invasive support is indicated but the gut is non-functional, inaccessible or insufficient. The guiding principle is "*if the gut works, use it*": EN is always preferred when feasible, and PN carries the higher burden of infectious, metabolic and mechanical complications.

Indications and Patient Selection

- ▶ PN is used **when invasive SNS is indicated and EN is impossible, inappropriate or insufficient** to meet nutritional needs.
- ▶ The decision to start instrumental SNS rests on four factors: (1) nutrient intake is likely to remain inadequate for **many days**; (2) there is important **muscle loss** (of any cause); (3) **nutrient requirements are increased** (inflammatory diarrhoea, enterocutaneous fistulas/exudates, a protein-catabolic inflammatory state); and (4) a reasoned judgment that SNS will improve clinical outcome or quality of life.
- ▶ **Conditions that contraindicate EN and thus favour PN:** intestinal ischaemia, mechanical bowel obstruction, peritonitis, GI haemorrhage, high-output proximal fistula, prolonged paralytic ileus, severe malabsorption (e.g., short-bowel syndrome), and intractable vomiting/diarrhoea where EN fails.
- ▶ In the ICU, current guidelines advise starting EN soon after resuscitation and stabilization; if the protein goal is not met after **7–10 days**, PN may be added — particularly if the catabolic state persists.
- ▶ **Perioperative:** patients with starvation-related malnutrition (SRM) or chronic disease-related malnutrition (CDM) awaiting major elective surgery benefit from **7–10 days** of preoperative SNS (EN/PN if voluntary intake is impractical).
- ▶ PN is generally **not** initiated in advanced incurable malignancy or advanced dementia with no interest in food, where it does not alter the disease trajectory.

Routes of Venous Access

- ▶ Because adult PN admixtures are **hyperosmolar** (>1200 mOsm/L, often >1800 mOsm/L) and frequently large-volume, they must be infused through a **dedicated central-vein port**.
- ▶ **Central (total) PN**: for malnourished patients needing support >7–14 days; catheter tip documented in the **superior vena cava** radiographically before infusion. The *subclavian route is preferred*; **jugular and femoral catheters should be avoided** because of difficulty keeping a dry, sterile dressing and higher complication rates.
- ▶ **Peripheral PN (PPN)**: for non-malnourished patients or **short-term** (<2 weeks) support; lower osmolality solutions. Limited by a high incidence of **phlebitis**, line infiltration and volume overload.
- ▶ Lipid emulsions are **isotonic** and can be given via either a central or peripheral vein.

Composition of PN Admixtures

- ▶ Supplied as **ready-to-use 2-chamber (amino acids + glucose)** or **3-chamber (amino acids + glucose + lipid)** bags; vitamins, trace elements and extra electrolytes are added just before infusion. Complex needs (especially acute disease-related malnutrition, ADM) justify a **computer-controlled compounder** to individualize composition.

Component	Key points (faithful to source)
Amino acids	Free (hydrated) crystalline amino acids; energy density 3.3 kcal/g (vs 4.0 in formed protein). 100 g free amino acids ≈ 83 g protein substrate . Provide all essential amino acids + nonessential N. Typical bags 4–7% amino acids.
Carbohydrate (dextrose)	Dextrose monohydrate , 3.4 kcal/g. Bags 20–25% glucose. Initial dose ≤ 200 g/day ; main metabolic hazard = hyperglycaemia.
Lipid emulsion	~ 10 kcal/g ; supplies essential n-6 and n-3 fatty acids. Soybean-oil based, or mixed (olive/soybean; or SMOF = 30% soybean, 30% MCT, 25% olive, 15% fish oil). Standard infusion ≤ 8 g/h (≈175 g = 1925 kcal/day in a 70-kg adult). Check triglycerides first; >400 mg/dL is a relative contraindication . To prevent essential fatty acid deficiency, give 250 mL of 20% soy lipid ≥twice weekly (CMDT).
Electrolytes	Sodium and potassium 1–2 mEq/kg/day ; calcium 10–15 mEq/day ; magnesium 8–20 mEq/day ; phosphorus 20–40 mmol/day (CMDT).
Trace elements	Zinc, copper, manganese, selenium, chromium. Iron is NOT added (incompatible with lipid; risk of free-radical catalysis) — give IV iron separately if needed. Copper and manganese omitted in cholestatic liver disease (impaired excretion). Extra zinc for high-output diarrhoea/fistula (1 L secretory diarrhoea ≈ 12 mg zinc loss).
Vitamins	Injectable adult multivitamin daily (A, D, E, K, B1, B2, B6, B12, niacinamide, dextranthenol, biotin, folic acid, ascorbic acid). Parenteral water-soluble vitamin needs are higher (urinary loss); ascorbic acid degrades in the bag.

Energy, Protein and Fluid Prescription

- ▶ **Energy**: total daily energy expenditure of a healthy sedentary adult ≈ **36 kcal/kg** (resting energy expenditure ≈75%); weight-based estimate **25–35 kcal/kg/day**; indirect calorimetry is the gold standard. Energy doses **>70% of TEE confer no extra protein-sparing** and risk hyperglycaemia, dyslipidaemia and volume expansion.

- ▶ Non-critically ill patients rarely need **>500 g glucose (1700 kcal)/day**; in ADM, limit to **≤350 g glucose (1200 kcal)/day** during the intense catabolic phase. *Hypocaloric, protein-generous* nutrition is recommended for the first ~2 weeks in fat-sufficient/obese ADM patients.
- ▶ **Protein**: safe intake 0.8 g/kg; **critically ill 1.2–2.0 g/kg/day**. CMTD: stable 0.8–1.2; moderate–severe stress ≥1.5; trauma/burns up to ~2.5 g/kg/day.
- ▶ **Fluid**: total provision should not normally exceed **~2 L/day** without abnormal losses; ~25–35 mL/kg or ~1 mL/kcal.

Initiation, Glycaemic Control & Monitoring

- ▶ Begin PN only after the patient is **haemodynamically stable**, with glucose/electrolyte/acid-base homeostasis established and able to tolerate the fluid load. Start at ~half the energy target (~100–150 g dextrose first 24 h), then advance as tolerated.
- ▶ **Insulin**: add subcutaneous/admixture regular insulin to keep glucose **<140 and >80 mg/dL** (180/100 mg/dL in critically ill diabetics). Benchmarks: basal endogenous secretion ≈**30 U/day**; ~**10 U insulin per 100 g glucose** in non-diabetic non-catabolic patients; ~**20 U/100 g** in type 2 diabetes.
- ▶ **Monitoring**: baseline urea, creatinine, electrolytes, glucose, magnesium, phosphate, calcium, albumin, triglycerides and LFTs; then daily basic panel + Mg/PO₄ during initiation, easing to 1–2×/week once stable; **triglycerides and LFTs weekly**; vitamins/trace elements every 3–6 months on long-term PN.
- ▶ **Nitrogen balance** (CMTD) = [24-h protein intake (g) ÷ 6.25] – [24-h urinary nitrogen (g) + 4]; a positive balance confirms adequate provision (Harrison: 1 g N = 6.25 g protein).
- ▶ **Discontinuation**: taper PN as oral/enteral intake rises; stop once the patient tolerates **one-half to two-thirds of requirements** enterally. Slow the rate to 50 mL/h before stopping to avoid reactive hypoglycaemia.

Complications

Category	Examples
Catheter-related (mechanical/insertion)	Pneumothorax, arterial laceration, air embolism, brachial plexus injury; catheter-related bloodstream infection (PN patients are at higher risk than other CVC patients); central venous thrombosis ; thrombotic/non-thrombotic occlusion.
Metabolic	Hyperglycaemia (most frequent); hypoglycaemia (reactive, on abrupt stop); hypertriglyceridaemia ; fluid/electrolyte and acid-base derangements; volume overload (mortality risk).
Hepatobiliary	Mild transaminase rise at 2–4 weeks (often self-limited); fatty liver from energy overfeeding; intrahepatic cholestasis after many weeks — reduced by cyclic PN (infused over only 12 h/day).
Refeeding syndrome	See below.
Long-term	Metabolic bone disease; micronutrient deficiencies (including iron).

Refeeding Syndrome

- ▶ Occurs in successfully adapted SRM during the **first week** when carbohydrate ($\pm$ sodium) is introduced too rapidly. Carbohydrate $\rightarrow$ insulin surge $\rightarrow$ **antinatriuretic** ECF expansion (refeeding **oedema**) plus intracellular shift of electrolytes.
- ▶ Hallmark biochemistry: **hypophosphataemia**, **hypokalaemia**, **hypomagnesaemia**; can cause haemolysis, cardiac arrhythmias and **left heart failure** (volume load + insulin-driven rise in resting energy expenditure on an atrophic LV + myocardial K/PO₄/Mg deficiency).
- ▶ **Acute thiamine-deficiency encephalopathy** (Wernicke) is a devastating but preventable complication — give **thiamine 100 mg daily for 5–7 days** before/with refeeding.
- ▶ **Prevention**: start low ($\sim$ 5–20 kcal/kg/day), advance slowly, restrict sodium, and frequently measure and replace phosphate, potassium and magnesium. (Refeeding oedema is benign — treat with elevation and sodium restriction; *avoid diuretics*.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Decision algorithm for nutritional support**: box flow — *Can the patient eat enough?* $\rightarrow$ No $\rightarrow$ *Is the gut functional & accessible?* $\rightarrow$ Yes = **Enteral nutrition**; No = **Parenteral nutrition** $\rightarrow$ branch to *Central PN* (>7 –14 days, *malnourished*, *hyperosmolar*) vs *Peripheral PN* (<2 weeks, *non-malnourished*). Label EN contraindications (obstruction, ischaemia, peritonitis, GI bleed) as the arrow into PN.
- ▶ **Triple-chamber PN bag**: three labelled compartments — *Amino acids* (3.3 kcal/g), *Dextrose monohydrate* (3.4 kcal/g), *Lipid emulsion* ($\sim$ 10 kcal/g) — with add-on ports labelled *Vitamins*, *Trace elements*, *Electrolytes*, feeding into a *central venous catheter*, tip in SVC.

Clinical / Diagnostic significance

- ▶ Choosing **route** (central vs peripheral) hinges on osmolality, expected duration and nutritional status — a frequent exam decision point.
- ▶ Pre-lipid **triglyceride** and baseline **electrolyte/phosphate/Mg** checks pre-empt the two commonest serious metabolic harms (hypertriglyceridaemia, refeeding syndrome).
- ▶ **Special populations**: *Renal failure* — do **not** restrict protein (RRT removes amino acids/vitamins/trace elements; increase provision). *Liver failure* — generous energy and protein, but spread protein through the day and tighten fluid/acid-base/electrolyte control to limit encephalopathy; omit copper/manganese. *Critical illness–nutrition paradox* — early energy provision matching expenditure may be **harmful**; avoid matching energy to expenditure while inflammation is severe.
- ▶ A multidisciplinary **nutrition support team** (physician, nurse, dietitian, pharmacist) demonstrably lowers complication rates.

High-yield exam pointers

- ▶ *"If the gut works, use it"* — EN is always first-line; PN only when the gut is unusable/inaccessible/insufficient.

- ▶ Adult PN is **hyperosmolar** → **central vein** (subclavian preferred; tip in SVC, X-ray confirmed; **avoid femoral/jugular**).
- ▶ Energy densities to memorize: amino acids **3.3**, dextrose **3.4**, lipid **~10 kcal/g**; 100 g amino acids ≈ 83 g protein.
- ▶ Starting glucose ≤**200 g/day**; insulin target glucose **80–140 mg/dL**; triglycerides **>400 mg/dL** = relative contraindication to lipid.
- ▶ **Iron is never added** to PN; copper/manganese omitted in cholestasis.
- ▶ **Refeeding syndrome triad**: ↓phosphate, ↓potassium, ↓magnesium; give **thiamine 100 mg/day**, start 5–20 kcal/kg/day.
- ▶ **Cyclic PN (12 h/day)** reduces PN-associated cholestasis; energy overfeeding causes fatty liver.
- ▶ Wean PN once **½–⅔ of needs** are tolerated enterally; slow rate before stopping to prevent rebound hypoglycaemia.
- ▶ Nitrogen balance = (protein intake/6.25) – (urinary N + 4).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Enteral and Parenteral Nutrition*" (Hoffer & Bistrian) and "*Nutritional Assessment*" (body-composition/inflammation context).
- ▶ **CMDT 2026** — "*Nutrition, Nutritional Disorders, & Obesity*" — nutritional-support routes, requirements, parenteral electrolyte/trace-element doses, nitrogen-balance equation, refeeding-syndrome management.



Pellagra

Asked in: Paper I Jul 2021 · Paper I May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Pellagra is the clinical deficiency syndrome of **niacin (vitamin B3)** and/or its precursor amino acid **tryptophan**. The name derives from the Italian *pelle agra* ("rough skin"). Niacin (nicotinic acid + nicotinamide) is the precursor of the coenzymes **NAD** and **NADP**, which drive numerous oxidation–reduction reactions and (as NAD) ADP-ribose transfer reactions in DNA repair and calcium mobilisation. Deficiency produces the classic photodistributed dermatitis, gastrointestinal and neuropsychiatric features summarised as the "**four Ds**": **Dermatitis, Diarrhoea, Dementia and Death**.

Niacin metabolism and biochemical basis

- ▶ **Sources & forms** — *Niacin* is a generic term for **nicotinic acid** and **nicotinamide** and their active derivatives. Roughly half the body's niacin is supplied by diet (meat, fish, poultry, nuts, eggs, dairy, legumes, fortified cereals) and half is synthesised endogenously from **tryptophan**.
- ▶ **Tryptophan conversion** — Tryptophan is converted to niacin with an efficiency of **60 : 1 by weight**; requirements are therefore expressed as **niacin equivalents**. This conversion needs **vitamin B6 (pyridoxine), riboflavin and iron** as cofactors — deficiency of any of these lowers niacin yield.

- ▶ **Coenzyme role** — Nicotinic acid and nicotinamide are precursors of **NAD and NADP**, central to redox metabolism; NAD also participates in **ADP-ribose transfer (DNA repair, Ca²⁺ mobilisation)**. Cellular NAD⁺ declines with ageing.
- ▶ **Maize/corn factor** — Niacin in corn and maize is **tightly (chemically) bound** and is not absorbed unless released by **alkaline hydrolysis** (e.g. lime-water/*nixtamalization*). Diets based on unfortified maize therefore predispose to pellagra.
- ▶ **Sorghum (jowar) factor** — Jowar contains usable niacin but a **high leucine content** that inhibits the conversion of tryptophan to niacin — the basis of epidemic pellagra in sorghum-eating populations of the Indian Deccan.
- ▶ **Excretion / biomarkers** — Urinary excretion products **2-pyridone** and **N-methyl (2-methyl) nicotinamide** fall in deficiency and are used diagnostically.

Aetiology and predisposing causes

Category	Examples (source-grounded)
Dietary / endemic	Corn- or maize-based diets (China, Africa, India); sorghum (jowar)-based diets; famine, displacement, refugee/camp populations; restrictive/selective eating (e.g. autism spectrum disorder), eating disorders
Alcoholism	Commonest cause in industrialised settings (poor intake + impaired metabolism)
Malabsorption	Inflammatory bowel disease, jejunoileitis, gastrectomy/gastroenterostomy, bariatric (gastric bypass) surgery
Drugs	Isoniazid (structural analogue of niacin — also seen with mass scale-up of INH TB-preventive therapy); 5-fluorouracil; 6-mercaptopurine/azathioprine; anticonvulsants; antidepressants; sulfonamides; chloramphenicol
Inherited — Hartnup disease	Autosomal recessive defect of neutral amino-acid transport (SLC6A19 gene) → intestinal & renal malabsorption of tryptophan ; presents with cerebellar ataxia, psychiatric symptoms, aminoaciduria and pellagra-like rash
Carcinoid syndrome	Tumour diverts up to ~60% of tryptophan to serotonin (normally ~1%), depleting tryptophan available for niacin synthesis

Clinical features — the "four Ds"

- ▶ **Dermatitis (the hallmark)** — A **photosensitive eruption**: initially intermittent painful/pruritic erythema and oedema of **sun-exposed skin**, evolving into sharply marginated, **hyperpigmented, scaling, keratotic plaques**; vesicles/bullae may form in severe cases.
 - *Distribution*: **dorsa of the hands** (glove/gauntlet pattern), **face in a symmetrical butterfly/malar distribution**, and the **neck and upper chest forming a collar** — **Casal's necklace** (*after Gaspar Casal*).
 - *Mucocutaneous*: **bright-red ("beefy") glossitis**, angular stomatitis, cheilitis, oral/perirectal ulcers; **half-and-half nails** described.
- ▶ **Diarrhoea** — From **proctitis and malabsorption** (atrophy of intestinal villi); often accompanied by anorexia, abdominal pain, nausea, vomiting; vaginitis and oesophagitis may occur.

- ▶ **Dementia / neuropsychiatric** — Early irritability, anxiety, insomnia, apathy, fatigue, depression and impaired memory progress to **confusion, hallucinations, psychosis, dementia**; seizures and, terminally, stupor and coma.
- ▶ **Death** — Untreated pellagra is progressive and **fatal within ~4–5 years**.
- ▶ **Early (non-specific) phase** — Loss of appetite, generalised weakness, irritability, mouth soreness, glossitis/stomatitis and weight loss precede the full triad.

Diagnosis and investigations

- ▶ **Primarily a clinical diagnosis** in advanced cases (characteristic photodistributed rash + GI + neuropsychiatric features); early deficiency requires a **high index of suspicion**.
- ▶ **Biochemical confirmation** — Reduced **urinary N-methylnicotinamide and 2-pyridone**; low **serum/plasma nicotinamide and nicotinic acid**. Reference deficiency threshold is **< 9.0 niacin equivalents** (recommended daily intake ~13–20 mg).
- ▶ **Therapeutic trial** — Rapid response to niacin supports the diagnosis: **neuropsychiatric symptoms improve within 24–48 h**, whereas cutaneous lesions take weeks to resolve.
- ▶ **Differential diagnosis** — Pyridoxine (B6) deficiency (pellagra-like dermatitis), porphyrias, polymorphous light eruption, chronic actinic dermatitis, photosensitive drug eruptions, cutaneous lupus; consider underlying carcinoid or Hartnup disease where diet is adequate.

Treatment and prevention

- ▶ **Replacement** — Nicotinamide is preferred over nicotinic acid because it does not cause flushing/headache.
 - *Harrison*: oral **nicotinamide or nicotinic acid 100–200 mg three times daily for up to 4 weeks**.
 - *Rook's*: **~500 mg/day** of nicotinamide (or nicotinic acid) over several weeks.
 - *CMDT*: oral **nicotinamide 10–150 mg/day**; advanced pellagra may be treated with parenteral nicotinic acid initially, then oral.
- ▶ **Supportive** — Treat coexisting deficiencies (general undernutrition, alcohol-use disorder) and correct precipitants (stop offending drug, manage malabsorption/carcinoid). Co-administer **pyridoxine with isoniazid** to prevent INH-induced pellagra/neuropathy.
- ▶ **Prevention** — Dietary diversification away from monotonous maize/sorghum; **niacin fortification of flour/cereals**; alkaline (lime) treatment of maize; treat at-risk groups (alcoholics, famine/displaced populations).

Niacin toxicity (pharmacologic high-dose, not deficiency)

- ▶ High-dose **nicotinic acid (~2 g/day, sustained-release)** is used for **hypertriglyceridaemia / low HDL** (useful in statin intolerance) but lacks proven cardiovascular benefit; **nicotinamide does not lower lipids**.
- ▶ **Flushing** — Prostaglandin-mediated (GPCR binding), starts in the face, with itching/paraesthesia/headache; subject to **tachyphylaxis**; mitigated by **aspirin pre-medication** and extended-release forms.

- ▶ **Hepatotoxicity** — Most serious effect of sustained-release niacin (raised AST/ALT, jaundice; rare fulminant hepatitis at 3–9 g/day). Other effects: **glucose intolerance**, **hyperuricaemia/gout**, **macular oedema**; combined with statins increases **rhabdomyolysis** risk. **Upper limit for non-therapeutic intake = 35 mg/day**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Casal's necklace / photodistributed dermatitis (front of body)**: Label — *symmetrical butterfly (malar) facial rash; Casal's necklace (collar over neck and upper chest); V of the neck; dorsa of hands — glove/gauntlet pattern; bright-red (beefy) glossitis & angular stomatitis; sun-exposed = photodistribution*.
- ▶ **Tryptophan–niacin pathway**: Boxes — *Dietary niacin (NAD/NADP in food) and Tryptophan → (60:1, needs B6 + riboflavin + iron) → Nicotinic acid / Nicotinamide → NAD / NADP → redox + DNA-repair reactions*. Add block-arrows: *Isoniazid (analogue, blocks), Carcinoid (diverts Trp → serotonin), Hartnup / SLC6A19 (blocks Trp absorption), Maize bound-niacin & sorghum-leucine (reduce availability)*.

Clinical / Diagnostic significance

- ▶ **"4 Ds"** mnemonic anchors recognition: photosensitive Dermatitis + Diarrhoea + Dementia → Death if untreated — an instantly examinable triad.
- ▶ **Casal's necklace** and **butterfly facial rash** in a photodistribution are pathognomonic visual clues at the bedside.
- ▶ Always seek a **precipitant**: alcohol, isoniazid therapy, maize/sorghum-predominant diet, malabsorption/bariatric surgery, carcinoid or Hartnup disease — deficiency in an apparently well-fed patient mandates this search.
- ▶ **Niacin-equivalents** concept explains why deficiencies of **B6, riboflavin and iron** (cofactors for tryptophan→niacin) and **carcinoid** can cause "secondary" pellagra.
- ▶ A prompt **therapeutic response** (neuropsychiatric within 48 h) is both treatment and confirmation.

High-yield exam pointers

- ▶ Niacin = **vitamin B3** = nicotinic acid + nicotinamide → coenzymes NAD/NADP.
- ▶ Tryptophan → niacin at **60 : 1 by weight**; cofactors **B6, riboflavin, iron**.
- ▶ **4 Ds** = **Dermatitis, Diarrhoea, Dementia, Death**; dermatitis is **photosensitive**.
- ▶ **Casal's necklace** = pigmented scaly collar of neck/upper chest (eponym *Gaspar Casal*).
- ▶ **Maize (bound niacin)** and **sorghum/jowar (high leucine)** are classic dietary causes — relevant to India.
- ▶ Secondary pellagra: **alcoholism, isoniazid, Hartnup disease (SLC6A19), carcinoid syndrome, 5-FU/6-MP, malabsorption**.
- ▶ Tongue = **bright-red/beefy glossitis**; nails = **half-and-half**.
- ▶ Diagnosis mainly **clinical**; biomarkers = ↓ urinary **N-methylnicotinamide & 2-pyridone**, ↓ serum niacin.

- ▶ Treatment = **nicotinamide preferred** (no flushing); high-dose **nicotinic acid** toxicity = flushing, hepatotoxicity, hyperglycaemia, hyperuricaemia (UL 35 mg/day).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Vitamin and Trace Mineral Deficiency and Excess" (niacin/pellagra section: metabolism, four Ds, Casal's necklace, treatment, toxicity).
- ▶ **Rook's Textbook of Dermatology, 10e** — "Nutritional Disorders Affecting the Skin" (vitamin B3/niacin: maize & sorghum-leucine mechanisms, Hartnup/SLC6A19, carcinoid, photodistributed dermatitis, Casal's necklace, half-and-half nails, diagnosis and management).
- ▶ **CMDT 2026** — "Nutrition, Nutritional Disorders, & Obesity" (clinical findings, diagnosis, current treatment doses, niacin toxicity).

Coverage note: Corpus coverage is solid across all three texts. The etymology (*pelle agra*) and the attribution of "Casal's necklace" to *Gaspar Casal* are universally accepted standard medicine, included although not explicitly stated in the chapter text (Harrison/Rook's name the sign without the eponymous person). Stated treatment doses differ slightly between sources and are quoted per text rather than reconciled.



Thiamine physiology and deficiency

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

Definition / Introduction — Thiamine (**vitamin B1**) was the first vitamin to be identified. It is a water-soluble B-complex vitamin whose active coenzyme form, **thiamine pyrophosphate (TPP)**, is essential for carbohydrate and branched-chain amino-acid metabolism and for energy generation. Body stores are small and can be depleted within a few weeks of a deficient diet, so thiamine deficiency develops rapidly and produces the classic syndromes of **beriberi** (wet and dry) and **Wernicke–Korsakoff syndrome**. It is a readily treatable, frequently under-diagnosed condition.

Physiology and biochemical functions

- ▶ **Active form:** thiamine is phosphorylated to **thiamine pyrophosphate (TPP)**, the coenzyme responsible for virtually all of its metabolic actions. **Magnesium** is required for activation of thiamine — a key point in management.
- ▶ **Oxidative decarboxylation of α -ketoacids** — TPP is the coenzyme for the dehydrogenase complexes that decarboxylate **pyruvate** (pyruvate dehydrogenase) and **α -ketoglutarate** (α -ketoglutarate dehydrogenase), linking glycolysis to the citric-acid cycle, and for **branched-chain α -ketoacid dehydrogenase**. It is thus essential for **ATP/energy generation**.
- ▶ **Transketolase reaction** — TPP is the coenzyme for transketolase in the **hexose monophosphate (pentose phosphate) shunt**, mediating interconversion of hexose and pentose phosphates and generating ribose and NADPH-linked intermediates.

- ▶ Functionally, TPP is a coenzyme for the **cleavage of carbon–carbon bonds** in carbohydrate and amino-acid metabolism.
- ▶ **Peripheral nerve conduction** — thiamine is postulated to play a role in nerve conduction, although the exact chemical reactions are not established; this underlies the neuropathy of deficiency.
- ▶ **Stores and kinetics** — body stores are small (unlike B12 or vitamin A); thiamine and folate are among the vitamins that deplete within **weeks** on a deficient diet. Therapeutic losses occur with **haemodialysis and diuretics**, which remove water-soluble vitamins.

Dietary sources, requirement and anti-thiamine factors

- ▶ **Median dietary intake** in well-nourished adults is ~2 mg/day; overt deficiency is associated with intake <0.3 mg per 1000 kcal/day. (The conventional adult RDA of ~1.1–1.2 mg/day is standard medicine, not detailed in the corpus.)
- ▶ **Rich sources:** yeast, organ meat, **pork**, legumes, beef, whole grains and nuts. **Milled/polished rice and refined grains contain little thiamine**, so deficiency is commoner in cultures heavily reliant on polished-rice diets.
- ▶ **Food processing/cooking** removes or destroys thiamine (high-heat or long-duration cooking).
- ▶ **Anti-thiamine factors:**
 - **Heat-labile thiaminases** — in **raw fish and shellfish** — enzymatically destroy the vitamin.
 - **Heat-stable polyhydroxyphenols (tannins)** — in **coffee, tea, Brussels sprouts and betel nuts** — inactivate the vitamin; large amounts of tea/coffee can theoretically lower thiamine stores.
- ▶ **Intestinal transport** is via thiamine transporter **ThTR2**; drugs such as **metformin and verapamil** can inhibit it and increase deficiency risk.

Causes / at-risk groups

- ▶ **Inadequate intake** — famine, displaced/refugee populations, disproportionate reliance on highly processed/polished-rice staples (the major global cause).
- ▶ **Alcohol use disorder** — the leading cause in industrialised countries: alcohol **impairs thiamine absorption**, inhibits **synthesis of TPP**, and **increases urinary excretion**.
- ▶ **Chronic illness** — e.g., cancer and chronic protein–calorie undernutrition.
- ▶ **Refeeding / carbohydrate load** — giving a large carbohydrate load (enteral/parenteral glucose) to a thiamine-depleted patient can **precipitate acute deficiency with lactic acidosis**; thiamine must always be replenished when an alcoholic patient is refed.
- ▶ **Bariatric/metabolic surgery** ("**bariatric Wernicke**"), malabsorption, **dialysis**.
- ▶ **Prolonged hyperemesis gravidarum**, anorexia and other eating disorders, poor nutritional status with parenteral glucose.
- ▶ **Chronic diuretic therapy** (hypertension, systolic heart failure) — increased urinary thiamine loss.
- ▶ **Maternal deficiency** → **infantile beriberi** in breast-fed children.
- ▶ May be an overlooked factor in **motor-vehicle accidents/head injury**.

Clinical syndromes of deficiency

- ▶ **Early/subclinical deficiency** — non-specific: **anorexia**, irritability, decreased short-term memory, muscle cramps, paraesthesia. Hard to recognise.
- ▶ **Beriberi** — classically divided into **wet** and **dry**, with considerable overlap; pain and paraesthesia occur in both.

Feature	Wet beriberi	Dry beriberi
Dominant system	Cardiovascular (impaired myocardial energy metabolism + dysautonomia)	Nervous system (peripheral nerves)
Setting	Deficiency + heavy exertion / high carbohydrate intake; may appear after ~3 months	Deficiency + inactivity / low-calorie intake
Features	Peripheral vasodilation → high-output congestive heart failure , enlarged heart, tachycardia , dyspnoea, pulmonary and peripheral oedema with warm extremities (may mimic cellulitis); peripheral neuritis	Symmetric motor + sensory peripheral neuropathy , diminished reflexes; legs > arms ; difficulty rising from a squatting position

- ▶ **Wernicke's encephalopathy (WE)** — the CNS manifestation, classically in alcoholics: the **triad** of (1) **ophthalmoplegia** (weakness of one or more extraocular muscles) with **horizontal nystagmus**, (2) **cerebellar/truncal ataxia**, and (3) **encephalopathy/global confusion (mental impairment)**.
- ▶ **Wernicke-Korsakoff syndrome (WKS)** — WE plus the **amnesic-confabulatory** state: **severe retrograde and anterograde amnesia**, **confabulation** and impaired learning. About **1 in 500** persons with alcohol use disorder develop the full syndrome, particularly those with an inherited **transketolase** abnormality. WKS is typically **under-diagnosed**.
- ▶ **Classic neuropathology** (universally accepted standard medicine): symmetric lesions of the **mammillary bodies**, **periaqueductal grey matter** and **medial (dorsomedial) thalamus**; chronic alcohol use is associated with ventricular enlargement / widened sulci on CT/MRI (often reversible with abstinence).

Diagnosis / investigations

- ▶ **Erythrocyte transketolase activity** measured **before and after** addition of TPP — a **>25% stimulation** (an "activity coefficient" of ≥ 1.25) is abnormal and indicates deficiency.
- ▶ **Direct assay** of thiamine and its phosphate esters in serum/blood by **HPLC**; normal range **~70–180 nmol/L**.
- ▶ **Empiric response** to thiamine is, in practice, often used to support the diagnosis.
- ▶ Other deficiencies (especially **magnesium**, required for thiamine activation) and inflammatory status should be assessed.

Treatment

- ▶ **Acute deficiency with cardiovascular or neurological signs**: **thiamine 200 mg IV three times daily** until no further improvement in acute symptoms, then **oral thiamine 10 mg/day** until recovery is complete (Harrison). **CMDT regimen**: **50–100 mg/day IV** initially, then **5–100 mg/day orally**.

- ▶ **Cardiovascular and ophthalmoplegic improvement** typically occurs **within 24 hours**; other features clear gradually. **Korsakoff psychosis** may be **permanent** or persist for months.
- ▶ **Correct magnesium** concomitantly — thiamine is only effective if magnesium is replete — and give other water-soluble vitamins.
- ▶ **Give thiamine BEFORE a glucose/carbohydrate load** in at-risk patients (alcoholics, refeeding) to avoid precipitating acute deficiency / Wernicke's.
- ▶ **Prognosis (WKS)**: roughly one-fourth resolve immediately, one-fourth over days, and about half achieve only partial or no benefit — emphasising early treatment.
- ▶ **Toxicity**: essentially none from food or supplements; rare hypersensitivity/anaphylaxis after high IV doses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Biochemical roles of thiamine pyrophosphate (TPP)**. Central box "Thiamine → Thiamine pyrophosphate (TPP)" with arrows to: "Pyruvate → Acetyl-CoA (pyruvate dehydrogenase)"; " α -Ketoglutarate → Succinyl-CoA (α -ketoglutarate dehydrogenase)"; "**Branched-chain α -ketoacids** (branched-chain ketoacid dehydrogenase)"; and "**Transketolase — HMP/pentose-phosphate shunt**". Side labels: "**Mg²⁺ required for activation**", "**Energy/ATP generation**".
- ▶ **Diagram 2 — Clinical spectrum of thiamine deficiency**. Root "**Thiamine deficiency**" branching to: "**Wet beriberi** — high-output cardiac failure, oedema"; "**Dry beriberi** — symmetric sensorimotor neuropathy, legs > arms"; "**Wernicke encephalopathy** — ophthalmoplegia + nystagmus, ataxia, confusion"; "**Korsakoff syndrome** — amnesia + confabulation"; "**Infantile beriberi** (maternal deficiency)".

Clinical / Diagnostic significance

- ▶ Always suspect thiamine deficiency in **alcoholics, post-bariatric, hyperemesis, refeeding and chronically ill/parenteral-nutrition** patients.
- ▶ **Wernicke's encephalopathy is a medical emergency** — treat empirically on clinical suspicion; do **not** wait for biochemistry, and **never give glucose first** in an at-risk patient.
- ▶ A patient on diuretics/dialysis with high-output cardiac failure unresponsive to standard therapy — consider **wet beriberi (Shoshin beriberi)**.
- ▶ Functional **erythrocyte transketolase activation coefficient** ≥ 1.25 is the classic confirmatory test.
- ▶ Co-existing **magnesium deficiency** causes apparent thiamine-refractoriness — always correct it.

High-yield exam pointers

- ▶ **Vitamin B1**; active coenzyme = **thiamine pyrophosphate (TPP)**; **Mg²⁺** needed for activation.
- ▶ Coenzyme for **pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase and transketolase (HMP shunt)**.
- ▶ Deficiency threshold **<0.3 mg/1000 kcal/day**; thiamine stores deplete within **weeks**.
- ▶ **Polished-rice diet, alcoholism, thiaminases (raw fish), tannins (tea/coffee/betel)** are key causes.

- ▶ **Wet beriberi** = high-output cardiac failure + oedema; **Dry beriberi** = symmetric peripheral neuropathy (legs > arms).
- ▶ **Wernicke triad** = ophthalmoplegia/nystagmus + ataxia + confusion; add amnesia + confabulation = Korsakoff.
- ▶ Diagnosis: erythrocyte transketolase, activation coefficient ≥ 1.25 ; thiamine 70–180 nmol/L by HPLC.
- ▶ Treatment: parenteral thiamine 200 mg IV TDS (or 50–100 mg/day), give before glucose, replace magnesium; CV/eye signs improve in 24 h, Korsakoff may be permanent.
- ▶ Refeeding an alcoholic with carbohydrate without thiamine can precipitate acute deficiency + lactic acidosis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Vitamin and Trace Mineral Deficiency and Excess" (thiamine physiology, food sources, beriberi, transketolase assay, treatment) and "Alcohol and Alcohol Use Disorders" (Wernicke's and Korsakoff's syndromes, transketolase deficiency, neuroimaging).
- ▶ **CMDT 2026** — "Nutrition, Nutritional Disorders, & Obesity" (wet/dry beriberi distinction, thiamine reference range 70–180 nmol/L, parenteral thiamine regimen and prognosis, magnesium requirement).

Coverage note: The corpus details the clinical syndromes, biochemistry and management thoroughly. The classic neuropathologic localisation of Wernicke's encephalopathy (mammillary bodies, periaqueductal grey, dorsomedial thalamus) and the conventional adult RDA (~1.1–1.2 mg/day) are universally accepted standard internal medicine included for completeness but are not spelt out in these specific chapters.



Total parenteral nutrition

Asked in: Paper I Dec 2023 • Paper I Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Total parenteral nutrition (TPN) is the delivery of a *nutritionally complete admixture* — crystalline amino acids, glucose, lipid emulsion, electrolytes, minerals, vitamins and trace elements — **directly into the bloodstream through a central vein**, when the *entire* nutrient requirement is met intravenously. It is one of three forms of **specialized nutritional support (SNS)** — the others being optimized voluntary nutrition and instrumental enteral nutrition (EN) — and is reserved for patients whose gastrointestinal (GI) tract cannot be used or is insufficient. Because of its high osmolarity (>1200 mOsm/L) and large volume, adult PN must be infused into a central vein.

Indications and contraindications

- ▶ **Core rule:** PN is used when invasive SNS is indicated *and* EN is **impossible, inappropriate, or insufficient** to meet the patient's needs. *If the gut works and is accessible, use it (EN) — PN is the second choice.*

- ▶ The decision to give EN or PN rests on **four factors**: (1) nutrient intake will likely remain inadequate for **many days**; (2) there is important **muscle loss** of any cause; (3) requirements are **increased** (inflammatory diarrhoea, enterocutaneous fistulae/exudates, an inflammatory protein-catabolic state); and (4) reasoned judgement that SNS will **improve clinical outcome or quality of life**.
- ▶ **Typical PN indications (non-functioning / inaccessible gut)**: mechanical **bowel obstruction**, **intestinal ischaemia**, **peritonitis**, **GI haemorrhage** (these four are absolute contraindications to EN), high-output **enterocutaneous fistula**, **short-bowel syndrome**, severe malabsorption, prolonged **paralytic ileus**; also when EN fails to achieve the protein goal after **7–10 days** in the ICU (PN is then added).
- ▶ **Not indicated / cautions**: a functioning accessible gut (EN preferred); terminal illness not mitigated by SNS; **advanced dementia** with little interest in food. PN must wait until the patient is **haemodynamically stabilized** and glucose/electrolyte/acid-base homeostasis is established. Serum triglyceride **>400 mg/dL** is a *relative contraindication* to lipid.

Composition and energy values of TPN

- ▶ Ready-to-use admixtures contain **4–7% hydrated amino acids** and **20–25% glucose**, supplied as **two-chamber** (amino acid + glucose) or **three-chamber** (amino acid + glucose + lipid) bags; vitamins, trace elements and extra electrolytes are added *just before infusion*. Individualized regimens use a **computer-controlled sterile compounder**.

Macronutrient	Form in PN	Energy yield	Key points
Amino acids	crystalline <i>free</i> amino acids	3.3 kcal/g	Hydration lowers density from 4.0 and cuts protein substrate ~17% — 100 g <i>free</i> AA = 83 g <i>protein substrate</i> ; provide all essential AAs
Carbohydrate	dextrose monohydrate	3.4 kcal/g	Main energy source; hydration lowers density from 4.0; initial dose ≤ 200 g/day
Lipid emulsion	soybean / olive / MCT / fish-oil blends	~10 kcal/g	Supplies essential n-6 and n-3 fatty acids ; infuse at ≤ 8 g/h (pure fish-oil slower)

- ▶ **Lipid emulsions**: pure soybean oil is giving way to **mixed emulsions** (medium-chain triglycerides, n-9 monounsaturated, n-3). US options include 80% olive/20% soybean, and a 30% soybean/30% MCT/25% olive/15% fish-oil blend. **Fish oil** may reduce infections and length of stay in the critically ill; soy-based emulsions are best avoided in the **first week** of PN in critical illness.
- ▶ **Minerals / micronutrients**: default doses target a healthy adult and must be individualized. **Multivitamins are unstable** — added to the bag just before delivery; parenteral water-soluble vitamin needs *exceed* oral needs, and **ascorbic acid degrades spontaneously** in PN. **Iron is NOT added to PN** (iron dextran is incompatible with lipid emulsions and may catalyse free-radical formation); give IV iron separately, delayed in suspected infection.
- ▶ **Zinc**: 1 L of secretory diarrhoea loses ~**12 mg zinc**; because of low bioavailability **12 mg parenteral zinc $\approx$ 30 mg oral zinc** (daily requirement ~15 mg).

Daily requirements and prescription targets

Parameter	Target (from chapter)
Total energy expenditure	~36 kcal/kg/day (resting EE ≈ 75% of total)
Protein / amino acids	0.8 g/kg (safe, healthy); 1.2–2.0 g/kg normal body weight (critically ill); minimum 0.65 g/kg
Glucose	start ≤200 g/day; ≤500 g/day (1700 kcal) non-critical; ≤350 g/day (1200 kcal) in acute disease-related malnutrition (ADM)
Lipid	≤50 g/day (500 kcal) in ADM; rate ≤8 g/h
Fluid	≤2 L/day unless abnormally high losses
Glucose control (insulin)	average 80–140 mg/dL (100–180 mg/dL in critically ill diabetics)

- ▶ **Insulin guidance:** regular insulin is added to the bag; ~10 units/100 g glucose for non-diabetic non-catabolic patients and ~20 units/100 g for type 2 diabetics; the next day's dose is based on today's requirement.
- ▶ **Permissive underfeeding** (under-provision of *all* nutrients) must not be confused with **hypocaloric nutrition** (reduced energy but *generous protein*). In fat-sufficient/obese ADM patients, hypocaloric, protein-generous PN is recommended for the first ~2 weeks; matching energy to expenditure early can be *harmful*.

Route, initiation, progression, monitoring and discontinuation

- ▶ **Access:** a dedicated lumen of a central venous catheter (subclavian or PICC preferred). **Jugular and femoral sites are avoided** — hard to keep a dry sterile dressing and higher complication rates.
- ▶ **Initiation:** begin only after haemodynamic stabilization and metabolic/acid-base homeostasis. Initial glucose ≤200 g/day to avoid hyperglycaemia and **refeeding syndrome**. Lipids are usually introduced *after the first week* to cover energy shortfalls (daily or 2–3×/week); check **triglycerides** first.
- ▶ **Monitoring:** urea, creatinine, electrolytes, glucose, **magnesium, phosphate, calcium** and albumin before starting; most monitored for the first few days then **twice weekly**. Capillary glucose several times daily. **Triglycerides and LFTs** at baseline and after PN is running. **Nitrogen balance** to gauge catabolism (urinary urea N: $N \text{ loss (g)} = \text{urea-N}/0.85 + 2$).
- ▶ **Discontinuation:** taper as oral/enteral intake rises; **stop once the patient tolerates one-half to two-thirds of requirement enterally**. Wean by optimizing voluntary nutrition — *do not* abruptly stop hoping to "stimulate appetite" (PN does not cause anorexia). **Cyclic PN** (infused over 12 h/day) reduces cholestasis with prolonged use.

Complications of TPN

Category	Complication	Prevention / management
Catheter	Insertion trauma (e.g., pneumothorax), catheter-related bloodstream infection (higher risk than other CVCs), central vein thrombosis	Aseptic insertion, dedicated port , meticulous dressing care, glycaemic control

Category	Complication	Prevention / management
Metabolic	Hyperglycaemia (most frequent), reactive hypoglycaemia, hypertriglyceridaemia, electrolyte/Mg/PO ₄ /acid-base derangement	Insulin to keep glucose 80–140; taper slowly; TG monitoring; limit lipid rate
Hepatobiliary	Transaminitis (within 2–4 weeks, usually self-limiting), hepatic steatosis (overfeeding), intrahepatic cholestasis (prolonged PN)	Avoid energy overfeeding; cyclic PN
Fluid	Volume overload (raises morbidity/mortality)	Limit fluid to ≤2 L/day; use a compounder; lowest appropriate glucose rate
Other	Toxic overfeeding (PN especially prone); artefactual hyperglycaemia/hyperkalaemia from sampling	Careful prescribing; clean blood draws from a dual-port CVC

- ▶ **Reactive hypoglycaemia** can follow abrupt stoppage of high-glucose, non-insulin PN — prevent by slowing the infusion to **50 mL/h for 1–2 h**, then 10% glucose or an oral snack.
- ▶ **Hypertriglyceridaemia** occurs when lipid infusion outpaces clearance (sepsis, renal failure, diabetes, glucocorticoids, multi-organ failure reduce clearance); risks include pancreatitis and impaired immunity — keep lipid ≤50 g/day in ADM.

Refeeding syndrome

- ▶ Occurs in patients with **successfully adapted starvation-related malnutrition (SRM)** during the first week of repletion when **carbohydrate and sodium are reintroduced too rapidly**.
- ▶ **Mechanism:** carbohydrate → **insulin surge** → (a) antinatriuretic effect → ECF expansion / **refeeding oedema**; (b) intracellular shift driving glucose-6-phosphate/glycogen synthesis → falling serum **phosphate, potassium and magnesium**, impairing skeletal/cardiac muscle and triggering **haemolysis**.
- ▶ **Left heart failure** has three causes: abrupt intravascular volume rise (insulin-mediated Na⁺ retention); increased demand on an **atrophic left ventricle** from a higher resting EE; and myocardial **K⁺/PO₄/Mg²⁺ deficiency**. **Arrhythmias** may occur.
- ▶ **Acute thiamine-deficiency encephalopathy (Wernicke's)** is a devastating but **preventable** complication — can be precipitated even by simple glucose infusion.
- ▶ **Prevention:** restrict sodium, **advance carbohydrate slowly**, start glucose ≤200 g/day, and **measure and replace phosphate, potassium, magnesium and thiamine** frequently.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled algorithm** — "Choosing the route of nutritional support": boxes/arrows reading *Can patient eat enough? → Yes: Optimized voluntary nutrition | No → Is the gut functional and accessible? → Yes: Enteral nutrition (EN) → No (obstruction / ischaemia / peritonitis / GI haemorrhage / high-output fistula / failed EN) → Parenteral nutrition (PN/TPN)***. Label the four EN contraindications and the four-factor decision rule.
- ▶ **Labelled diagram** — "Central venous access for TPN": label **subclavian vein, SVC tip, dedicated PN lumen, sterile dressing**; annotate "high osmolarity >1200 mOsm/L → central vein," "avoid jugular/femoral."

Clinical / Diagnostic significance

- ▶ TPN is **life-saving but high-risk** — EN and PN carry equivalent overall complication rates *except* that PN adds catheter and bloodstream-infection risk and is far more prone to **toxic overfeeding**; hence "*if the gut works, use it.*"
- ▶ **Glycaemic control** (80–140 mg/dL) and **strict catheter asepsis with a dedicated port** are the two interventions that most reduce TPN morbidity.
- ▶ **Baseline electrolytes, Mg, PO₄, Ca, triglycerides and transferrin saturation** identify patients at risk of refeeding syndrome and functional iron deficiency before starting.
- ▶ In critical illness (ADM), early energy provision near/above expenditure is **not beneficial and may be harmful**; favour **hypocaloric, protein-generous** regimens while inflammation is severe.

High-yield exam pointers

- ▶ TPN = complete IV nutrition via a **central vein**; osmolarity >1200 mOsm/L.
- ▶ Energy values: AA 3.3, dextrose monohydrate 3.4, lipid ~10 kcal/g; 100 g AA = 83 g protein substrate.
- ▶ **Initial glucose** ≤200 g/day; ADM ≤350 g; non-critical ≤500 g; **lipid** ≤8 g/h (≤50 g/day in ADM); **fluid** ≤2 L/day.
- ▶ Protein: 0.8 g/kg healthy, 1.2–2.0 g/kg critically ill.
- ▶ **Iron is never added to PN**; multivitamins added just before infusion; **ascorbic acid degrades** in the bag.
- ▶ Most frequent metabolic complication = **hyperglycaemia**; most feared early complication = **refeeding syndrome** (low PO₄/K⁺/Mg²⁺ + thiamine deficiency).
- ▶ **Triglyceride >400 mg/dL** = relative contraindication to lipid; transaminitis appears within 2–4 weeks; cyclic PN (12 h/day) for cholestasis.
- ▶ Stop PN once ½–⅔ of **requirement** is tolerated enterally; wean by optimizing voluntary intake, never abruptly.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 346 "Enteral and Parenteral Nutrition" (Hoffer & Bistrian).

Coverage note: All doses, energy values, osmolarity, insulin ratios and complication data are taken verbatim from Ch 346. The chapter uses the term "PN"; "Total PN" (entire requirement given IV) is the universally accepted clinical term and is used here. A few standard-textbook specifics not stated explicitly in Ch 346 are flagged as universally accepted: the *subclavian/PICC* preference (the chapter states only that jugular/femoral are avoided), *short-bowel syndrome* as a classic PN indication (chapter lists fistulae/malabsorption), the *pneumothorax* example of insertion trauma, and naming acute thiamine-deficiency encephalopathy *Wernicke's*. Peripheral PN is implied by the chapter (high osmolarity mandates a central vein) but not detailed.



Refeeding syndrome

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Re-feeding syndrome (RFS)* is a constellation of potentially fatal **fluid and electrolyte shifts** that occur when nutrition (oral, enteral or parenteral) is reintroduced too rapidly to a previously **starved or severely malnourished** patient. The hallmark biochemical lesion is **hypophosphataemia** developing in the first week of re-feeding, accompanied by **hypokalaemia**, **hypomagnesaemia**, **thiamine depletion**, **sodium-water retention** and **hyperglycaemia**. The clinical consequences—cardiac arrhythmia, heart failure, respiratory failure, neuromuscular and haematological dysfunction—are largely **preventable**, making early recognition of the at-risk patient the single most important step.

Pathophysiology — the metabolic switch and the electrolytes/minerals involved

- ▶ **Starvation (adaptation phase):** prolonged semi-starvation lowers insulin, raises glucagon, and switches metabolism from carbohydrate to **fat and protein (ketone/free-fatty-acid)** fuel. The body downregulates resting energy expenditure and conserves visceral mass at the cost of muscle. Crucially, **total-body phosphate, potassium and magnesium are progressively depleted**, yet *serum* levels are often maintained because these ions leave the shrinking intracellular compartment — masking the deficit.
- ▶ **Re-feeding (anabolic switch):** an abrupt carbohydrate (glucose) load **stimulates insulin secretion**. Insulin drives **glucose, phosphate, potassium and magnesium into cells** for glycogen and protein synthesis, and reactivates the depleted Na^+/K^+ -ATPase pump — unmasking the profound deficits as plasma levels crash.
- ▶ **Phosphate (the cardinal disturbance):** carbohydrate refeeding stimulates **intracellular glucose-6-phosphate and glycogen synthesis**, consuming phosphate to form phosphorylated intermediates and ATP/2,3-DPG, producing severe **redistributive hypophosphataemia**

(movement of phosphate from ECF into cells/bone). This compromises every ATP-dependent process — skeletal and cardiac muscle function and red-cell integrity (haemolysis).

- ▶ **Potassium & magnesium:** insulin-driven cellular uptake produces **hypokalaemia and hypomagnesaemia**; hypomagnesaemia further impairs PTH function and renal K^+/PO_4 handling and is itself arrhythmogenic.
- ▶ **Thiamine (vitamin B₁):** re-introduced carbohydrate sharply increases demand for thiamine as the cofactor of pyruvate dehydrogenase/transketolase; in an already depleted patient this precipitates **acute thiamine-deficiency encephalopathy (Wernicke)** — *a devastating, preventable complication of refeeding, occurring even with simple glucose infusion* (Harrison).
- ▶ **Sodium, water and glucose:** carbohydrate-stimulated insulin has an **antinatriuretic effect**, expanding ECF volume, especially if sodium is given liberally → **refeeding oedema** and, in predisposed patients, **left heart failure**. Excess glucose provision also causes **hyperglycaemia**.

Mineral / factor	Direction in RFS	Mechanism	Main danger
Phosphate	↓↓ (hypophosphataemia)	Insulin-driven cellular uptake + consumption in glucose-6-P/ATP synthesis	ATP depletion → cardiac/respiratory/neuromuscular failure, haemolysis
Potassium	↓ (hypokalaemia)	Insulin shifts K^+ intracellularly via Na^+/K^+ -ATPase	Arrhythmia, weakness, ileus
Magnesium	↓ (hypomagnesaemia)	Cellular uptake; total-body depletion	Arrhythmia, refractory hypo- K /hypo- Ca , tetany
Thiamine (B ₁)	depleted	Carbohydrate load increases coenzyme demand	Wernicke encephalopathy, lactic acidosis
Sodium / water	retained	Insulin antinatriuresis → ECF expansion	Refeeding oedema, congestive heart failure
Glucose	↑ (hyperglycaemia)	Excess CHO load + insulin resistance	Osmotic diuresis, hyperosmolar state, infection

Who is at risk

- ▶ **Core principle:** risk reflects the **degree of antecedent depletion** — the more malnourished/starved the patient, the greater the risk, and (in anorexia data) the degree of refeeding hypophosphataemia correlates with severity of malnutrition on admission more than with the calories prescribed.
- ▶ **Clinical high-risk groups (textbook):**
 - **Anorexia nervosa** and other eating disorders — *particularly high risk*; especially those <70–75% of expected body weight (Sleisenger).
 - **Starvation-related malnutrition (SRM)** and **chronic disease-related malnutrition / cachexia (CDM)** — malignancy, chronic infection (e.g. TB), inflammatory/autoimmune disease, advanced cardiac/renal/hepatic/pulmonary disease.
 - **Chronic alcohol use disorder** (combined phosphate/thiamine/Mg depletion).

- **Prolonged fasting / starvation, hunger strikes, prolonged unfed ICU stay**, post-operative patients fed after long catabolic periods.
- **Malabsorption / high GI losses** — short bowel, fistulae, chronic diarrhoea/vomiting, after bariatric surgery.
- **Elderly with sarcopenia and comorbidities**; uncontrolled diabetes (insulin therapy causes redistributive hypophosphataemia, as in DKA treatment).
- ▶ **NICE high-risk criteria** (standard screening framework — see Coverage note). A patient is **high risk** with **one** of: BMI <16 kg/m²; unintentional weight loss >15% in 3–6 months; little/no intake >10 days; low baseline K⁺, PO₄³⁻ or Mg²⁺. **Or two** of: BMI <18.5 kg/m²; weight loss >10% in 3–6 months; little/no intake >5 days; history of alcohol misuse or drugs (insulin, chemotherapy, antacids, diuretics).

Clinical features / manifestations

- ▶ **Cardiac**: arrhythmias (atrial/ventricular), and **left heart failure** from three mechanisms — abrupt rise in intravascular volume (fluid + insulin-mediated Na⁺ retention), increased cardiac demand on an **atrophic left ventricle** from raised resting energy expenditure, and myocardial K⁺/PO₄/Mg deficiency; sudden cardiac death.
- ▶ **Neuromuscular (hypophosphataemia)**: weakness, lethargy, confusion, dysarthria, dysphagia, ophthalmoplegia, nystagmus, ataxia, paraesthesiae, a **Guillain–Barré-like ascending paralysis**, seizures and coma; serious sequelae (paralysis, seizures) typically at phosphate <0.25 mmol/L (<0.8 mg/dL). Rhabdomyolysis may occur.
- ▶ **Respiratory**: diaphragmatic weakness and reversible respiratory failure at phosphate 0.5–0.8 mmol/L (1.5–2.5 mg/dL) — may impede ventilator weaning.
- ▶ **Haematological**: erythrocyte microspherocytosis and **haemolysis**, impaired oxyhaemoglobin dissociation (low 2,3-DPG), and defective leucocyte/platelet function.
- ▶ **Neurological (thiamine)**: acute **Wernicke encephalopathy** — confusion, ophthalmoplegia, ataxia.
- ▶ **Fluid**: benign **refeeding oedema** (dependent, from renal Na⁺ reabsorption and poor vessel integrity) — must be distinguished from heart failure; **diuretics should not be used**.

Prevention

- ▶ **Identify the at-risk patient before feeding** and check **baseline K⁺, PO₄³⁻, Mg²⁺, Na⁺, glucose** and renal function.
- ▶ **Start low, go slow**: begin at only **5–20 kcal/kg/day** for the first few days (depending on severity), advancing calories cautiously over ~7 days; once past the refeeding window, build to **30–35 kcal/kg/day** and **~1.5 g protein/kg/day** (CMDT). In enteral feeding, at-risk patients warrant conservative initiation/advancement; parenteral nutrition is begun at **about half the estimated energy requirement** (~100–150 g dextrose) for the first 24 h and increased daily as tolerated.
- ▶ **Give thiamine before/with the first feed**: **thiamine 100 mg daily for at least 5–7 days** (and other B vitamins) to prevent Wernicke encephalopathy.
- ▶ **Correct/replace electrolytes proactively** — supplement phosphate, potassium and magnesium and replete deficits, ideally before or alongside calories rather than withholding feed.

- ▶ **Restrict sodium and fluid** to minimise refeeding oedema and cardiac overload; increase carbohydrate provision slowly.
- ▶ **Monitor intensively:** serum **phosphate and magnesium** every 6–12 h (every 6–8 h after feeds begin) during at least the first week; daily weights, fluid balance, heart rate, respiratory rate and signs of failure; **cardiac telemetry** in severely malnourished patients.

Treatment

- ▶ **Slow or temporarily reduce the calorie load** if electrolytes fall, and aggressively **replace phosphate, potassium and magnesium** while continuing thiamine.
- ▶ **IV phosphate replacement** (Harrison) for severe hypophosphataemia <0.75 mmol/L (<2 mg/dL) — neutral sodium/potassium phosphate, initial **0.2–0.8 mmol/kg elemental phosphorus** over 6 h (e.g. 10–50 mmol/6 h); measure serum Ca^{2+} and PO_4^{3-} every 6–12 h; **reduce dose 50%** if creatinine >2.5 mg/dL, correct hypocalcaemia first:

Serum phosphorus	Infusion rate	Duration	Total administered
<0.8 mmol/L (<2.5 mg/dL)	2 mmol/h	6 h	12 mmol
<0.5 mmol/L (<1.5 mg/dL)	4 mmol/h	6 h	24 mmol
<0.3 mmol/L (<1 mg/dL)	8 mmol/h	6 h	48 mmol

- ▶ **Hypokalaemia / hypomagnesaemia:** replace with IV/oral KCl and magnesium; **correct magnesium** as it is required for sustained K^+ and PO_4 repletion and for PTH action.
- ▶ **Refeeding oedema:** elevate the area and **restrict sodium** — *do not give diuretics*; distinguish from true heart failure.
- ▶ **Heart failure / arrhythmia:** supportive management, telemetry, treat the underlying electrolyte deficits.
- ▶ **Glycaemic control:** keep glucose <140 – 180 mg/dL using hypocaloric glucose $\pm$ lipid and minimal-dose insulin.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **"Metabolic switch" flow diagram:** Starvation (low insulin, fat/ketone fuel, depleted total-body $\text{PO}_4/\text{K}^+/\text{Mg}^{2+}$) → **Carbohydrate re-feed** → **↑Insulin** → branches to: (1) cellular uptake of PO_4^{3-} → **hypophosphataemia** → **↓ATP/2,3-DPG**, (2) cellular uptake of K^+ → **hypokalaemia**, (3) cellular uptake of Mg^{2+} → **hypomagnesaemia**, (4) **thiamine consumption** → **Wernicke**, (5) **renal Na^+ /water retention** → **oedema/heart failure**. End-organ boxes labelled: *Cardiac arrhythmia/HF, Respiratory failure, Neuromuscular weakness/seizures, Haemolysis*.
- ▶ **Timeline bar:** Day 0 (start feed) → Days 1–3 (nadir phosphate, highest risk) → Day 7 (refeeding window closes); annotate "monitor $\text{PO}_4/\text{K}^+/\text{Mg}^{2+}$ every 6–12 h" and "thiamine 100 mg/day ×5–7 days".

Clinical / Diagnostic significance

- ▶ **Diagnosis is biochemical + temporal:** a falling phosphate ($\pm \text{K}^+, \text{Mg}^{2+}$) within the **first week** of re-instituted nutrition in an at-risk patient. Serum phosphate at presentation can be normal (masked by prerenal azotaemia/depletion) and falls *hours* after feeding/insulin — so **serial** measurement, not a single baseline, is required.
- ▶ **Investigations:** daily basic metabolic panel, **phosphate and magnesium**, glucose; ECG/telemetry for arrhythmia and QTc; CK if rhabdomyolysis suspected (CK may peak 1–2 days after the phosphate nadir).
- ▶ **Management pearls:** the safe-feeding rule is *prevention beats rescue*; never withhold thiamine waiting for confirmation; replace electrolytes **before** escalating calories; refeeding can occur by **any route** including oral.

High-yield exam pointers

- ▶ **Cardinal lab abnormality** = hypophosphataemia; the triad $\text{PO}_4^{3-} \downarrow, \text{K}^+ \downarrow, \text{Mg}^{2+} \downarrow$ plus thiamine deficiency and fluid overload.
- ▶ **Trigger** = carbohydrate/glucose load → **insulin surge** driving intracellular shift of phosphate/potassium/magnesium.
- ▶ **Highest-risk group** = **anorexia nervosa**, especially <70–75% expected body weight; also chronic alcoholism, prolonged starvation, malabsorption, cancer cachexia, elderly.
- ▶ **NICE one-major criterion:** BMI <16, weight loss >15%/3–6 mo, intake >10 days, or low baseline $\text{K}/\text{PO}_4/\text{Mg}$.
- ▶ **Prevent:** start 5–20 kcal/kg/day, advance over 7 days; **thiamine 100 mg/day ×5–7 days**; restrict sodium; monitor PO_4/Mg 6–12 hourly.
- ▶ **Treat severe hypophosphataemia IV:** 0.2–0.8 mmol/kg elemental P over 6 h; replace K and Mg concurrently.
- ▶ **Refeeding oedema is benign** — **never treat with diuretics**; distinguish from heart failure.
- ▶ **Acute thiamine-deficiency (Wernicke) encephalopathy** can follow plain glucose infusion — always give thiamine first.

- ▶ Serious paralysis/seizures occur at phosphate <0.25 mmol/L (<0.8 mg/dL); respiratory/cardiac failure at 0.5 – 0.8 mmol/L.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Enteral and Parenteral Nutrition" (refeeding syndrome: carbohydrate–insulin mechanism, phosphate/potassium/magnesium deficiencies, left heart failure, thiamine encephalopathy) and "Malnutrition and Nutritional Assessment" (SRM/CDM/ADM and at-risk groups); "Disorders of Bone and Mineral Metabolism / Fluid and Electrolyte Disturbances" (redistributive hypophosphataemia, clinical thresholds, and IV phosphate therapy table).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease** — "Feeding and Eating Disorders" (anorexia nervosa <70 – 75% expected body weight as highest-risk group; refeeding hypophosphataemia; 6–8-hourly electrolyte monitoring, telemetry).
- ▶ **CMDT 2026** — "Nutrition, Nutritional Disorders & Obesity" (definition, 5–20 kcal/kg/day initiation advancing to 30–35 kcal/kg/day and 1.5 g protein/kg/day, thiamine 100 mg/day $\times 5$ – 7 days, refeeding oedema — avoid diuretics).
- ▶ **Coverage note:** The exact numerical NICE 2006 (CG32) **high-risk thresholds** (BMI/weight-loss/days-without-intake cut-offs) are not stated verbatim in this corpus; they are included as universally accepted standard internal-medicine screening criteria. All other figures (calorie ranges, thiamine dose, phosphate thresholds and IV phosphate dosing) are taken directly from Harrison/CMDT/Sleisenger as cited.

♦ ♦ ♦

Miscellaneous

♦ ♦ ♦

Anatomy of the spinal cord

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

Definition / Introduction — The spinal cord is the thin, tubular caudal extension of the central nervous system housed within the bony vertebral canal, carrying — within a small cross-sectional area — almost the entire motor output and sensory input of the trunk and limbs. It originates at the medulla, ends caudally as the **conus medullaris**, and is continued by the fibrous **filum terminale** to the coccyx. Because of this dense packing of ascending and descending tracts, focal cord lesions produce devastating, anatomically predictable syndromes, making cord anatomy the key to bedside lesion localisation.

Gross anatomy and vertebro-segmental relationships

- ▶ **Length & shape:** ~45 cm in the adult male and 42–43 cm in the adult female (Harrison quotes ~46 cm); the vertebral column is ~70 cm, so the cord fills only the upper two-thirds of the canal. It is oval/cylindrical, flattened dorsoventrally.
- ▶ **Enlargements:** the **cervical enlargement** (C5–T1) supplies the upper limbs (brachial plexus) and the **lumbosacral enlargement** (L3–S2) supplies the lower limbs (lumbosacral plexus).

- ▶ **Segments:** 31 segments — 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal — each defined by an exiting ventral (motor) root and an entering dorsal (sensory) root.
- ▶ **Conus & cauda equina:** because the cord grows more slowly than the vertebral column, the adult cord ends at ~L1–L2. *Descent of the conus:* L4–L5 at 20 weeks' gestation → L3 at term → adult L1–L2 by ~2 months of age. Below this, the lumbosacral roots travel a long intrathecal course as the **cauda equina** around the filum terminale — the safe target for lumbar puncture (below L2).
- ▶ **Cord-segment vs vertebral-body mismatch (localisation rule):** the first 7 cervical nerves exit **above** the same-numbered vertebra (8 cervical segments but 7 cervical vertebrae); all lower nerves exit **below** the same-numbered vertebra. Cord segments therefore lie progressively higher than their vertebral spinous processes — upper cervical ≈ same level, lower cervical ≈ 1 higher, upper thoracic ≈ 2 higher, lower thoracic ≈ 2–3 higher, lumbar cord ≈ T10–T12, sacral cord ≈ T12–L1.
- ▶ **External surface landmarks:** ventral (anterior) median fissure, dorsal (posterior) median sulcus (with dorsal median septum), dorsolateral sulcus (dorsal rootlet entry), and a less distinct ventrolateral sulcus (ventral rootlet exit). These divide each half into dorsal, lateral and ventral funiculi.
- ▶ **Coverings:** pia, arachnoid and dura — continuous with cerebral meninges; CSF lies in the subarachnoid space; the cord is anchored to dura by the **dentate (denticulate) ligaments**.

Cross-sectional anatomy — grey matter, Rexed laminae and white funiculi

- ▶ **Grey matter** is centrally placed, **butterfly / H-shaped**, comprising a **dorsal (posterior) horn**, a **ventral (anterior) horn**, and a **lateral horn**, joined across the midline by the grey commissure around the **central canal** (an extension of the fourth ventricle).
- ▶ **Lateral horn / intermediolateral column:** T1–L2 = preganglionic **sympathetic** neurons; S2–S4 intermediolateral zone = preganglionic **parasympathetic** (sacral) outflow.
- ▶ **Anterior horn motor neurons:** large **alpha** motor neurons (extrafusal skeletal muscle) and small **gamma** motor neurons (intrafusal muscle-spindle fibres); somatotopy — flexor neurons dorsal to extensor neurons, limb-girdle laterally, axial muscles medially.
- ▶ **Rexed cytoarchitectonic laminae (I–IX, plus X):**

Lamina	Named nucleus / zone
I	Nucleus posteromarginalis (posterior marginal nucleus)
II	Substantia gelatinosa of Rolando (pain/temperature)
III–IV	Nucleus proprius (nucleus proprius dorsalis)
V	Nucleus reticularis (zone anterior to lamina IV)
VI	Base of dorsal horn
VII	Intermediate zone — contains nucleus dorsalis of Clarke + intermediolateral column
VIII	Ventral horn interneuronal zone

Lamina	Named nucleus / zone
IX	Anterior horn cell columns (alpha/gamma motor neurons)
X	Dorsal & ventral grey commissure (peri-central canal)

- The **zone (tract) of Lissauer** (posterolateral tract) caps the dorsal horn, carrying short ascending/descending pain fibres.

Ascending (sensory) tracts

- General rule: **dorsal columns and spinocerebellar/pyramidal tracts** lie **ipsilateral**; the **spinothalamic tracts** ascend **contralateral** to the body half they serve (decussating in the cord).

Ascending tract	Modality	Decussation & key features
Dorsal columns — <i>fasciculus gracilis</i> (Goll) medial = lower limb; <i>fasciculus cuneatus</i> (Burdach) lateral = upper limb	Joint position, vibration, fine/discriminative touch, two-point discrimination	1st-order fibres ascend uncrossed → synapse in gracile/cuneate nuclei (medulla) → 2nd-order internal arcuate fibres cross → medial lemniscus → VPL thalamus
Lateral spinothalamic (neospinothalamic)	Sharp, localised pain and temperature	2nd-order neuron decussates via ventral white commissure , ascends 1–2 segments higher ; lamination — cervical fibres dorsomedial, sacral fibres ventrolateral (basis of <i>sacral sparing</i>)
Ventral (anterior) spinothalamic	Light (crude) touch & pressure	Crosses in ventral white commissure → VPL
Spinoreticulothalamic (paleospinothalamic)	Poorly localised, dull/aching pain	Short axons synapse in brainstem reticular formation → intralaminar thalamic nuclei
Dorsal & ventral spinocerebellar	Unconscious proprioception, lower half of body	To cerebellum (dorsal via Clarke's column)
Cuneocerebellar & rostromcerebellar	Unconscious proprioception, upper half of body	To cerebellum

Descending (motor) tracts

Descending tract	Origin	Course / location in cord	Function
Lateral corticospinal (pyramidal)	Brodmann area 4 (MI, precentral), area 6 (premotor/SMA), areas 3,1,2 (postcentral), 5 & 7 (sup. parietal), cingulate	~90% of ~1 million pyramidal fibres decussate at the medullary pyramids → lateral funiculus ; terminate laminae IV–IX	Skilled distal-limb movement; inhibits antigravity (antagonist) muscles
Ventral (anterior) corticospinal	Same cortical areas	~10% uncrossed , ventral funiculus (cross in cord, lamina VIII)	Axial/proximal control

Descending tract	Origin	Course / location in cord	Function
Rubrospinal (corticorubrospinal)	Red nucleus (input from cortical areas 4, 6, 1–3)	Crosses, descends in lateral funiculus	Distal flexor tone
Vestibulospinal	Lateral & medial vestibular nuclei	Lateral/ventral funiculus (uncrossed)	Facilitates antigravity (extensor) tone, posture
Lateral & medial reticulospinal	Medullary & pontine reticular formation	Ventrolateral/ventral funiculus	Modulate axial/proximal tone (medial facilitates, lateral inhibits)
Tectospinal	Superior colliculus	Ventral funiculus	Reflex head/neck orientation to visual/auditory stimuli

Blood supply and venous drainage

- **Single anterior spinal artery** (from paired vertebral branches) runs in the ventral median fissure and supplies the **anterior two-thirds** of the cord (anterior + lateral horns, central grey, corticospinal & spinothalamic tracts) via **sulcal (sulco-commissural) arteries**.
- **Paired posterior spinal arteries** (from vertebral or PICA) supply the **posterior one-third** — the dorsal columns and dorsal horns.
- **Radiculomedullary (radicular) feeders** from the aorta reinforce the cord segmentally. The dominant lumbar feeder is the **great anterior radicular artery of Adamkiewicz** (*artery of the lumbar enlargement*), most often entering on the **left between T9 and T12** ($\approx 75\%$).
- **Three longitudinal vascular regions**: upper/cervicothoracic (richly supplied), the **intermediate/mid-thoracic region** ($\sim T4-T8$) — the **relatively poorly perfused "watershed" zone**, and the richly supplied lower thoracolumbosacral region. The watershed and the anterior territory (high metabolic demand of anterior horn cells) are most vulnerable to ischaemia.
- **Veins** mirror the arteries (anteromedial/anterolateral and posterior trunks) and drain into the valveless **internal vertebral venous plexus (Batson's plexus)** — a route for haematogenous spread of pelvic/prostatic tumours and infection to the spine.

Clinically important cord syndromes (localisation pay-off)

Syndrome	Tracts involved	Hallmark signs
Complete transection (transverse myelopathy)	All tracts at one level	Loss of all modalities + UMN paraplegia/quadruplegia below; autonomic loss; initial spinal shock (flaccid areflexia)
Brown-Séquard (hemicord)	Hemisecion	Ipsilateral UMN weakness + dorsal-column loss; contralateral pain/temperature loss (1–2 levels below); typically extramedullary

Syndrome	Tracts involved	Hallmark signs
Central cord	Decussating spinothalamic ± anterior horns	"Cape/suspended" dissociated loss of pain/temperature with preserved touch/position; arms > legs weakness; syringomyelia, hyperextension injury
Anterior cord / anterior spinal artery occlusion	Anterior two-thirds	Para/quadriplegia + dissociated pain/temperature loss with preserved vibration & position (dorsal columns spared)
Posterolateral column (subacute combined degeneration)	Dorsal + lateral columns	Sensory ataxia, +Romberg, vibration/position loss + UMN signs — B12, copper, HIV, nitrous oxide, HTLV-1 (HAM/TSP)
Posterior column (tabes dorsalis)	Dorsal columns/roots	Sensory ataxia, lightning pains, Argyll Robertson pupils, Charcot joints
Foramen magnum	Decussating pyramidal fibres	"Around-the-clock" limb involvement, crural paresis, suboccipital pain

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Spinal cord cross-section (composite "tract map"):** draw the H-shaped grey matter and label — dorsal (posterior) horn, ventral (anterior) horn, lateral horn (intermediolateral column), central canal, ventral median fissure, dorsal median sulcus, dorsal root + ganglion, ventral root. On the white matter label ascending tracts (left): fasciculus gracilis, fasciculus cuneatus, dorsal & ventral spinocerebellar tracts, lateral spinothalamic, ventral spinothalamic (show somatotopy C→T→L→S with sacral outermost in spinothalamic, lateral in dorsal columns); and descending tracts (right): lateral corticospinal, ventral corticospinal, rubrospinal, vestibulospinal, reticulospinal, tectospinal.
- ▶ **Vascular supply diagram:** label anterior spinal artery (anterior 2/3), paired posterior spinal arteries (posterior 1/3), anterior sulcal artery, circumflex (perimedullary) arteries, radiculomedullary feeders / artery of Adamkiewicz.

Clinical / Diagnostic significance

- ▶ **Lesion localisation:** a sharply demarcated sensory level plus a band of segmental signs marks the upper border of a cord lesion; remember sensory level is set ~1–2 segments below a unilateral spinothalamic lesion (crossing fibres). Useful landmarks: **nipple = T4, umbilicus = T10, Beevor's sign = T9–T10 lesion.**
- ▶ **Conus medullaris vs cauda equina:** conus → early/symmetric saddle anaesthesia (S3–S5), prominent bladder/bowel/sexual dysfunction, lax anal tone, absent bulbocavernosus (S2–S4) and anal (S4–S5) reflexes, relatively preserved power; cauda equina → asymmetric radicular pain, leg weakness/areflexia, later sphincter involvement.
- ▶ **Intramedullary vs extramedullary:** intramedullary lesions give poorly localised burning pain and sacral sparing, late corticospinal signs; extramedullary lesions give early radicular pain, early sacral sensory loss and spastic paraparesis.

- ▶ **Investigation of choice: MRI with gadolinium** of the whole spine excludes treatable **compressive myelopathy** (metastasis, epidural abscess/haematoma, disc, spondylosis) before intrinsic causes. **Horner's syndrome** signals a cervicothoracic (T1) lesion; autonomic dysreflexia complicates lesions above T6.

High-yield exam pointers

- ▶ 31 segments: 8C, 12T, 5L, 5S, 1Co; cervical enlargement C5–T1, lumbosacral L3–S2.
- ▶ Adult cord ends at L1–L2; LP done **below L2** through the cauda equina.
- ▶ **8 cervical segments but 7 cervical vertebrae** — explains the exit rule and cord-vertebra mismatch.
- ▶ **Gracilis (Goll) = medial/leg; cuneatus (Burdach) = lateral/arm**; dorsal columns cross in the medulla.
- ▶ **Spinothalamic decussates in the cord** (ventral white commissure), ascends 1–2 levels above entry; **sacral fibres lie outermost** → *sacral sparing* in intramedullary lesions.
- ▶ ~90% of corticospinal fibres decussate at the pyramids → lateral corticospinal tract.
- ▶ **Anterior spinal artery = anterior 2/3; posterior spinal arteries = posterior 1/3**; artery of Adamkiewicz (left, T9–T12) feeds the lumbar enlargement; T4–T8 = **watershed zone**.
- ▶ **Batson's (internal vertebral venous) plexus** — valveless route for pelvic/prostate metastasis.
- ▶ **Lateral horn**: sympathetic T1–L2, parasympathetic S2–S4.
- ▶ Classic syndromes: **Brown-Séquard**, **central cord (dissociated/cape)**, **anterior cord (ASA)**, **SACD**, **tabes dorsalis** — know the tract pattern for each.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Diseases of the Spinal Cord" (S.L. Hauser): cord anatomy relevant to clinical signs, segment–vertebra relationships, tract map (Fig. 453-1), and cord syndromes.
- ▶ **Brazis, Masdeu & Biller** — *Localization in Clinical Neurology*, Chapter 5 "Spinal Cord": gross & cross-sectional anatomy, Rexed laminae, detailed ascending/descending tract tables, arterial supply (anterior/posterior spinal arteries, artery of Adamkiewicz, vascular regions), venous drainage (Batson plexus), and the spinal cord syndromes.
- ▶ Coverage note: the spec flags Harrison's anatomy as brief — the depth (laminae, tract tables, blood supply, named nuclei) is drawn from Brazis Ch. 5, which covers this purely-anatomical topic comprehensively; no fabrication required.



Autophagy mechanism in health and disease

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

Definition / Introduction — **Autophagy** ("self-eating") is an evolutionarily conserved, lysosome-dependent **catabolic process** by which cytoplasmic constituents — long-lived and misfolded proteins, protein aggregates, damaged organelles, lipid droplets and even intracellular microbes — are sequestered, delivered to the lysosome and degraded, with recycling of the resulting amino acids, fatty acids and nucleotides. Together with the **ubiquitin–proteasome system (UPS)** it forms the two major degradative arms of the cellular **proteostasis network**. At basal levels it provides continuous **quality control**; it is sharply upregulated by starvation, hypoxia, oxidative stress and infection to liberate nutrients and remove damage. Its discovery earned *Yoshinori Ohsumi* the 2016 Nobel Prize in Physiology or Medicine.

Types of autophagy

Type	How cargo reaches the lysosome	Key features
Macroautophagy	Cargo enclosed by a <i>de novo</i> double-membrane phagophore → autophagosome → fuses with lysosome (autolysosome)	The major, best-studied form; "autophagy" usually denotes this; can be bulk or selective
Microautophagy	Direct invagination/engulfment of cytosol by the lysosomal membrane	Constitutive, bulk turnover; no autophagosome
Chaperone-mediated autophagy (CMA)	<i>Hsc70</i> recognises a KFERQ motif and translocates the protein across the lysosomal membrane via LAMP-2A	Highly selective, single-protein, no vesicle; degrades α -synuclein (along with macroautophagy)

Molecular machinery and regulation

- **Stages of macroautophagy** (sequential): induction → **nucleation** (phagophore/isolation-membrane formation) → **elongation** (autophagosome engulfs cargo) → **fusion** with lysosome (autolysosome) → **degradation** by acid hydrolases → recycling of building blocks.
- **Core ATG (autophagy-related) machinery**: the *ULK1* kinase complex initiates; the **Beclin-1 / class III PI3-kinase (VPS34)** complex nucleates the membrane; two ubiquitin-like conjugation systems — the **ATG12–ATG5–ATG16L1** complex and lipidation of **LC3 (ATG8)** to **membrane-bound LC3-II** — drive elongation and closure (LC3-II is the standard autophagosome marker).
- **Nutrient sensing — the master switches** (Harrison, *Biology of Aging*):
 - **mTORC1** (activated by amino acids, insulin/IGF-1 and growth factors in the fed state) **inhibits** autophagy; its inactivation by dietary restriction or **rapamycin/sirolimus** reduces protein synthesis and **increases autophagy**.
 - **AMP-activated protein kinase (AMPK)**, activated by a low energy charge (high AMP), exercise and **metformin**, **promotes** autophagy.
 - **Sirtuins (SIRT1/NAD-dependent)**, **FGF21**, **spermidine** and **resveratrol** also induce autophagy and extend lifespan.

- ▶ **Selective autophagy** (cargo-specific): **mitophagy** (removal of damaged mitochondria, governed by *PINK1/Parkin*); **xenophagy** (capture and lysosomal killing of intracellular bacteria, with cargo tagged by ubiquitin and **galectins**); **aggrephagy** (clearance of ubiquitinated protein aggregates); ER-phagy; ferritinophagy.

Physiological roles in health

- ▶ **Proteostasis / quality control**: recognises and degrades misfolded proteins, large aggregates and condensates that escape or overwhelm the UPS (the autophagy–lysosomal pathway is "highly responsive to nutrient deprivation and damage").
- ▶ **Energy and nutrient homeostasis**: during fasting/starvation it recycles macromolecules to maintain the amino-acid and ATP supply.
- ▶ **Organelle turnover**: mitophagy replenishes the mitochondrial pool and limits ROS generation; also clears damaged ER and peroxisomes.
- ▶ **Innate immunity**: xenophagy is a *cell-autonomous* defence — bacterial invasion triggers sequestration of the pathogen in an autophagosome and its destruction on lysosomal fusion; NOD2 sensing of bacteria activates autophagy.
- ▶ **Neuronal survival**: particularly important to neurons, which cannot dilute aggregates by division.
- ▶ **Longevity, development, antigen presentation and tissue remodelling**.

Autophagy in disease

System / disease	Link to autophagy
Neurodegeneration (AD, PD, FTD, HD)	Autophagy is impaired , so toxic aggregates accumulate — $A\beta$ / τ , α -synuclein (Lewy bodies), polyglutamine <i>mutant huntingtin</i> , <i>SOD1</i> , <i>TDP-43</i> ; in HD there is a failure of cargo recognition ; <i>PINK1/Parkin</i> mitophagy defects in autosomal-recessive PD; <i>GBA</i> (glucocerebrosidase) mutations impair lysosomal clearance of α -synuclein
Cancer	Double-edged : early, it is <i>tumour-suppressive</i> (a form of programmed cell death/"type II", limiting genomic instability and ROS); in established tumours it is <i>pro-survival</i> , enabling cells to withstand hypoxia and nutrient stress and conferring chemoresistance ; cytotoxic agents can induce autophagy
Crohn's disease / IBD	Susceptibility loci impair autophagy and bacterial handling: <i>ATG16L1</i> , <i>IRGM</i> (immunity-related GTPase M), <i>NOD2</i> , <i>LRRK2</i>
Aging	"Disabled macroautophagy" and loss of proteostasis are hallmarks of aging ; pro-longevity interventions (rapamycin, metformin, spermidine, resveratrol, caloric restriction) converge on the autophagic machinery
Storage / metabolic myopathy & cardiomyopathy	Danon disease — X-linked <i>LAMP2</i> deficiency → defective autophagosome–lysosome fusion → autophagic-vacuole accumulation → HCM + ventricular pre-excitation/WPW + skeletal myopathy ; Pompe disease (GSD II) — autosomal-recessive deficiency of lysosomal acid α -glucosidase (acid maltase) → lysosomal glycogen and autophagic build-up

System / disease	Link to autophagy
Drug-induced autophagic vacuolar myopathy/neuropathy	Amphiphilic cationic drugs — chloroquine, hydroxychloroquine, amiodarone — and colchicine cause painless proximal weakness with autophagic vacuoles on muscle (and nerve) biopsy
Infection	Pathogens (e.g., intracellular bacteria, HIV) subvert or are targeted by autophagy; xenophagy is a key host defence
Heart failure / cardiometabolic	Enhanced autophagy is among the proposed cardiorenal-protective mechanisms of SGLT2 inhibitors

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Macroautophagy pathway (flow diagram).** Labels: *Cargo* (damaged mitochondrion / protein aggregate / intracellular bacterium) → *Phagophore* (isolation membrane) → *Autophagosome* (double membrane, LC3-II on membrane) → *Lysosome* → *Autolysosome* → *Acid hydrolases* → *Recycled amino acids / fatty acids*. Add regulators: *mTORC1* — *inhibits* (active when fed); *AMPK* / *starvation* / *rapamycin* — *activate*; *ULK1 complex*; *Beclin-1* / *VPS34 (PI3K-III)*; *ATG12-ATG5-ATG16L1*.
- ▶ **Health-vs-disease balance.** A central "Autophagy" box; left arm *Health* (proteostasis, organelle quality control, innate immunity/xenophagy, longevity) and right arm *Disease* with an "impaired/dysregulated autophagy" arrow to *neurodegeneration, cancer, Crohn's disease, Danon/Pompe myopathy*.

Clinical / Diagnostic significance

- ▶ Muscle biopsy showing autophagic vacuoles → think **Danon, Pompe, or chloroquine/hydroxychloroquine/amiodarone/colchicine toxicity** (a treatable, reversible cause).
- ▶ A young male with hypertrophic cardiomyopathy plus a WPW/pre-excitation ECG pattern strongly suggests **Danon disease (LAMP2)** — pre-excitation is ~5× commoner than in idiopathic/familial HCM; gene therapy delivering functional LAMP2 is in trials.
- ▶ **mTOR inhibitors (sirolimus, everolimus)** used in transplantation and oncology act in part by inducing autophagy.
- ▶ **Chloroquine/hydroxychloroquine inhibit autophagic flux** (block lysosomal acidification) — the rationale for combining them with chemotherapy in trials.
- ▶ **Pharmacologic autophagy induction** (rapamycin, metformin, spermidine, caloric restriction) is being explored for **aging and neurodegeneration**.
- ▶ Enzyme replacement (Pompe) and emerging gene therapy (Danon) directly target the lysosomal/autophagy defect.

High-yield exam pointers

- ▶ Autophagy = **lysosomal** degradation; UPS = **proteasomal** — together they constitute the **proteostasis network**.
- ▶ **Three types:** macroautophagy, microautophagy, chaperone-mediated autophagy (*Hsc70 / KFERQ / LAMP-2A*).

- ▶ **mTORC1 inhibits; AMPK and starvation activate** — both converge on the *ULK1* complex.
- ▶ **Stages:** phagophore → autophagosome → autolysosome; **LC3-II** = autophagosome marker.
- ▶ **Yoshinori Ohsumi** — **2016 Nobel Prize** for autophagy mechanisms.
- ▶ **Danon** = **LAMP2** (defective autophagosome–lysosome fusion); **Pompe** = **acid maltase deficiency** (GSD II).
- ▶ **Crohn's disease autophagy genes:** *ATG16L1*, *IRGM*, *NOD2*, *LRRK2*.
- ▶ **Cancer** = a **double-edged sword** (tumour-suppressive early, pro-survival/chemoresistant later).
- ▶ **Chloroquine/HCQ, amiodarone, colchicine** → autophagic vacuolar myopathy; chloroquine/HCQ are **autophagy inhibitors**.
- ▶ Impaired autophagy underlies aggregate accumulation in **AD, PD, FTD, HD**; *PINK1/Parkin* defects impair **mitophagy**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Protein Quality Control and Cellular Stress Responses*" (proteostasis network, autophagy–lysosomal pathway vs UPS); "*Cancer Cell Biology*" and "*Principles of Cancer Treatment*" (autophagy as programmed cell death and drug-induced autophagy); "*Biology of Aging*" (loss of proteostasis, mTOR/AMPK/SIRT1, rapamycin/metformin/spermidine); "*Molecular Mechanisms of Microbial Pathogenesis*" (xenophagy/innate immunity, phagophore–autophagosome stages); "*Inflammatory Bowel Disease*" (*ATG16L1*, *IRGM*, *NOD2*, *LRRK2*); "*Glycogen Storage Diseases and Other Inherited Disorders of Carbohydrate Metabolism*" (Pompe/GSD II, Danon/LAMP2); "*The Cardiomyopathies*" (Danon, LAMP2 HCM); "*Disorders of the Autonomic Nervous System... / Peripheral Neuropathy*" and "*Muscular Dystrophies and Other Muscle Diseases*" (chloroquine/hydroxychloroquine/amiodarone/colchicine autophagic vacuolar neuropathy and myopathy); "*Heart Failure: Pathophysiology and Diagnosis*" (SGLT2-inhibitor effects); "*Neurodegenerative Disorders*" (impaired autophagy in AD/PD/FTD/HD, mitophagy, α-synuclein/GBA).
- ▶ **Coverage note:** The spec flags this topic as a *gap* — Harrison 22e has **no dedicated autophagy chapter**, so the answer is synthesised across the chapters above. Harrison explicitly supports the named disease links and the macroautophagy/chaperone-mediated terminology, the phagophore→autophagosome→autolysosome stages, mTOR/AMPK regulation, and *ATG16L1/IRGM/NOD2/LRRK2*. A few standard cell-biology specifics not spelled out in this corpus — *microautophagy*, *ULK1*, *Beclin-1/VPS34*, *LC3/ATG8 (LC3-II)* and *ATG12–ATG5 conjugation systems*, and the *Ohsumi 2016 Nobel Prize* — are included as universally accepted textbook biology and are accurate.



Autosomal inherited diseases

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

Definition / Introduction — *Autosomal inherited diseases* are monogenic (single-gene, *Mendelian*) disorders caused by a pathogenic variant in a gene residing on one of the 22 **autosomes** (chromosomes 1–22), as distinct from genes on the X or Y sex chromosomes. Because autosomes are present in two homologous copies and segregate randomly at meiosis, both sexes are affected with equal frequency. Depending on whether one or both alleles must be mutated to express the phenotype, transmission is **autosomal dominant (AD)** or **autosomal recessive (AR)**. Of all human monogenic disorders, ~65% are AD, ~25% are AR, and ~5% are X-linked.

Basic genetic terminology

- ▶ **Allele** — an alternative form of a gene at a given locus; the normal/common allele is *wild type*. Each person carries two alleles per autosomal locus (one maternal, one paternal).
- ▶ **Homozygous** — identical alleles at a locus; **heterozygous** — different alleles; **compound heterozygote** — two *different* mutant alleles at the same locus (common in AR disease, e.g. CFTR).
- ▶ **Genotype vs phenotype** — the genetic constitution vs the observed trait.
- ▶ **Mendelian transmission** follows the principles of allelic segregation; the mode of inheritance is established by **pedigree analysis** using standard symbols.

Autosomal dominant (AD) disorders

- ▶ **Definition** — a pathogenic variant in a *single* allele is sufficient to cause disease; the affected individual is usually heterozygous (Aa).
- ▶ **Pedigree characteristics:**
 - Disease appears in *successive generations* (*vertical transmission*); it does **not** appear in the offspring of unaffected individuals (no generation-skipping, unless reduced penetrance).
 - **Males and females affected equally**; *male-to-male* (father→son) transmission is possible (distinguishes from X-linked).
 - Each child of an affected (heterozygous) parent has a **50% risk** of being affected (alleles segregate randomly at meiosis).
 - Unless a new germline mutation has occurred, an affected child has an affected parent; children with a normal genotype do not transmit the disease.
- ▶ **Molecular mechanisms** (varied, unlike the uniform loss-of-function of AR):
 - **Gain of function** — constitutive activation (e.g. *RET* in MEN 2).
 - **Dominant-negative effect** — mutant protein interferes with the wild-type product within a multimeric complex (e.g. type I collagen *COL1A1/COL1A2* in osteogenesis imperfecta; mutant thyroid hormone receptor β).
 - **Haploinsufficiency** — one normal allele cannot maintain a normal phenotype (common with transcription-factor and rate-limiting enzyme genes, e.g. heme-synthesis enzymes in porphyria).

- **Examples:** Huntington's disease, myotonic dystrophy, Marfan's syndrome, neurofibromatosis types 1 and 2, von Hippel–Lindau disease, MEN 1 and MEN 2, hypertrophic cardiomyopathy, autosomal dominant polycystic kidney disease (*PKD1/PKD2*), Holt–Oram syndrome (*TBX5*), achondroplasia, familial hypercholesterolaemia, osteogenesis imperfecta.

Autosomal recessive (AR) disorders

- **Definition** — the disease is expressed only when *both* alleles are mutated; the affected individual (of either sex) is a **homozygote** or a **compound heterozygote**. Mutated alleles typically cause complete or partial **loss of function** and frequently involve metabolic enzymes, receptors, or signalling proteins.
- **Pedigree characteristics:**
 - Disease typically appears in a *single sibship* without affected ancestors (*horizontal pattern*).
 - Usually both parents are unaffected **heterozygous carriers**; for a carrier × carrier mating, offspring risk = **25% affected : 50% carrier : 25% unaffected** (Punnett 1:2:1).
 - **Consanguinity** raises the risk because relatives share alleles (identity by descent); AR disorders are also commoner in geographically/genetically isolated populations (restricted gene pool).
 - **Pseudodominance** — when an affected homozygote mates with a heterozygous carrier, 50% of children are affected, mimicking dominant (vertical) transmission.
 - New mutations rarely manifest in AR disease because they usually produce an asymptomatic carrier state.
- **Heterozygote (carrier) state** — usually clinically silent, but may show subtle phenotypes under stress (e.g. sickle crises in sickle trait during dehydration/hypoxia). A **selective heterozygote advantage** explains the high frequency of some AR alleles — sickle-cell heterozygotes are relatively protected from *Plasmodium* (malaria), maintaining the mutant allele in malaria-endemic regions.
- **Examples:** cystic fibrosis (*CFTR*, ΔF508), sickle-cell anaemia (β-globin Glu6Val/E6V), β-thalassaemia, phenylketonuria, Friedreich's ataxia, Wilson's disease, haemochromatosis (*HFE*), congenital adrenal hyperplasia (21-hydroxylase deficiency), autosomal recessive polycystic kidney disease (*PKHD1*, fibrocystin).

AD vs AR — comparison

Feature	Autosomal dominant	Autosomal recessive
Alleles needed	One mutant allele (heterozygous)	Both alleles mutant (homozygote/compound het)
Pedigree pattern	Vertical, successive generations	Horizontal, single sibship
Sex distribution	Equal	Equal
Risk to offspring	50% (affected × normal)	25% (carrier × carrier)
Parental consanguinity	Not characteristic	Often increased

Feature	Autosomal dominant	Autosomal recessive
Typical mechanism	Gain of function / dominant-negative / haploinsufficiency	Loss of function (enzymes, receptors)
Common confounder	Reduced penetrance, variable expressivity, new mutation	Pseudodominance, carrier state
Examples	Huntington's, Marfan's, NF1, ADPKD, HCM	CF, sickle-cell, thalassaemia, PKU, Wilson's

Trinucleotide (nucleotide) repeat expansion disorders

Several autosomal diseases arise from **dynamic mutations** — expansion of a tandem nucleotide repeat above a critical threshold. The expanded DNA is unstable and tends to lengthen further at each cell division; longer repeats correlate with greater severity and earlier onset (**anticipation**). A *premutation* is a small intermediate increase.

Disease	Locus	Repeat	Normal/ Disease length	Inheritance	Gene product
Huntington's disease	4p16.3	CAG	6–34 / 37–180	AD	Huntingtin
Myotonic dystrophy (DM1)	19q13.3 2	CTG	5–30 / 200–1000	AD (variable penetrance)	Myotonin protein kinase (DMPK)
Spinocerebellar ataxias (SCA1, 2, 3, 6, 7, 12)	various	CAG	e.g. SCA1 6–39 / 40–88	AD	Ataxins, etc.
Dentatorubral-pallidoluysian atrophy (DRPLA)	12p13.3 1	CAG	7–23 / 49–75	AD	Atrophin 1
Friedreich's ataxia	9q21.11	GAA	7–22 / 200–900	AR	Fratxin

(Fragile X and spinobulbar muscular atrophy are X-linked and are not autosomal.)

Factors modifying autosomal inheritance

- **Incomplete (reduced) penetrance** — proportion of mutation carriers expressing the phenotype is <100%; dominant pedigrees may *skip generations* via unaffected transmitting carriers (e.g. HCM from myosin-binding protein C variants). Penetrance is often *age-dependent* (Huntington's, familial ALS).
- **Variable expressivity** — same variant produces a different severity/organ pattern in different individuals (e.g. MEN 1, cystic fibrosis, neurofibromatosis), influenced by **modifier genes** and environment.
- **Allelic heterogeneity** — many different variants in one gene cause the same phenotype (β -thalassaemia; ~2000 *CFTR* variants).
- **Locus (non-allelic) heterogeneity** — similar phenotype from variants at *different* loci (osteogenesis imperfecta from *COL1A1* or *COL1A2*; familial HCM from many sarcomeric genes).

- ▶ **Phenotypic heterogeneity / pleiotropy** — different phenotypes from variants in one gene (laminopathies from *LMNA*; *FGFR2* → Crouzon's or Pfeiffer's syndrome).
- ▶ **Phenocopy** — a non-genetic condition mimicking the inherited disorder (toxin-induced chorea resembling Huntington's).
- ▶ **New (de novo) mutations & paternal age** — many AD cases are new germline mutations; rates rise with advanced **paternal age** (achondroplasia, Marfan's, neurofibromatosis). **Gonadal (germline) mosaicism** can cause recurrence in siblings despite unaffected parents.
- ▶ **Knudson "two-hit" mechanism** — in dominantly inherited cancer-predisposition syndromes (retinoblastoma, MEN 1, NF1/NF2), an inherited germline loss of one tumour-suppressor allele is followed by somatic inactivation (loss of heterozygosity) of the second — dominant at the pedigree level but biallelic loss in the tumour.
- ▶ **Genomic imprinting / uniparental disomy** — parent-of-origin-dependent expression on autosomes: **Prader-Willi syndrome** (loss of *paternal* 15q) vs **Angelman's syndrome** (loss of *maternal* 15q); **Beckwith-Wiedemann syndrome** (dysregulated *IGF2* at 11p); Albright's hereditary osteodystrophy (*GNAS1*).
- ▶ **Mosaicism** — postzygotic somatic mutation (e.g. activating *GSα* in McCune-Albright syndrome).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **AD vs AR pedigree charts** — draw two 3-generation pedigrees using standard symbols. Labels: *square = male, circle = female, filled = affected, half-filled = carrier, horizontal line = mating, double line = consanguineous union, arrow = proband*. For **AD**: affected individuals in every generation, male-to-male transmission, ~50% offspring affected. For **AR**: affected only in one sibship, unaffected carrier parents, consanguineous loop.
- ▶ **Punnett (segregation) square** — $Aa \times Aa$ cross giving $1 AA : 2 Aa : 1 aa$ (AR 25% affected); and $Aa \times aa$ cross giving 50% affected (AD / pseudodominance). Label genotype ratios and risk percentages.

Clinical / Diagnostic significance

- ▶ **Family history & pedigree** are the essential first step — record first-degree relatives, ethnicity, ages, consanguinity, and update periodically because of age-dependent penetrance.
- ▶ **Genetic testing** — direct DNA sequencing (PCR-based), targeted variant panels, **multiplex gene panels** (useful for locus-heterogeneous diseases such as HCM, Charcot-Marie-Tooth), and **whole-exome/whole-genome sequencing (WES/WGS)** for undiagnosed syndromes; large rearrangements via FISH, MLPA, cytogenomic microarray (CNV detection).
- ▶ **Interpretation caveats** — allelic heterogeneity means a negative panel does not exclude disease; beware the **variant of uncertain significance (VUS)**.
- ▶ **Counselling & prevention** — informed consent before testing, risk estimation, **carrier screening** (especially in consanguineous couples/high-risk ethnic groups), **cascade testing** of relatives, prenatal diagnosis, presymptomatic testing, and newborn screening for treatable metabolic AR disorders (e.g. PKU). Counsel about psychological impact and discrimination risk.

- ▶ **Population genetics** — Hardy-Weinberg equilibrium ($p^2 + 2pq + q^2 = 1$) allows carrier-frequency and disease-risk estimation in a population.

High-yield exam pointers

- ▶ Monogenic disorders $\approx$ 65% AD : 25% AR : 5% X-linked.
- ▶ **AD** = vertical, every generation, M=F, 50% offspring risk, male-to-male transmission possible; mechanisms = gain-of-function / dominant-negative / haploinsufficiency.
- ▶ **AR** = horizontal, one sibship, carrier parents, 25% risk, linked to **consanguinity**; mechanism = loss of function (often enzymes).
- ▶ **Heterozygote advantage**: sickle trait protects against malaria — explains high β -globin allele frequency.
- ▶ **Anticipation** = worsening/earlier onset across generations from expanding triplet repeats (Huntington's, myotonic dystrophy).
- ▶ **Pseudodominance** (affected $\times$ carrier in AR) mimics AD inheritance.
- ▶ **Reduced penetrance** causes apparent generation-skipping in AD pedigrees.
- ▶ **Imprinting**: paternal 15q loss $\rightarrow$ Prader-Willi; maternal 15q loss $\rightarrow$ Angelman.
- ▶ **Knudson two-hit** underlies dominantly inherited tumour-suppressor syndromes (retinoblastoma, MEN 1, NF).
- ▶ Advanced **paternal age** increases new AD mutations (achondroplasia, Marfan's).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Principles of Human Genetics*" (modes of Mendelian inheritance, AD/AR mechanisms, penetrance/expressivity, allelic & locus heterogeneity, trinucleotide repeat disorders, imprinting, population genetics, heterozygote advantage).
- ▶ Harrison's Principles of Internal Medicine, 22e — "*The Integration of Inherited Genetics into Clinical Practice*" (genetic testing strategy, gene panels, WES/WGS, VUS, counselling, cascade testing).

Coverage note: This is a core human-genetics topic with no dedicated subspecialty textbook assigned in the spec; the answer is fully grounded in Harrison 22e's two genetics chapters. CMDT was not required for this conceptual topic. All disease examples, repeat lengths, loci, and inheritance assignments are taken verbatim from Harrison's tables.



Biosimilar

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

Definition / Introduction — A **biosimilar** is a biological medicinal product that is **highly similar** to an already-licensed reference biologic (the *originator* or *innovator*), with **no clinically meaningful differences** from it in terms of safety, purity and potency (efficacy), despite minor differences in clinically inactive components. Because biologics are large, complex proteins manufactured in living cells, an exact copy is impossible; hence a biosimilar is *similar* — not *identical* — distinguishing it fundamentally from a small-molecule **generic**, which is a chemically identical copy. Biosimilars are approved through an **abbreviated, comparability-based pathway** that relies on the *totality of evidence* rather than repeating the full development programme of the reference product. They are increasingly important in internal medicine because they expand access to costly biologics (monoclonal antibodies, growth factors, insulins, anticytokines) once patents expire.

Biologic vs biosimilar vs generic — why a biosimilar is not a generic

- ▶ **Small molecules** (e.g., aspirin ~180 Da) are chemically synthesised, fully structurally defined, and can be reproduced exactly; a copy is therefore a true **generic**.
- ▶ **Biologics** (e.g., a monoclonal antibody ~150 kDa) are produced by **recombinant DNA technology in living cell lines**, carry post-translational modifications (e.g., glycosylation), and show inherent **batch-to-batch microheterogeneity** — even the originator varies slightly between lots.
- ▶ Consequently the copy can only be a **biosimilar**, demonstrated by a **stepwise comparability exercise**, not a simple pharmacokinetic bioequivalence study.

Feature	Generic (small molecule)	Biosimilar
Comparator	Chemical originator	Reference biologic
Size / complexity	Small (<1 kDa), simple	Large protein (often >100 kDa), complex
Manufacture	Chemical synthesis	Living cells (recombinant DNA)
Structural identity	Identical copy possible	"Highly similar", not identical
Approval standard	Bioequivalence (PK only)	Biosimilarity / totality of evidence
US pathway	ANDA — section 505(j)	section 351(k) (BPCIA)
Comparative clinical trial	Not required	Required (PK/PD ± efficacy & immunogenicity)
Immunogenicity testing	Not relevant	Mandatory
Automatic substitution	Yes	Only if granted interchangeability

The biosimilar approval pathway — "totality of evidence"

Development is an **inverted pyramid** (reverse of the originator's): the bulk of evidence is **analytical**, with a confirmatory, comparative clinical study at the apex.

- ▶ **Step 1 — Analytical / structural & functional characterisation** (foundation): primary/higher-order structure, glycosylation, charge variants, aggregates, and bioactivity, using state-of-the-art assays to confirm the molecule is *highly similar*.
- ▶ **Step 2 — Nonclinical comparison**: comparative in-vitro receptor-binding/functional assays and, where needed, animal **pharmacokinetic (PK)**, **pharmacodynamic (PD)** and **toxicology** studies.
- ▶ **Step 3 — Comparative clinical PK/PD study**: confirms similar exposure (C_{max}, AUC) and pharmacodynamic effect in humans — analogous to **phase 1** of drug development.
- ▶ **Step 4 — Comparative clinical efficacy & safety study** in a sensitive patient population, with **immunogenicity** as a co-primary safety endpoint — a focused version of **phase 3**.
- ▶ The aim is to **demonstrate biosimilarity, not to re-establish efficacy de novo**; any residual uncertainty after analytics is resolved by the targeted clinical step.

Key regulatory concepts

- ▶ **Immunogenicity** — the central safety concern unique to biologics. All biologics can provoke **anti-drug antibodies (ADAs)**, including **neutralising antibodies** that reduce efficacy or cause infusion/hypersensitivity reactions; biosimilars must show immunogenicity **no worse than** the reference product. (This is a *Type B*, idiosyncratic, often dose-independent adverse reaction in Harrison's classification.)
- ▶ **Extrapolation of indications** — if biosimilarity is robustly proven in one (sensitive) indication, the biosimilar may be licensed for **other approved indications of the reference product without separate trials**, provided there is scientific justification (same mechanism, receptor, PK).
- ▶ **Interchangeability** — a **separate, higher US designation (BPCIA)** permitting **pharmacy-level substitution without prescriber intervention**; it typically requires additional **switching studies**. *Biosimilar ≠ automatically interchangeable.*
- ▶ **Naming & traceability** — the FDA assigns a **4-letter suffix** to the nonproprietary name (e.g., *adalimumab-atto*) so that adverse events can be attributed to the exact product; **batch traceability** is essential for pharmacovigilance.
- ▶ **Pharmacovigilance** — because pre-licensing studies are small and short, **post-marketing surveillance** (risk-management plans, spontaneous reporting e.g. FDA MedWatch) is required to detect rare/late immunogenic and adverse events, exactly as for any new biologic.

Regulatory frameworks and representative examples

Region / body	Framework	Term used
USA (FDA)	BPCIA 2009 → 351(k) pathway; first US biosimilar filgrastim-sndz (Zarxio) , 2015	Biosimilar
EU (EMA)	First biosimilar guidelines (2005–06); first approval somatropin (Omnitrope) , 2006	Biosimilar
WHO	Guidelines on Similar Biotherapeutic Products (SBPs) , 2009	SBP
India (CDSCO + DBT)	Guidelines on Similar Biologics , 2012 (revised 2016)	Similar Biologic

- ▶ Examples of biosimilar molecules: growth factors/hormones — filgrastim, epoetin (erythropoietin), somatropin, insulin glargine; monoclonal antibodies / fusion proteins — infliximab, rituximab, trastuzumab, adalimumab, bevacizumab, etanercept.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ "Totality-of-evidence" inverted pyramid (biosimilar) vs upright pyramid (originator). Draw two opposed triangles. *Biosimilar (inverted, wide top → narrow base)*: top wide band = Analytical structural & functional characterisation; next = Nonclinical (in-vitro, animal PK/PD/tox); next = Comparative human PK/PD; apex (smallest) = Comparative clinical efficacy, safety & immunogenicity. *Originator (upright)*: base = Discovery / analytics; widening up through Phase 1 → Phase 2 → Phase 3 (largest, efficacy). Label the contrast: "emphasis reversed — analytics-heavy, clinically-light."
- ▶ Generic vs biosimilar molecule schematic. Small ring/molecule labelled "Small molecule, ~180 Da — identical generic" beside a large Y-shaped antibody labelled "Biologic mAb, ~150 kDa — biosimilar (highly similar, not identical)", with arrows noting chemical synthesis vs living-cell production and glycosylation / microheterogeneity.

Clinical / Diagnostic significance

- ▶ **Cost & access**: biosimilars are markedly cheaper than originators, improving affordability of biologics in rheumatoid arthritis, IBD, psoriasis, oncology, anaemia of CKD and chemotherapy-induced neutropenia.
- ▶ **Switching**: non-medical (cost-driven) switching from originator to biosimilar is generally supported by accumulating real-world evidence, but **document the product and batch** at each switch and monitor for loss of response or immunogenic reactions.
- ▶ **Immunogenicity vigilance**: watch for **infusion reactions, secondary loss of efficacy and neutralising-antibody formation**; these may be indistinguishable clinically from those of the reference biologic and warrant ADA testing where available.
- ▶ **Reporting**: attribute and report adverse events to the **specific product by brand/suffix and batch number** (MedWatch / national pharmacovigilance) — generic prescribing by INN alone is inadequate for biologics.
- ▶ **Extrapolated indications** are legitimate; the candidate should not assume a biosimilar is "untested" in an indication merely because no dedicated trial exists.

High-yield exam pointers

- ▶ A biosimilar is "**highly similar with no clinically meaningful differences**" — *similar, never identical*; this is the single most examined definition.
- ▶ **Generic = identical copy (bioequivalence)**; **biosimilar = highly similar copy (biosimilarity/totality of evidence)**.
- ▶ Approval rests on a **stepwise comparability exercise** dominated by **analytical characterisation** (inverted pyramid), with a confirmatory comparative clinical + **immunogenicity study**.

- ▶ US pathway = 351(k) under the BPCIA 2009; EU EMA pioneered the field (first biosimilar Omnitrope, 2006); WHO term = SBP; India uses "Similar Biologic" (CDSCO/DBT 2012, rev 2016).
- ▶ Interchangeability is a separate designation requiring switching data — a biosimilar is *not* automatically substitutable.
- ▶ Extrapolation of indications is permitted with scientific justification.
- ▶ Immunogenicity (anti-drug / neutralising antibodies) is the key safety endpoint and a *Type B* adverse reaction.
- ▶ 4-letter suffix naming + batch traceability underpin biosimilar pharmacovigilance.

SOURCE & COVERAGE

Harrison 22e — Ch 71 "Principles of Clinical Pharmacology" (clinical-trial phases 1–3, premarketing vs postmarketing surveillance, Type A/Type B adverse drug reactions, FDA MedWatch reporting, and therapeutic monoclonal-antibody examples — rituximab, infliximab, abatacept).

Coverage note (gap flagged): The term *biosimilar* is **not defined in Harrison Ch 71**, which covers general clinical pharmacology and drug development but not biosimilars specifically. The biosimilar-specific content above — the definition, the small-molecule-generic vs biosimilar distinction, the *totality-of-evidence* comparability pathway, interchangeability, extrapolation, naming/traceability, and the regulatory frameworks (US BPCIA 351(k), EMA, WHO SBP, India CDSCO/DBT Similar Biologic guidelines 2012/2016) and named example products — is **universally accepted standard regulatory pharmacology** supplied to satisfy the ask, and is anchored to Ch 71 only for the underlying scaffolding (trial phases, ADR classification, immunogenicity as a Type B reaction, and post-marketing pharmacovigilance). Specific dates/identifiers (e.g., Zarxio 2015, Omnitrope 2006) are standard and accurate but lie outside the provided chapter.



Cell culture technique and application

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

Definition / Introduction — **Cell culture** (tissue culture) is the *in-vitro* maintenance and propagation of living cells, isolated from a multicellular organism, under controlled physico-chemical conditions (sterility, defined nutrient medium, 37 °C, buffered pH, humidified CO₂). It allows cells to be grown outside the body for diagnostic, research and therapeutic purposes. The technique is foundational to **cytogenetics** (chromosome/karyotype analysis), **diagnostic virology**, **vaccine and biologic manufacture**, **stem-cell and disease modelling**, and **drug discovery/toxicology**. In internal medicine its single most important clinical application is the cultured-cell **karyotype** used to characterise the numerical and structural chromosomal disorders that occur in ~1 % of the general population, 8 % of stillbirths and ~50 % of spontaneous abortions.

Types / Classification of Cell Culture

Basis of classification	Type	Key features / examples
Origin & lifespan	Primary culture	Cells freshly isolated from tissue by enzymatic/mechanical dissociation or <i>explant</i> outgrowth; retain donor karyotype; limited lifespan
	Finite (diploid) cell line	Subcultured (passaged) primary cells; divide a limited number of times (~50; <i>Hayflick limit</i>) then senesce; remain diploid — e.g., human diploid fibroblasts WI-38, MRC-5
	Continuous (immortalised) cell line	Transformed cells dividing indefinitely; often aneuploid — e.g., <i>HeLa</i> , <i>Vero</i> (used to isolate SARS-CoV-1)
Growth pattern / substrate	Adherent (monolayer)	Anchorage-dependent; grow as a sheet on treated plastic/glass; most fibroblasts/epithelia
	Suspension culture	Anchorage-independent; grow free in medium — e.g., haematopoietic/leukaemic cells
Architecture	Organ / explant & 3-D culture	Tissue fragment cultured with retained architecture; modern extension = organoids/assembloids and <i>organ-on-chip</i>

Requirements and General Methodology

- ▶ **Asepsis** — all manipulation in a **laminar-flow biosafety cabinet**; antibiotics (penicillin–streptomycin) and antifungals added to suppress contamination.
- ▶ **Growth medium** — a balanced salt solution with glucose, amino acids, vitamins and buffers (e.g., *Eagle's MEM*, *RPMI-1640*, *DMEM*), supplemented with **serum** (foetal calf serum) as a source of growth factors and hormones.
- ▶ **pH/gas control** — sodium-bicarbonate buffering equilibrated against 5 % CO₂ in a humidified 37 °C incubator; *phenol red* acts as a pH indicator.
- ▶ **Substrate & sub-culture (passage)** — adherent cells grow until *confluent*, then are detached with **trypsin-EDTA** and split (passaged) into fresh flasks.

- ▶ **Cryopreservation** — surplus cells frozen in serum + DMSO and stored in liquid nitrogen (−196 °C) as a cell bank.
- ▶ **Quality** — cultures monitored for confluence, viability (trypan-blue exclusion), and contamination (bacteria, fungi, mycoplasma).

Lymphocyte Culture and Karyotyping (the core cytogenetic technique)

Chromosomal (cytogenetic) disorders — *aneuploidy* and structural rearrangements (deletions, duplications, translocations, inversions, ring/dicentric chromosomes, Robertsonian translocations) — are characterised by analysing chromosomes at the **metaphase** stage, when they are maximally condensed and display the short (**p**) and long (**q**) arms about the centromere.

- ▶ **Sample** — peripheral venous blood in **sodium heparin**; alternatively bone marrow (direct/short culture for leukaemias), skin fibroblasts, **amniocytes** (amniocentesis) or **chorionic villi** (CVS) for prenatal work.
- ▶ **Mitogenic stimulation** — T-lymphocytes are driven into division by the mitogen **phytohaemagglutinin (PHA)**, cultured in medium + serum at 37 °C/5 % CO₂ for ~72 h.
- ▶ **Metaphase arrest** — **colchicine / colcemid** depolymerises the mitotic spindle, arresting cells in metaphase.
- ▶ **Hypotonic treatment** — 0.075 M KCl swells the cells and disperses the chromosomes.
- ▶ **Fixation** — **methanol : glacial acetic acid (3:1)** (*Carnoy's fixative*).
- ▶ **Spreading & banding** — cells dropped onto a slide and stained; **G-banding** (trypsin–Giemsa) is standard (also Q-, R-, C-banding) giving each chromosome a reproducible band pattern.
- ▶ **Analysis** — metaphase spreads are imaged and chromosomes ordered by size, centromere position and banding into a **karyogram**, reported in *ISCN* nomenclature (e.g., 47,XX,+21 for trisomy 21). Conventional karyotype resolution is ~5–10 Mb.
- ▶ **Indications (Harrison Table 479-4)** — *prenatal* (advanced maternal age, abnormal ultrasound, positive serum screen); *neonatal/childhood* (multiple congenital anomalies, intellectual disability/developmental delay, autism, failure to thrive, short stature, disorders of sexual development, childhood cancer); *adult* (infertility, recurrent miscarriage, familial cancer, familial chromosomal rearrangement).

Molecular cytogenetic methods now complement culture-based karyotyping: **FISH** (locus/probe-specific), and **chromosomal microarray (CMA)**, which detects copy-number variants (e.g., 22q11/DiGeorge) far below karyotype resolution.

Applications of Cell Culture

Field	Application	Detail (source-grounded)
Cytogenetics / genetics	Karyotyping; FISH; prenatal diagnosis	Constitutional & cancer chromosome analysis from cultured lymphocytes, amniocytes, CVS, marrow
Diagnostic virology	Virus isolation & quantification	Inoculation of <i>Vero</i> cell cultures → cytopathic effect (CPE) ; titres by plaque assay (PFU) and TCID ₅₀ (endpoint-dilution)

Field	Application	Detail (source-grounded)
Vaccines & biologics	Manufacture	Viral vaccines, vaccine vectors, gene-therapy vectors and oncolytic viruses are grown and precisely titrated in cell culture
Immunology	Monoclonal antibodies	B-cell × myeloma fusion (hybridoma , Köhler & Milstein) — standard immunology technique
Regenerative / disease modelling	iPSC, organoids	Somatic cells (skin fibroblasts/blood) reprogrammed with Oct3/4, Klf-4, Sox2, c-Myc (<i>Yamanaka factors</i>) — now via non-integrating Sendai virus / mRNA / episomal vectors — expanded indefinitely and differentiated; 3-D organoids/assembloids model neurologic disease
Pharmacology / toxicology	Drug & target screening	iPSC-derived cells/organoids screen therapeutic agents, detect off-target/toxic effects, uncover targets
Gene & cell therapy	Engineered cellular products	Platform for CRISPR-Cas9 gene-editing and <i>ex-vivo</i> cell products (e.g., CAR-T, isogenic disease/control lines)
Cancer cytogenetics	Diagnosis/prognosis	Cultured marrow reveals diagnostic/prognostic translocations in leukaemias and solid tumours

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Metaphase chromosome / karyogram schematic** — label: *short arm (p), long arm (q), centromere, telomere, G-band pattern, sister chromatids*; with an inset karyogram strip showing autosome pairs 1–22 + sex chromosomes (e.g., 46,XY) — derived from Harrison Fig. 479-1.
- ▶ **Flow diagram of lymphocyte culture for karyotyping** — boxes: *Heparinised blood* → *PHA + medium/serum, 37 °C/5 % CO₂ × 72 h* → *Colcemid (metaphase arrest)* → *Hypotonic KCl* → *Carnoy's fixative* → *Drop on slide + G-banding* → *Microscopy/karyogram* → *ISCN report*.

Clinical / Diagnostic significance

- ▶ **Definitive diagnosis** of constitutional aneuploidies and structural rearrangements (Down, Turner, Klinefelter, cri-du-chat, translocation Down) and of cancer-associated chromosomal abnormalities guiding diagnosis, prognosis and **targeted therapy** (actionable lesions in leukaemias/solid tumours).
- ▶ **Prenatal diagnosis** — cultured amniocytes/chorionic villi give a foetal karyotype/CMA; a positive **non-invasive cfDNA screen (NIPT)** is generally confirmed by amniocentesis/CVS.
- ▶ **Virology** — culture isolation remains a reference method for replicating/infectious virus, complementing antigen and PCR/NAAT assays; precise infectious titres (PFU, TCID₅₀) are essential for safe vaccine/vector dosing.
- ▶ **Therapeutics & research** — patient-specific **iPSC lines/organoids** model monogenic and polygenic disease on the patient's own genetic background and serve as drug-screening and toxicity platforms; cell culture underpins monoclonal-antibody and engineered cell-therapy production.

- ▶ **Pitfalls** — culture failure/contamination (mycoplasma), maternal-cell contamination of prenatal samples, *confined placental mosaicism*, and the limited (~5–10 Mb) resolution of conventional karyotype (overcome by CMA/FISH).

High-yield exam pointers

- ▶ **Cell culture** = in-vitro growth of cells under sterile, nutrient-rich, 37 °C/5 % CO₂ conditions.
- ▶ **Primary culture** → finite cell line (Hayflick limit ~50 divisions, diploid) → continuous/immortalised line (aneuploid, e.g., HeLa/Vero).
- ▶ Karyotype recipe mnemonic: **blood** → PHA (72 h) → colcemid → KCl (hypotonic) → 3:1 methanol-acetic fixative → G-banding → metaphase analysis.
- ▶ Chromosomes are studied at **metaphase**; **p** = short, **q** = long arm; report by ISCN (e.g., 47,XX,+21).
- ▶ Cytogenetic disorders occur in ~1 % of population, ~50 % of spontaneous abortions.
- ▶ Virology titres: TCID₅₀ (endpoint dilution) and **plaque-forming units (PFU)**; Vero cells, CPE.
- ▶ **iPSC** = somatic cells reprogrammed by Oct3/4, Klf-4, Sox2, c-Myc (Yamanaka factors); now via non-integrating Sendai/mRNA/episomal vectors → organoids.
- ▶ CMA/FISH detect sub-microscopic copy-number variants missed by routine karyotype.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (chromatin/metaphase chromosome structure, p/q arms, cytogenetic disorders, indications for cytogenetic/cytogenomic analysis — Table 479-4); "Principles of Medical Virology" (cell-culture viral isolation, Vero cells, CPE, plaque assay/PFU, TCID₅₀, vaccine/vector titration); "Pathobiology of Neurologic Diseases" (induced pluripotent stem cells, Yamanaka reprogramming factors, non-integrating vectors, organoids/assembloids, drug screening); "Circulating Nucleic Acids as Liquid Biopsies / Prenatal diagnosis" (amniocentesis, CVS, traditional karyotype resolution ~5–10 Mb, chromosomal microarray).

Coverage note: Harrison 22e explicitly states that **chromosomal-analysis (cell-culture karyotyping) techniques were detailed in previous editions** and gives only the indications and chromosome biology in the current text. Accordingly, the **step-by-step lymphocyte-culture/karyotyping protocol** (PHA stimulation, colcemid arrest, hypotonic KCl, Carnoy's fixative, G-banding), the **Hayflick limit**, media (RPMI/DMEM/MEM), and the **hybridoma (Köhler–Milstein)** method are presented as *universally accepted standard cytogenetics/immunology* rather than verbatim 22e content; all chapter-specific numbers, cell lines and reprogramming factors cited above are taken faithfully from the corpus. No dedicated subspecialty textbook or CMDT chapter was specified for this lab-technique topic.



Circle of Willis

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

Definition / Introduction — The *circle of Willis* is the anastomotic arterial polygon (a heptagon) lying on the ventral surface of the brain within the **interpeduncular fossa/cistern** at the base of the brain, encircling the optic chiasm, infundibulum and midbrain. It is the single most important intracranial anastomosis: the carotid (anterior) and vertebrobasilar (posterior) arterial systems unite here so that, with a *competent* circle, occlusion of one feeding vessel may pass unnoticed. A truly **complete** circle is found in only ~20–25% of subjects; configurational variation is the rule, not the exception.

Constituent arteries (the seven-sided ring)

The circle is closed by paired vessels linked anteriorly and posteriorly by single/short communicating arteries:

Position	Contributing artery	Connects
Anterior (single)	Anterior communicating artery (AComA)	the two A1 segments of the ACAs — closes the <i>rostral</i> part of the circle
Anterolateral (paired)	Anterior cerebral arteries (A1 / precommunal segment)	ICA terminus → AComA
Lateral (paired)	Internal carotid arteries (terminal/supraclinoid)	the carotid "input" to the circle
Posterolateral (paired)	Posterior communicating arteries (PComA)	ICA → PCA; the <i>link between anterior and posterior circulations</i>
Posterior (paired)	Posterior cerebral arteries (P1 / precommunal segment)	basilar bifurcation → PComA
Posterior apex (single)	Basilar artery bifurcation	vertebrobasilar "input" to the circle

- ▶ The two **vertebral arteries** (segments V1–V4) join at the *pontomedullary junction* to form the **basilar artery**, which runs the length of the pons and bifurcates into the two PCAs at the *pontine–midbrain junction* within the interpeduncular cistern.
- ▶ Vessels that **arise from** the circle but are **not** structural members of the ring include the **middle cerebral artery (MCA)**, **anterior choroidal artery**, the deep perforators, and (from the posterior limb) the superior cerebellar and pontine branches.
- ▶ **Origin of the feeding trunks:** the **brachiocephalic trunk**, **left common carotid** and **left subclavian** arise from the aortic arch; the brachiocephalic trunk divides into the right subclavian and right common carotid; the **vertebral arteries arise from the subclavians**. Thus the circle ultimately receives blood from *all three* arch vessels.
- ▶ **Embryological note:** the PCA is developmentally a branch of the ICA (carried on the PComA); as the basilar system matures the P1 segment takes over — failure of this transition leaves the *fetal-type* PCA.

Internal carotid artery and its circle-related branches

The ICA is divided into four portions — **cervical (C1, no branches)**, **petrous (C2)**, **cavernous (C3)** and **supraclinoid/intracranial (C4)**. After piercing the dura, the intracranial ICA, in order, gives off:

- ▶ **Ophthalmic artery** — first major intradural branch (orbital, extraorbital, ocular branches; *central retinal artery* at the "bayonet" point; long & short posterior ciliary arteries) — basis of *amaurosis fugax* in carotid disease.
- ▶ **Superior hypophyseal artery** — to pituitary/hypothalamus.
- ▶ **Posterior communicating artery (PComA)** — joins the PCA to form the **posterolateral portion** of the circle; its penetrating branches supply the **anterior & posterior hypothalamus, optic tract and posterior optic chiasm, and the anterior & ventral thalamic nuclei**.
- ▶ **Anterior choroidal artery (AChA)** — arises from the posterior wall of the ICA *distal to PComA, proximal to the ICA terminus* (so it is **not** part of the circle). It supplies the **posterior limb of the internal capsule, optic tract, lateral geniculate body, medial globus pallidus, tail of caudate, midbrain/cerebral peduncle** and the choroid plexus of the temporal horn — a strategic vessel vulnerable during aneurysm clipping.
- ▶ ICA finally **bifurcates into the ACA and MCA**.

Deep penetrating (perforating) branches of the circle

The communicating and proximal cerebral segments give off small **central/ganglionic perforators** to the diencephalon and basal ganglia — these are *functional end-arteries* and account for lacunar syndromes:

- ▶ **Anteromedial group** — from the ACA (A1) and AComA → anterior hypothalamus, septal region, optic chiasm, anterior commissure, columns of fornix.
- ▶ **Anterolateral group (lateral striate / lenticulostriate)** — from the **stem of the MCA** → putamen, outer globus pallidus, posterior limb of internal capsule, caudate body, corona radiata.
- ▶ **Posteromedial group** — from PComA and P1 PCA → hypothalamus, subthalamus, medial thalamus, rostral midbrain.
- ▶ **Posterolateral group (posterior/thalamogeniculate striate)** — from the postcommunal PCA → thalamus and geniculate bodies.
- ▶ **Medial striate artery (recurrent artery of Heubner)** — from the A1–A2 junction → anteroinferior limb of internal capsule, anterior putamen/caudate, tip of outer globus pallidus.

Collectively the **medial, lateral and posterior striate arteries** perfuse the **striatum and thalamus**; their occlusion produces pure-motor, pure-sensory or sensorimotor *lacunar* strokes.

Anatomical variations and persistent fetal anastomoses

- ▶ **Incomplete circle** in ~75–80% of people — most often a hypoplastic/absent communicating segment or A1 atresia.
- ▶ **Fetal (embryonic) PCA** in ~20–25%: the PCA arises from the ICA via a large PComA and the **P1 segment is atretic**, so the occipital lobe depends on the *anterior* circulation (carotid occlusion can then infarct the PCA territory). Harrison: both PCAs arise from the basilar in 75%, one from the ipsilateral ICA in 20%, and both from the ICAs in 5%.
- ▶ **Persistent primitive carotid–vertebrobasilar anastomoses** (failed embryonic regression) — *persistent trigeminal artery* (the **most frequent**, ~0.2% of adults), *persistent acoustic (otic) artery*, *persistent hypoglossal artery*, and *persistent proatlantal artery*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Circle of Willis (inferior/basal view).** Draw the heptagon and label: *Anterior communicating artery, Anterior cerebral artery (A1), Internal carotid artery, Middle cerebral artery, Anterior choroidal artery, Posterior communicating artery, Posterior cerebral artery (P1), Basilar artery, Superior cerebellar artery, Vertebral artery, Anterior spinal artery.* Add the four perforator groups: *anteromedial, anterolateral, posteromedial, posterolateral.*
- ▶ **Diagram 2 — Vascular territories on a coronal hemisphere section.** Label: *ACA, MCA (superior & inferior divisions), MCA deep (lenticulostriate) branches, anterior choroidal artery, PCA, PCA deep branches; caudate, putamen, globus pallidus, internal capsule (anterior & posterior limbs), thalamus, hippocampal formation.*

Clinical / Diagnostic significance

- ▶ **Collateral reserve:** with a competent circle, even complete ICA occlusion may be asymptomatic; an incomplete circle predisposes to **border-zone (watershed) infarction** during systemic hypotension or carotid stenosis.
- ▶ **Saccular ("berry") aneurysms** cluster at the branch points of the circle — classically the **ACoMA**, the **PCoMA-ICA junction**, and the **MCA bifurcation** — and rupture causes **subarachnoid haemorrhage**. A **PCoMA aneurysm** characteristically produces a *painful, pupil-involving third (oculomotor) nerve palsy*.
- ▶ **Imaging:** the circle and its variants are mapped by **CT/MR angiography** and **digital subtraction angiography (DSA)**; transcranial Doppler assesses collateral flow and vasospasm.
- ▶ **Surgical relevance:** balloon test occlusion before carotid sacrifice tests circle competence; **AChA** and **lenticulostriate perforators** are "eloquent" end-arteries readily injured during aneurysm clipping.
- ▶ **Stroke localisation:** deep perforator occlusion → lacunar syndromes; proximal large-vessel occlusion → cortical territorial syndromes (MCA, ACA, PCA).

High-yield exam pointers

- ▶ Circle lies in the **interpeduncular fossa**, encircling optic chiasm, infundibulum and midbrain; it is a **heptagon**.
- ▶ **Anterior half** = carotid system (ICA, A1-ACA, ACoMA); **posterior half** = vertebrobasilar system (P1-PCA, basilar); **PCoMA is the bridge** between them.
- ▶ **ACoMA** closes the circle anteriorly; **two PCoMAs** close it posterolaterally.
- ▶ **MCA and anterior choroidal artery** are **NOT part of the circle** — common viva trap.
- ▶ **Complete circle** in only ~20–25%; **fetal PCA** in ~20–25% (atretic P1).
- ▶ **ACoMA** = commonest site of berry aneurysm; **PCoMA aneurysm** = **pupil-involving CN III palsy**.
- ▶ **Recurrent artery of Heubner** = medial striate branch of ACA; **lenticulostriate** = deep branches of MCA (lacunar strokes, hypertensive haemorrhage).
- ▶ **Persistent trigeminal artery** = commonest persistent carotid–basilar anastomosis (~0.2%).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Introduction to Cerebrovascular Diseases*" (anterior vs posterior circulation, ICA/ACA/MCA/PCA segments, PCA-origin percentages, lacunar/lenticulostriate anatomy, competent-circle collateral concept).
- ▶ Brazis, Masdin & Biller, *Localization in Clinical Neurology* — "*Vascular Syndromes of the Forebrain, Brainstem, and Cerebellum*" (dedicated neurovascular anatomy: ICA C1–C4 segments and branches, PComA/AChA/Heubner territories, perforator groups, circle constituents, ~20–25% complete-circle figure, persistent carotid–vertebrobasilar anastomoses).

Coverage note: This is pure vascular anatomy; Harrison covers it only as background to stroke syndromes, so the structural depth (segmental nomenclature, perforator groups, persistent fetal anastomoses) is drawn from Brazis. Aneurysm-site frequency and the PComA-aneurysm CN III palsy are universally accepted standard internal-medicine points included for completeness.



Newer anticoagulants

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

Definition / Introduction — *Newer anticoagulants* are agents developed to overcome the limitations of the classical drugs (unfractionated heparin and vitamin K antagonists such as warfarin) — namely the need for parenteral administration or routine laboratory monitoring, the slow onset/offset, the narrow therapeutic window, and numerous food/drug interactions. The term encompasses the synthetic pentasaccharide **fondaparinux**, the parenteral **direct thrombin inhibitors** (argatroban, bivalirudin, desirudin), and, most importantly for current practice, the oral **direct-acting oral anticoagulants (DOACs)** — the direct thrombin inhibitor *dabigatran* and the direct factor Xa inhibitors *rivaroxaban*, *apixaban* and *edoxaban*. DOACs target a single activated clotting factor, have rapid onset, predictable pharmacokinetics, and are given in fixed doses without routine coagulation monitoring.

Classification of newer anticoagulants

Class	Target	Drugs	Route
Synthetic pentasaccharide	Factor Xa (via antithrombin)	Fondaparinux	SC
Parenteral direct thrombin (IIa) inhibitors	Thrombin active site ± exosite 1	Argatroban, Bivalirudin, Desirudin (lepirudin withdrawn)	IV/SC
Oral direct thrombin inhibitor	Thrombin (IIa)	Dabigatran etexilate	Oral
Oral direct factor Xa inhibitors ("-xabans")	Factor Xa	Rivaroxaban, Apixaban, Edoxaban	Oral

- ▶ The DOACs are **small molecules that bind reversibly to the active site** of their target enzyme, inhibiting *free and clot-bound* factor (unlike heparin, which acts only on circulating factors and cannot inhibit fibrin-bound thrombin).
- ▶ Mnemonic for Xa inhibitors: the "**-xa-bans**" (riv-a-ROXA-ban) all *ban factor Xa*; *dabigatran* is the lone direct thrombin inhibitor.

Direct oral anticoagulants — comparative pharmacology

Characteristic	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin (IIa)
Prodrug	No	No	No	Yes (etexilate)
Bioavailability	80%	60%	50%	6%
Usual dosing	once daily (bid)	twice daily	once daily	twice daily
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal excretion	33%	25%	35%	80%
Key interactions	CYP3A4 + P-gp	CYP3A4 + P-gp	P-gp	P-gp

- ▶ **Dabigatran** is the only prodrug (absorbed as dabigatran etexilate, converted by esterases); its very low bioavailability explains *dyspepsia* (the capsule contains tartaric acid) and the need for an intact capsule.
- ▶ **Renal clearance is the critical safety pivot**: dabigatran (80% renal) is the most dialysable and the most affected by chronic kidney disease; factor Xa inhibitors are less renally dependent. All require dose reduction or avoidance in significant renal impairment.
- ▶ Potent **dual P-gp + CYP3A4 inhibitors** (e.g., azole antifungals, ritonavir) raise drug levels; strong inducers (rifampicin, carbamazepine, phenytoin, St John's wort) lower them — these are the main interactions to avoid.

Indications and dosing

Licensed indications (all four DOACs unless stated):

- ▶ **Non-valvular atrial fibrillation** — stroke prevention (NOT in mechanical heart valves or moderate–severe rheumatic mitral stenosis).
- ▶ **Treatment of venous thromboembolism (VTE)** — DVT and PE, and secondary prevention.
- ▶ **Thromboprophylaxis after elective hip or knee arthroplasty** — dabigatran, rivaroxaban, apixaban (edoxaban only in Japan).
- ▶ **Secondary prevention in coronary/peripheral artery disease** — low-dose rivaroxaban with aspirin (*COMPASS* regimen).

Indication	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
AF stroke prevention	20 mg OD (15 mg if CrCl 15–49)	5 mg BD (2.5 mg BD if ≥ 2 ABC)	150 mg BD (75 mg BD if CrCl 15–30)	60 mg OD (30 mg if CrCl 15–50, wt ≤ 60 kg, or potent P-gp inhibitor)

Indication	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Acute VTE	15 mg BD ×21 d → 20 mg OD	10 mg BD ×7 d → 5 mg BD	150 mg BD <i>after</i> ≥5 d parenteral	60 mg OD <i>after</i> ≥5 d parenteral
VTE — extended (after 6 mo)	10 mg OD	2.5 mg BD	—	—
Hip/knee prophylaxis	10 mg OD	2.5 mg BD	220 mg OD	—
CAD/PAD (with aspirin)	2.5 mg BD	—	—	—

- ▶ **ABC dose-reduction criteria for apixaban in AF** = Age >80 y, Body weight <60 kg, serum Creatinine ≥1.5 mg/dL — reduce to 2.5 mg BD if *any two* are present.
- ▶ **Single-drug ("all-oral") regimens**: only *rivaroxaban* and *apixaban* can be started without a heparin lead-in for VTE; *dabigatran* and *edoxaban* require ≥5 days of parenteral anticoagulant (LMWH) first.
- ▶ Rivaroxaban 15/20 mg **must be taken with food** to ensure absorption; apixaban and edoxaban are food-independent.
- ▶ Landmark non-inferiority trials vs warfarin in AF: *RE-LY* (dabigatran), *ROCKET AF* (rivaroxaban), *ARISTOTLE* (apixaban), *ENGAGE AF-TIMI 48* (edoxaban).

Parenteral newer agents

- ▶ **Fondaparinux** — synthetic analogue of the antithrombin-binding pentasaccharide (MW 1728). It binds only to antithrombin and is *too short to bridge thrombin*, so it catalyses **factor Xa inhibition only**. Given SC once daily; 100% bioavailable; plasma half-life **17 h**; cleared **unchanged renally** (contraindicated if CrCl <30 mL/min). Dose: **2.5 mg OD** (prophylaxis/ACS), 5–10 mg OD by weight for VTE treatment. It **does not cause HIT** (no PF4 binding, no cross-reactivity) and so is useful in HIT, but **has no antidote** (protamine ineffective).
- ▶ **Parenteral direct thrombin inhibitors** — used chiefly in *heparin-induced thrombocytopenia (HIT)* and PCI:
 - *Argatroban* — univalent active-site inhibitor, **hepatically metabolised**, half-life ~45 min, monitored by aPTT; drug of choice in **HIT with renal failure**.
 - *Bivalirudin* — bivalent (active site + exosite 1) 20-amino-acid hirudin analogue, shortest half-life (~25 min), partly renally cleared; an alternative to heparin in PCI and HIT.
 - *Desirudin* — recombinant hirudin; renally cleared.

Monitoring, reversal and management of bleeding

- ▶ **Routine monitoring is not required**. When assessment is needed (adherence, overdose, pre-urgent surgery, suspected accumulation): a *normal PT* largely excludes clinically relevant levels of factor Xa inhibitors and a *normal aPTT/thrombin time* excludes dabigatran. Quantitative assays = **chromogenic anti-Xa assay** (calibrated) for the xabans; **dilute thrombin time / ecarin clot time** for dabigatran. Apixaban has minimal effect on PT, so anti-Xa assay is needed.

- ▶ **Bleeding — general measures:** hold the drug, local haemostasis, fluids/blood products; **activated charcoal** if ingested within ~2–4 h; *vitamin K is of no value*. Calculate residual effect from last dose and renal function.
- ▶ **Specific reversal agents:**
 - **Idarucizumab** — humanised monoclonal antibody *fragment* that binds dabigatran with very high affinity; **5 g IV** (two 2.5 g vials); rapidly normalises aPTT/dilute thrombin time. If unavailable, **activated PCC 50 units/kg**.
 - **Andexanet alfa** — recombinant, catalytically inactive **decoy factor Xa** that sequesters the xabans (and also heparin/LMWH). *Low dose* = 400 mg bolus + 4 mg/min infusion (≤ 120 min); *high dose* = 800 mg bolus + 8 mg/min. High dose if last dose was large (rivaroxaban >10 mg / apixaban >5 mg) and taken <8 h ago. If unavailable, **four-factor PCC 25–50 units/kg** (≈ 2000 units).
 - Fondaparinux and argatroban/bivalirudin have **no licensed antidote**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Coagulation cascade with drug targets:** draw the common pathway — *Factor X* → *Xa* → (*prothrombinase*) → *Prothrombin (II)* → *Thrombin (IIa)* → *Fibrinogen* → *Fibrin*. Label arrows blocking **Factor Xa: Rivaroxaban, Apixaban, Edoxaban, Fondaparinux** (via antithrombin) and blocking **Thrombin (IIa): Dabigatran, Argatroban, Bivalirudin**. Show **Warfarin** acting upstream on synthesis of factors *II, VII, IX, X* (and *proteins C, S*). Mark **Idarucizumab** → dabigatran and **Andexanet alfa** → Xa inhibitors as reversal arrows.
- ▶ **Antithrombin-mediated inhibition schematic:** antithrombin bridging unit — heparin neutralises both *Xa* and *IIa*; LMWH mainly *Xa*; **fondaparinux only Xa** (pentasaccharide too short to bridge thrombin).

Clinical / Diagnostic significance

- ▶ **Advantages over warfarin:** fixed oral dosing, rapid onset/offset, predictable response, no routine INR monitoring, few food and fewer drug interactions, and **significantly less intracranial haemorrhage**.
- ▶ **Disadvantages/cautions:** higher-dose dabigatran, rivaroxaban and edoxaban cause **more GI bleeding**; renal clearance limits use in advanced CKD; cost; short half-life means missed doses rapidly lose protection.
- ▶ **Contraindications / avoid:** mechanical prosthetic valves and moderate–severe rheumatic mitral stenosis (warfarin superior — *RE-ALIGN* showed harm with dabigatran); **pregnancy and lactation** (cross placenta/breast milk — use LMWH); triple-positive **antiphospholipid syndrome** (DOACs inferior to warfarin); severe renal/hepatic impairment.
- ▶ **Peri-procedural:** stop DOAC 1–2 days before moderate/high-risk procedures (longer if renal impairment); unlike warfarin, **no heparin "bridging" is needed** because of rapid offset.
- ▶ **Special populations:** in cancer-associated VTE, apixaban/edoxaban/rivaroxaban are acceptable alternatives to LMWH but are **avoided in GI/genitourinary tumours** (bleeding) and where chemotherapy interactions exist.

High-yield exam pointers

- ▶ DOACs = dabigatran (anti-IIa) + rivaroxaban / apixaban / edoxaban (anti-Xa); only dabigatran is a *prodrug*.
- ▶ Dabigatran is 80% renally excreted → most affected by CKD and the only DOAC removed by dialysis.
- ▶ Apixaban has the least GI bleeding and is often preferred in CKD; remember the ABC reduction rule (Age>80, Body wt<60, Creatinine≥1.5).
- ▶ Dabigatran & edoxaban need a ≥5-day parenteral lead-in for VTE; rivaroxaban & apixaban are all-oral.
- ▶ Idarucizumab → dabigatran; Andexanet alfa → factor Xa inhibitors; 4-factor PCC is the fallback for both.
- ▶ Fondaparinux = pure anti-Xa pentasaccharide, $t_{1/2}$ 17 h, no HIT, no antidote.
- ▶ DOACs are contraindicated in mechanical valves, rheumatic MS, pregnancy and antiphospholipid syndrome — these patients need warfarin.
- ▶ DOACs cause less intracranial bleeding than warfarin but sometimes more GI bleeding.
- ▶ Qualitative tests: PT for xabans, aPTT/TT for dabigatran; quantitative = anti-Xa assay and dilute thrombin/ecarin clot time respectively.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Antiplatelet, Anticoagulant, and Fibrinolytic Drugs" (parenteral anticoagulants, fondaparinux, parenteral direct thrombin inhibitors, warfarin, and the Direct Oral Anticoagulants section incl. Table 123-9 pharmacology comparison, dosing, monitoring and reversal).
- ▶ CMDT 2026 — "Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy" (Tables 16-9/16-10: DOAC dosing, transitions; DOAC-associated major-bleeding reversal guidance with idarucizumab and low/high-dose andexanet alfa; cancer-associated VTE and APS cautions).
- ▶ Trial names (RE-LY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48, COMPASS, REALIGN) are universally accepted landmark internal-medicine references; COMPASS appears in Harrison's further reading.



Oral antifungal therapy

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Antifungal agents are drugs that selectively kill (fungicidal) or inhibit (fungistatic) fungi while sparing the eukaryotic human host. Because fungi, like human cells, are eukaryotes, the number of exploitable selective targets is small, so far fewer antifungal than antibacterial agents exist. **Orally bioavailable** agents are the backbone of outpatient and step-down therapy and act on one of four fungus-specific targets: the **cell-membrane sterol ergosterol** (azoles, allylamines, polyenes), the **cell-wall β -1,3-glucan** (triterpenoids/echinocandins), **nucleic-acid synthesis** (flucytosine) and the **mitotic spindle** (griseofulvin). Early appropriate therapy plus source control and immune reconstitution determine outcome.

Classification of antifungal agents by target (oral agents in bold)

Target site	Class	Agents	Oral availability
Cell membrane — ergosterol synthesis (inhibit lanosterol 14 α -demethylase)	Azoles (triazoles/tetrazole)	Fluconazole, Itraconazole, Voriconazole, Posaconazole, Isavuconazole, Oteseconazole (older imidazoles—ketoconazole, clotrimazole, miconazole—mainly topical)	Oral + IV (oteseconazole oral only)
Cell membrane — squalene epoxidase	Allylamine	Terbinafine (naftifine topical)	Oral + topical
Cell membrane — bind/extract ergosterol	Polyene	Amphotericin B (IV); Nystatin (oral non-absorbed, topical)	AmB IV only; nystatin oral-luminal
Cell wall — β-1,3-glucan synthase	Triterpenoid	Ibrexafungerp	Oral
Cell wall — β -1,3-glucan synthase	Echinocandins	Caspofungin, anidulafungin, micafungin, rezafungin	IV only
Nucleic-acid (DNA/RNA) synthesis	Pyrimidine analogue	Flucytosine (5-FC)	Oral (+ IV)
Mitotic spindle / microtubules	—	Griseofulvin	Oral

Oral azoles — mechanism, spectrum and indications

- **Mechanism:** inhibit fungal cytochrome-P450 **lanosterol 14 α -demethylase**, blocking conversion of lanosterol to ergosterol; accumulation of toxic methylated sterol intermediates and ergosterol depletion arrest growth — azoles are **fungistatic**. Advantages over amphotericin B: oral + IV forms and absence of nephrotoxicity.
- **Fluconazole** — oral/IV, long half-life, excellent penetration of CSF, ocular fluid and urine; minimal toxicity (rare hepatotoxicity; high dose $\rightarrow$ alopecia, dry mouth, metallic taste; even low doses in pregnancy linked to miscarriage/stillbirth). *No activity against molds or most endemic dimorphic fungi*; weaker against *C. glabrata*/*C. krusei*. **Indications:** preferred for **coccidioidal**

meningitis; consolidation/maintenance therapy of **cryptococcal meningitis**; **mucosal (oropharyngeal, oesophageal, vulvovaginal) candidiasis**; candidaemia in non-critically-ill, non-neutropenic patients; step-down once a susceptible *Candida* is identified; prophylaxis in high-risk liver and allogeneic marrow transplant.

- ▶ **Itraconazole** — oral capsule/suspension + IV; *broader than fluconazole* (molds, endemic dimorphic fungi). **Drug of choice for mild–moderate histoplasmosis and blastomycosis**; also sporotrichosis, chronic coccidioidomycosis, phaeohyphomycosis, tinea/onychomycosis. Limitations: poor CSF penetration, erratic capsule absorption (monitor levels), potent CYP3A4 inhibitor, hepatotoxicity and **negative inotropy** → **may precipitate CHF**. *SUBA-itraconazole* gives improved/predictable absorption.
- ▶ **Voriconazole** — oral/IV; far broader than fluconazole (covers *C. glabrata/C. krusei*, **Aspergillus**, *Scedosporium*, endemic dimorphs) **but NOT Mucorales**; penetrates CSF and ocular fluid. **Preferred agent for invasive aspergillosis**. Metabolised by CYP2C9/3A4/2C19 (genetic polymorphism → variable levels — *monitor*); toxicities: visual disturbances, photosensitivity/skin-cancer risk, hepatotoxicity, and the azole-unique **fluorosis-associated periostitis**.
- ▶ **Posaconazole** — oral suspension/tablet + IV; *broader than voriconazole, includes Mucorales*. Antifungal prophylaxis in neutropenic leukaemia and allogeneic HSCT; **treatment of fluconazole/itraconazole-refractory oropharyngeal candidiasis; salvage for aspergillosis, mucormycosis, fusariosis**. Tablet > suspension absorption; may cause pseudohyperaldosteronism** (hypokalaemia, oedema, hypertension).
- ▶ **Isavuconazole** — oral/IV; broad spectrum like posaconazole. FDA-approved for **aspergillosis** (non-inferior to voriconazole) and **mucormycosis**; less hepatotoxic, fewer P450 interactions, no skin/bone/visual toxicity.
- ▶ **Oteseconazole** — newest azole (a **tetrazole**), oral only; potent anti-*Candida* (incl. azole-resistant) and endemic-dimorph activity; long half-life allows **once-weekly** dosing. Approved for **recurrent vulvovaginal candidiasis**; no hepatotoxicity/P450 interactions but **contraindicated in women of reproductive potential** (fetal ocular toxicity).

Other oral agents

- ▶ **Terbinafine (allylamine)**: inhibits **squalene epoxidase**, blocking ergosterol synthesis and causing toxic squalene accumulation (fungicidal). Penetrates poorly beyond skin/nails, so reserved for **onychomycosis and dermatophytosis (ringworm)** — as effective as itraconazole; usual dose **250 mg orally daily** (≈6 weeks fingernail, ≈12 weeks toenail). Risk of **hepatotoxicity** (and rare cutaneous reactions).
- ▶ **Flucytosine (5-fluorocytosine)**: taken up by fungal cytosine permease and **converted intracellularly to 5-fluorouracil**, which inhibits fungal DNA/RNA synthesis. Always used in **combination** (synergy + avoids resistance) — chiefly with **amphotericin B for induction of cryptococcal meningitis** (good CSF penetration, rapid CSF sterilisation) and for candidal meningitis/endocarditis. Toxicity: **bone-marrow suppression** and hepatotoxicity (worse when combined with AmB).

- ▶ **Ibrexafungerp (triterpenoid):** oral β -1,3-glucan synthase inhibitor (cell-wall target) with potent anti-*Candida* activity that is retained at the low pH of the vaginal mucosa; approved for **acute and recurrent vulvovaginal candidiasis**; contraindicated in pregnancy/lactation.
- ▶ **Griseofulvin:** binds fungal microtubules and disrupts the mitotic spindle; deposited in keratin precursor cells, rendering new keratin resistant to dermatophyte invasion. Approved for **dermatophyte infection of skin, hair and nails** — particularly **tinea capitis** (given with selenium sulfide/ketoconazole shampoo; examine family members). Side-effects: GI upset, headache, urticaria, photosensitivity.
- ▶ **Nystatin (oral polyene):** binds ergosterol; not absorbed from the gut, so the **oral suspension** ("swish-and-swallow") acts luminally for **oropharyngeal candidiasis**; also topical for vaginal candidiasis.

Parenteral comparators (for completeness — no oral form)

- ▶ **Amphotericin B (polyene):** broadest-spectrum, **fungicidal** — forms extramembranous sponge-like aggregates that **extract ergosterol** from the fungal membrane. **No licensed oral formulation**; remains preferred for **mucormycosis, fusariosis**, and induction of cryptococcal meningitis and severe endemic mycoses. Limited by **nephrotoxicity** and infusion reactions (fever, chills); **lipid formulations** (liposomal AmB, AmB lipid complex) reduce toxicity.
- ▶ **Echinocandins (caspofungin, anidulafungin, micafungin, rezafungin):** **IV only**; inhibit β -1,3-glucan synthase; fungicidal for *Candida*, fungistatic for *Aspergillus*; no activity vs *Cryptococcus*, Mucorales or endemic dimorphs. **First-line for candidaemia/invasive candidiasis** (minimal toxicity and interactions, active vs all *Candida*). Rezafungin allows weekly dosing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **"Antifungal targets on the fungal cell" schematic:** draw a fungal cell with labelled concentric layers — **Cell wall (β -1,3-glucan)** → arrow from *Echinocandins* and *Ibrexafungerp* (triterpenoid) labelled "inhibit β -1,3-glucan synthase"; **Cell membrane (ergosterol)** → *Azoles* labelled "inhibit lanosterol 14 α -demethylase / ergosterol synthesis", *Terbinafine* labelled "inhibit squalene epoxidase", *Amphotericin B* / *Nystatin* (polyenes) labelled "bind & extract ergosterol → pore"; **Nucleus/DNA** → *Flucytosine* labelled "5-FU → 5-FU, inhibits DNA/RNA"; **Microtubules/mitotic spindle** → *Griseofulvin*.
- ▶ **Ergosterol biosynthesis pathway bar:** Squalene → (squalene epoxidase, blocked by *terbinafine*) → Lanosterol → (14 α -demethylase, blocked by *azoles*) → Ergosterol → (bound/extracted by *amphotericin B*, *nystatin*). Labels: Squalene, Squalene epoxidase, Lanosterol, 14 α -demethylase, Ergosterol.

Clinical / Diagnostic significance

- ▶ **Route dictates use:** oral azoles, terbinafine, flucytosine, ibrexafungerp and griseofulvin enable outpatient and **step-down** ("IV-to-oral switch") therapy after initial IV induction; AmB and echinocandins anchor severe/inpatient disease.

- ▶ **Spectrum gaps to remember:** fluconazole — *no molds*; voriconazole — *no Mucorales*; echinocandins — *no Cryptococcus/Mucorales/dimorphs*; **posaconazole and isavuconazole cover Mucorales** (the only azoles that do).
- ▶ **Therapeutic drug monitoring** is required for itraconazole (capsule), voriconazole (CYP2C19 polymorphism) and posaconazole suspension to ensure efficacy and limit toxicity.
- ▶ **Drug interactions:** azoles are CYP inhibitors (itraconazole/voriconazole/posaconazole — clinically major); echinocandins and oteseconazole have minimal interactions.
- ▶ **Resistance:** rising azole/echinocandin-resistant *C. glabrata* and *C. auris* and azole-resistant *A. fumigatus* — echinocandins are preferred empirically for candidaemia, de-escalated to fluconazole once susceptibility is known.

High-yield exam pointers

- ▶ **Four targets:** ergosterol membrane (azoles, allylamines, polyenes), glucan cell wall (echinocandins, triterpenoids), DNA (flucytosine), spindle (griseofulvin).
- ▶ Azoles inhibit 14 α -demethylase → fungistatic; AmB extracts ergosterol → fungicidal; terbinafine inhibits squalene epoxidase.
- ▶ Itraconazole = DOC for mild–moderate histoplasmosis & blastomycosis; voriconazole = DOC for invasive aspergillosis; fluconazole = DOC for coccidioidal meningitis + cryptococcal consolidation.
- ▶ AmB + flucytosine = induction for cryptococcal meningitis (synergy, CSF penetration).
- ▶ Posaconazole/isavuconazole cover Mucorales; voriconazole does **not**.
- ▶ Terbinafine/griseofulvin = dermatophytes (onychomycosis, tinea capitis); nystatin oral = oral thrush.
- ▶ **Signature toxicities:** voriconazole — visual disturbance + periostitis + photosensitivity; posaconazole — pseudohyperaldosteronism; itraconazole — CHF; flucytosine — marrow suppression; AmB — nephrotoxicity; terbinafine — hepatotoxicity.
- ▶ **Newer oral agents:** ibrexafungerp & oteseconazole for (recurrent) vulvovaginal candidiasis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Pathogenesis, Diagnosis, and Treatment of Fungal Infections" (antifungal drugs: amphotericin B, azoles, echinocandins, ibrexafungerp, flucytosine, terbinafine, topical agents) — primary source for mechanisms, spectra and indications.
- ▶ **Harrison's 22e** — "Fungal Skin Infections / Dermatophytes" (griseofulvin, terbinafine, itraconazole for skin–hair–nail dermatophytosis).
- ▶ **CMDT 2026** — "Mycotic Infections" and "Dermatologic Disorders" (oral dosing and use: terbinafine 250 mg/day, itraconazole 200 mg/day, griseofulvin for tinea capitis, fluconazole for tinea versicolor).

Coverage note: Harrison 22e does not list griseofulvin in its core antifungal-drug section; its dermatophyte use is taken from Harrison's fungal-skin material and CMDT, and griseofulvin's microtubule/mitotic-spindle mechanism is standard, universally accepted textbook pharmacology.



Bioavailability and protein binding

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

Definition / Introduction — **Bioavailability (F)** is the *fraction of an administered dose that reaches the systemic circulation in an unchanged, active form* after a non-intravenous route; by definition an intravenous dose has $F = 1$ (100%). **Plasma protein binding** describes the reversible association of drug with circulating proteins (chiefly albumin and α_1 -acid glycoprotein); only the **unbound (free) fraction** can cross membranes, reach target receptors, undergo glomerular filtration and hepatic metabolism, and so determines pharmacological effect. Both parameters are key determinants of drug *disposition* (absorption, distribution, metabolism, excretion) and explain much of the inter-individual and disease-related variability in drug response that the clinician must anticipate.

Bioavailability — concept and determinants

- ▶ F integrates two events: (1) the *fraction absorbed* across the gut wall, and (2) the *fraction surviving presystemic (first-pass) elimination* in gut wall and liver.
- ▶ Bioavailability is <100% for two main reasons (Harrison): **incomplete absorption**, or **metabolism/elimination before entering the systemic circulation** (first-pass effect).
- ▶ Compared with the same intravenous dose, a non-IV dose shows a **later and lower peak plasma concentration** and a **smaller area under the time–concentration curve (AUC)**; F is estimated as the ratio $AUC(\text{oral})/AUC(\text{IV})$, dose-corrected.
- ▶ **Factors reducing absorption**: incomplete release from the dosage form, destruction at the site of administration, poor solubility/lipophilicity, GI transit and gastric pH, food, and gut efflux transporters.

- **P-glycoprotein** (product of the *ABCB1/MDR1* gene) on the apical enterocyte and canalicular hepatocyte pumps drug back into lumen/bile, limiting bioavailability (e.g. digoxin); it is also a key element of the blood–brain barrier.

Route	Bioavailability	First-pass effect	Comment
Intravenous	100% (reference)	Bypassed	Most rapid, fully predictable
Intramuscular / subcutaneous	High, usually ~75–100%	Bypassed	Depends on perfusion, solubility
Sublingual / buccal / transdermal	Variable–high	Bypassed	Route for high first-pass drugs (GTN)
Rectal	Partial bypass	Partial	Lower haemorrhoidal veins skip liver
Oral	Lowest / most variable	Maximal	Gut wall + portal–hepatic extraction

First-pass (presystemic) elimination — and its clinical exploitation

- An orally administered drug must traverse **enterocyte** → **portal vein** → **liver** before reaching the systemic circulation; metabolism or biliary/luminal excretion at any step constitutes **presystemic (first-pass) extraction** (Harrison).
- **Drugs unusable orally:** *Nitroglycerin* is almost completely extracted presystemically, so it is given by the **sublingual, transdermal or intravascular** routes that bypass the liver.
- **High first-pass drugs needing larger oral doses:** *verapamil* — typical IV dose 1–5 mg versus a usual single **oral dose of 40–120 mg** (Harrison) — also propranolol, morphine, lidocaine, nifedipine, midazolam.
- **First-pass exploited therapeutically:** *low-dose aspirin* irreversibly acetylates cyclo-oxygenase in platelets within the portal blood, yet is **deacylated on first pass through the liver**, giving platelet inhibition with relative systemic sparing.

Clinical implications of altered bioavailability

- **Liver disease (cirrhosis):** reduced first-pass metabolism (hepatocyte dysfunction, altered architecture, **porto-systemic shunts**) raises oral bioavailability — for high-extraction drugs such as **morphine, meperidine (pethidine), midazolam and nifedipine the oral bioavailability is almost doubled**, so oral doses must be reduced (Harrison).
- **Heart failure / shock:** gut hypoperfusion and mucosal oedema slow or reduce drug absorption, blunting the effect of oral therapy; parenteral routes are preferred in the unstable patient.
- **Formulation matters:** slow-/sustained-release products deliberately slow absorption to smooth peak–trough swings; altered dissolution explains why expired or degraded drug fails.
- **Bioequivalence & generic substitution:** two products are *bioequivalent* when their rate (C_{max} , T_{max}) and extent (AUC) of absorption are statistically comparable; for **narrow-therapeutic-index drugs (warfarin, phenytoin, digoxin, levothyroxine, antiepileptics, immunosuppressants)** even small bioavailability differences between brands/generics can cause sub-therapeutic failure or toxicity, so switching warrants monitoring.

- ▶ **Drug interactions affecting F:** antacids/cholestyramine bind drugs in the gut (↓ absorption); proton-pump inhibitors/H₂-blockers raise gastric pH and reduce dissolution of weak bases (e.g. ketoconazole); P-glycoprotein/CYP3A inducers (rifampin, St John's wort) lower bioavailability of substrates.

Plasma protein binding — principles

- ▶ Only **free (unbound) drug** is pharmacologically active and available for distribution, metabolism and renal filtration; **drug response correlates with free, not total, plasma concentration** (Harrison).
- ▶ Bound and free drug exist in rapid equilibrium; binding acts as a **circulating reservoir** that buffers fluctuations and prolongs duration of action.

Binding protein	Drugs bound	Behaviour in disease
Albumin	Acidic / neutral drugs — warfarin, phenytoin, NSAIDs/salicylates, sulfonamides, valproate, diazepam	Falls in nephrotic syndrome, cirrhosis, malnutrition, burns, pregnancy → ↑ free fraction
α ₁ -acid glycoprotein (AAG)	Basic drugs — lidocaine, quinidine/quinine, propranolol, verapamil, tricyclics	Acute-phase reactant — rises in MI, infection, surgery, malaria, cancer → ↓ free fraction
Lipoproteins / globulins	Lipophilic drugs (e.g. cyclosporine)	Vary with lipid status

- ▶ *Corpus example:* in malaria, plasma **protein binding of quinine to α₁-acid glycoprotein increases to ~90%**, reducing free drug — illustrating how an acute illness alters the active fraction (Harrison, antimalarials chapter).

Clinical implications of altered protein binding

- ▶ The **"highly bound drug" rule:** the smaller the free fraction, the greater the effect of any change — *a fall in binding from 99% to 98% doubles the free concentration (1% → 2%)* and can precipitate toxicity even though *total* level is unchanged (Harrison).
- ▶ **Hypoalbuminaemia / uraemia (CKD, cirrhosis, nephrosis):** reduced binding **increases free drug and drug effect**; uraemia additionally displaces phenytoin from albumin (uraemic toxins compete) — hence free drug should be monitored.
- ▶ **Acute-phase states (MI, sepsis, surgery, trauma):** transient rise in AAG **increases binding of basic drugs and may reduce efficacy** (Harrison).
- ▶ **Displacement (protein-binding) drug interactions** (*universally taught examples*): sulfonamides / phenylbutazone / NSAIDs displace **warfarin** (transient ↑ INR, bleeding); **valproate** displaces **phenytoin**; sulfonamides and ceftriaxone displace **bilirubin** from neonatal albumin, risking **kernicterus**. Clinically, displacement alone is usually transient because the liberated drug is rapidly redistributed and cleared — it becomes dangerous mainly when **clearance is simultaneously impaired** and the drug is narrow-index.
- ▶ **Therapeutic drug monitoring (TDM) caveat:** for highly bound drugs, total levels mislead when binding is abnormal. For **phenytoin** the usual total target is **10–20 mg/L**, but falls to **~5–10 mg/L in uraemia and severe hypoalbuminaemia**; the **free phenytoin** target is **0.5–2.0 mg/L** and should

be measured (or a corrected/Sheiner–Tozer estimate used) in renal/hepatic disease and low albumin (CMDT, therapeutic drug monitoring).

- ▶ **Distribution & special compartments:** highly bound drugs have limited tissue and CNS penetration; binding influences volume of distribution and the success of removal by dialysis (poorly bound drugs are dialysable).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Plasma concentration–time curves (IV vs oral):** x-axis *Time*, y-axis *Plasma concentration*; overlay an **IV bolus curve** (high early peak, single exponential decline) and an **oral curve** (delayed lower C_{max} , later T_{max} , smaller AUC). Label: C_{max} , T_{max} , $AUC(IV)$, $AUC(oral)$, " $F = AUC(oral)/AUC(IV)$ ", and shade the area difference as "incomplete bioavailability".
- ▶ **First-pass elimination schematic:** boxes/arrows *Gut lumen* → *Enterocyte* → *Portal vein* → *Liver* → *Systemic circulation*; label **P-glycoprotein efflux** (enterocyte apex), **CYP3A4 metabolism** (enterocyte + hepatocyte), **biliary excretion**, and the routes that *bypass* it: **sublingual / transdermal / IV / rectal (lower veins)**.

Clinical / Diagnostic significance

- ▶ Predicts when to **avoid the oral route** (GTN) or **escalate the oral dose** (verapamil, propranolol) for high first-pass drugs.
- ▶ Mandates **dose reduction of high-extraction oral drugs in cirrhosis** and a **switch to parenteral therapy in shock/heart failure**.
- ▶ Justifies **monitoring free (not total) drug** for phenytoin (and other highly bound, narrow-index drugs) in **renal failure, hepatic failure and hypoalbuminaemia**.
- ▶ Explains brand–generic non-equivalence concerns and the need for re-titration/monitoring after switching narrow-index drugs.
- ▶ Frames clinically important **drug interactions** at absorption (chelation, pH, P-gp/CYP induction) and at protein-binding/displacement levels.

High-yield exam pointers

- ▶ **F = fraction reaching systemic circulation in active form; IV = 100%; $F = AUC(oral)/AUC(IV)$.**
- ▶ Two causes of low F: **incomplete absorption + presystemic (first-pass) elimination**.
- ▶ **GTN** — complete first-pass extraction → never oral; **verapamil** IV 1–5 mg vs oral 40–120 mg.
- ▶ **Cirrhosis doubles oral bioavailability** of morphine, pethidine, midazolam, nifedipine → reduce dose.
- ▶ **Only free drug is active;** for a 99%-bound drug a 1% fall in binding **doubles** free concentration.
- ▶ **Albumin** → **acidic drugs** (warfarin, phenytoin); **α_1 -acid glycoprotein** → **basic drugs** (lidocaine, quinidine) and rises as an **acute-phase reactant**.
- ▶ **Hypoalbuminaemia/uraemia** ↑ free phenytoin → **monitor free level (0.5–2.0 mg/L)**; total target falls to 5–10 mg/L.

- ▶ Classic displacement: **sulfonamides** → **warfarin** (bleeding); **sulfonamides** → **bilirubin** → **kernicterus** in neonates.
- ▶ **Narrow-therapeutic-index drugs** (warfarin, digoxin, phenytoin, levothyroxine, immunosuppressants) are most vulnerable to both bioavailability and protein-binding changes.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Principles of Clinical Pharmacology*" (absorption and bioavailability, first-pass/presystemic elimination, P-glycoprotein, clinical implications of altered protein binding and clearance, disease effects on drug disposition); and the antimalarial-agents chapter (quinine binding to α 1-acid glycoprotein in malaria; phenytoin/warfarin as highly protein-bound drugs).
- ▶ **CMDT 2026** — Appendix "*Therapeutic Drug Monitoring*" (phenytoin total vs free target ranges; protein binding reduced in uraemia/hypoalbuminaemia; free-level monitoring).
- ▶ *Coverage note*: the quantitative bioequivalence limits (FDA 80–125% AUC/C_{max}), the explicit albumin-vs-AAG drug lists, the Sheiner–Tozer corrected-phenytoin equation, and the classic displacement examples (warfarin–sulfonamide, valproate–phenytoin, bilirubin–kernicterus) are standard, universally accepted clinical pharmacology included to complete the answer; Harrison 22e states the underlying free-drug and altered-binding principles but does not tabulate these specific examples.



Cloning principle and methods

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

Definition / Introduction — *Cloning* is the production of multiple genetically **identical** copies of a biological entity — a defined segment of DNA (a **gene**), a cell, or a whole organism. In clinical molecular medicine the term usually means **molecular (gene/DNA) cloning**: the insertion of a defined DNA fragment of interest into a self-replicating DNA molecule (a **vector**), introduction of this **recombinant DNA** into a host cell (commonly *Escherichia coli*), and faithful amplification of the fragment as the host divides — yielding limitless identical copies for sequencing, expression or therapy. The technique exploits two universal properties of DNA emphasised in Harrison: its **double-stranded base-pair complementarity** (A–T, G–C) and its **faithful semiconservative replication**, which together permit a fragment to be copied with high fidelity. Recombinant DNA and RNA technology underpins the large-scale manufacture of peptide hormones, growth factors, cytokines, clotting factors and vaccines (e.g., recombinant insulin analogues, mRNA SARS-CoV-2 vaccines, siRNA therapeutics).

Types of cloning

Type	What is copied	Core method	Product/use
Molecular / gene (DNA) cloning	A DNA fragment / gene	Recombinant DNA technology — vector + host	Gene amplification, sequencing, recombinant proteins

Type	What is copied	Core method	Product/use
Cellular cloning	A single cell	Clonal expansion in culture	Cell lines, hybridomas (monoclonal antibodies)
Reproductive (organism) cloning	A whole organism	Somatic cell nuclear transfer (SCNT)	<i>Dolly the sheep</i> (1996); identical animal
Therapeutic cloning	Patient-specific stem cells	SCNT into enucleated oocyte → blastocyst	Autologous embryonic stem cells / iPSC-type cells for regenerative therapy

Principle — recombinant DNA technology

- ▶ **Restriction–ligation principle:** sequence-specific bacterial enzymes cut DNA at defined sites; the same cut ends on insert and vector are **complementary**, so they can be re-joined by a ligase to create a single hybrid (**recombinant**) molecule.
- ▶ **Self-replication principle:** the vector carries an **origin of replication**, so once inside a dividing host cell it (and its insert) is copied many-fold — *amplification by biological cloning*.
- ▶ **Selection principle:** a marker (usually antibiotic resistance) on the vector lets only successfully transformed cells survive, so that each surviving colony is a **clone** descended from one cell carrying one recombinant molecule.
- ▶ **Complementarity** also allows the alternative *in vitro* amplification route — the **polymerase chain reaction (PCR)** — and the detection of clones by **hybridisation** with labelled probes.

Essential tools — enzymes and vectors

Tool	Function in cloning
Restriction endonucleases (Type II)	Cut double-stranded DNA at specific <i>palindromic</i> recognition sites (e.g., <i>EcoRI</i> = GAATTC), generating either staggered " sticky " (cohesive) ends or blunt ends
DNA ligase (T4)	Seals the phosphodiester backbone, covalently joining insert to vector → recombinant DNA
Reverse transcriptase	Synthesises complementary DNA (cDNA) from an mRNA template (intron-free copy of a gene)
DNA polymerase / thermostable <i>Taq</i> polymerase	Fills/extends strands; drives PCR-based amplification of the insert
Alkaline phosphatase / terminal transferase, nucleases	Prevent vector self-ligation; tailor ends
Vectors	Carrier DNA that replicates in the host and carries the insert (see range below)

Vector hierarchy by insert capacity (choice depends on fragment size):

- ▶ **Plasmids** — small circular bacterial DNA; inserts up to ~10 kb; carry *ori* + selectable marker (e.g., ampicillin resistance) + a multiple-cloning site.
- ▶ **Bacteriophage λ** (~15–20 kb) and **cosmids** (~45 kb) — larger inserts, packaged into phage.

- ▶ **Bacterial artificial chromosomes (BACs)** — up to ~300 kb; **yeast artificial chromosomes (YACs)** — up to ~1 Mb; used for genomic libraries and genome mapping.
- ▶ **Expression vectors** — contain a promoter/enhancer so the cloned gene is *transcribed and translated* into protein in the host.
- ▶ **Viral vectors** (for mammalian cells / gene therapy) — retroviral, **lentiviral**, **adeno-associated viral (AAV)**, adenoviral, herpesviral; AAV cargo is limited to ~5 kb because the wild-type genome is only ~4.7 kb.

Steps of molecular cloning

- ▶ **Generate the DNA fragment (insert):** isolate genomic DNA and digest it with a restriction enzyme, **or** copy an expressed gene into intron-free **cDNA** using reverse transcriptase, **or** amplify the target by **PCR** with specific primers.
- ▶ **Cut the vector** with the *same* restriction enzyme so its ends are complementary to the insert's ends.
- ▶ **Ligation:** mix insert + linearised vector with **DNA ligase** → covalently sealed **recombinant DNA** molecules.
- ▶ **Introduce into a host cell** (**transformation** of *E. coli* by heat-shock/electroporation, **or** **transfection/transduction** of mammalian cells with a viral vector).
- ▶ **Selection and screening:** plate on antibiotic-containing medium so only vector-bearing cells grow; identify clones carrying the *insert* by **blue–white (α -complementation, X-gal/IPTG) screening**, **colony hybridisation** with a labelled probe, **colony PCR**, or restriction mapping.
- ▶ **Amplify and harvest:** grow a positive colony (a pure **clone**) to mass-produce identical copies of the fragment for sequencing, probe production, or — with an expression vector — recombinant protein.

Gene libraries and alternative methods

- ▶ **Genomic library** — clones representing the *entire* genome (introns + exons + regulatory + non-coding DNA), made from restriction fragments of total genomic DNA.
- ▶ **cDNA library** — clones of only the *expressed* genes of a tissue (made from its mRNA via reverse transcriptase); tissue-specific and intron-free.
- ▶ **PCR cloning** — rapid *in vitro* amplification of a defined sequence; can replace biological cloning for sequence analysis and enables genetic testing on minute DNA amounts (blood, buccal cells, archival tumour) — heavily used in molecular diagnostics.
- ▶ **Expression cloning** — selecting clones by the *function/protein* they produce.

Reproductive and therapeutic cloning (organism-level)

- ▶ **Somatic cell nuclear transfer (SCNT):** the nucleus of an adult somatic (donor) cell is transferred into an **enucleated oocyte**; the reconstructed egg is activated to develop. Transferred to a surrogate it yields a genetically identical animal (**reproductive cloning** — *Dolly*, 1996).
- ▶ **Therapeutic cloning:** the SCNT blastocyst is used instead to derive **patient-specific pluripotent stem cells** for autologous regenerative therapy, avoiding immune rejection. (Human reproductive cloning is banned on ethical grounds.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Plasmid gene-cloning workflow:** draw a circular **plasmid vector** labelling *origin of replication*, *selectable marker* (amp^R), and *multiple-cloning/restriction site*; show a **foreign DNA fragment** cut by the *same restriction enzyme*; arrows to **DNA ligase** → **recombinant plasmid** → **transformation into E. coli** → **selection on antibiotic plate** → **colony (clone) amplification**. Labels: *target DNA*, *restriction enzyme*, *sticky ends*, *vector*, *ligase*, *recombinant DNA*, *host cell*, *antibiotic selection*, *clone*.
- ▶ **Sticky-end ligation inset:** two complementary single-stranded overhangs (e.g., ...G / AATTC... of *EcoRI*) annealing and being sealed; label *5' overhang*, *complementary base pairing*, *phosphodiester bond*, *DNA ligase*.

Clinical / Diagnostic significance

- ▶ **Recombinant therapeutics (expression cloning):** human insulin and insulin analogues with favourable kinetics, growth hormone, erythropoietin, clotting factor concentrates, GLP-1 agonists, recombinant hepatitis B (HBsAg) and **mRNA vaccines**, and **siRNA drugs** (e.g., for hypercholesterolaemia) — all enabled by cloning genes into expression systems.
- ▶ **Monoclonal antibodies** via cloned/hybridoma technology underpin much of modern targeted therapy.
- ▶ **Gene therapy (cloning into viral vectors):** therapeutic genes are cloned as **cDNA** into **lentiviral** vectors (β -thalassaemia, sickle cell disease, X-linked SCID, adrenoleukodystrophy, metachromatic leukodystrophy) or **AAV** vectors (spinal muscular atrophy, RPE65 retinal dystrophy, haemophilia A/B with *factor IX Padua*, Duchenne microdystrophin). Vectors are classed as **integrating** (retro-/lentiviral, risk of insertional mutagenesis/LMO-2 leukaemia) vs **non-integrating/episomal** (AAV, adenoviral, plasmid).
- ▶ **Genome editing** extends cloning: a **CRISPR–Cas9/guide-RNA** complex (e.g., disrupting *BCL11A* to re-activate fetal haemoglobin) is delivered for sickle cell disease/thalassaemia, with optional AAV-supplied repair templates via homology-directed repair.
- ▶ **Molecular diagnostics built on the same principles:** PCR/qPCR, RFLP, Southern blotting, FISH, microarray/DNA chips, MLPA, and next-generation (massively parallel) sequencing for inherited-disease, oncology and infectious-pathogen testing.

High-yield exam pointers

- ▶ **Recombinant DNA** = insert + vector joined by **ligase** after cutting with the **same restriction endonuclease**.
- ▶ **Restriction enzymes** recognise short **palindromes** and give **sticky** or **blunt ends** (Arber, Smith, Nathans — Nobel 1978).
- ▶ Cloning vectors in ascending capacity: **plasmid** < **phage λ** < **cosmid** < **BAC** < **YAC**; expression vectors add a promoter; viral vectors transduce mammalian cells.
- ▶ **cDNA** (reverse transcriptase) is **intron-free**; a **cDNA library** = expressed genes, a **genomic library** = whole genome.

- ▶ **Selection** by antibiotic resistance; **screening** by **blue–white (α -complementation)**, colony hybridisation or colony PCR.
- ▶ **PCR** = rapid cell-free amplification alternative; requires **primers** + **thermostable polymerase** (Mullis — Nobel 1993).
- ▶ **SCNT** produced **Dolly (1996)** — reproductive cloning; therapeutic cloning yields **patient-specific stem cells**.
- ▶ Cloning into **expression/viral vectors** delivers recombinant insulin, vaccines, clotting factors and **gene therapies** (lentiviral vs AAV; integrating vs episomal).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (DNA structure, base-pair complementarity, replication, recombinant DNA/RNA technology, PCR, recombinant therapeutics); "The Practice of Genetics in Clinical Medicine" (PCR, RFLP, Sanger vs massively-parallel/next-generation sequencing, FISH, Southern blotting, MLPA, DNA microarrays); "Gene and Cell-Based Therapy in Clinical Medicine" (cloning into retroviral/lentiviral/AAV/adenoviral vectors, cDNA inserts, integrating vs non-integrating vectors, CRISPR–Cas9 genome editing, insertional mutagenesis).
- ▶ **Coverage note (spec gap = true):** Harrison 22e is a clinical-genetics text and does **not** detail the classical wet-lab molecular-cloning workflow (restriction-enzyme digestion, sticky/blunt-end ligation, plasmid/cosmid/BAC/YAC vectors, bacterial transformation, antibiotic selection, blue–white screening, and genomic vs cDNA libraries) or somatic-cell nuclear transfer. These elements are supplied here from **universally accepted standard molecular biology** (consistent with Harrison's stated principles of DNA complementarity, replication and recombinant DNA technology) and are flagged as such; every Harrison-grounded specific (PCR, RFLP, FISH, Southern blot, NGS, viral vectors, AAV ~5 kb cargo limit, CRISPR/BCL11A, factor IX Padua, recombinant insulin/mRNA/siRNA) has been verified against the chapters above.



Complement pathway, functions and regulation

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

Definition / Introduction — The **complement system** is a tightly regulated cascade of more than 30 plasma and membrane proteins that forms a major effector arm of **innate immunity** and bridges it to **adaptive immunity**. Activation proceeds through three initiating routes — the **classical**, **lectin (mannose-binding)** and **alternative** pathways — that all converge on the cleavage of **C3**, feed into a common **terminal pathway**, and culminate in the lytic **membrane attack complex (MAC, C5b–9)**. Its central outputs are **opsonisation** of microbes, generation of **inflammatory anaphylatoxins**, **cytolysis** of pathogens, and **clearance of immune complexes and apoptotic cells**. Because uncontrolled activation injures host tissue, the system is restrained by a panel of soluble and membrane-bound **regulatory proteins** whose failure produces a distinct group of human diseases.

Activation pathways

Feature	Classical pathway	Lectin (MBL) pathway	Alternative pathway
Principal trigger	Antigen–antibody immune complexes (IgM, IgG1/2/3) binding C1q	Mannose / terminal sugars on microbial surfaces	Spontaneous C3 "tick-over" (C3(H ₂ O)); microbial, fungal, viral, tumour and "altered-self" surfaces — antibody-independent
Recognition / initiating proteins	C1 complex = C1q–C1r–C1s → C4, C2	MBL / ficolins + MASP-1, MASP-2 → C4, C2	C3, factor B, factor D, properdin (P)
C3 convertase	C4b2a	C4b2a	C3bBb (stabilised by properdin)
C5 convertase	C4b2a3b	C4b2a3b	C3bBbC3b
Immune link	Links innate + adaptive (specific antibody)	Innate pattern recognition	Innate amplification loop

- ▶ **Terminal (common) pathway**: all three converge on **C3 cleavage** → C3a + C3b, then C5 → C5a + C5b; C5b sequentially recruits C6, C7, C8 and **multiple C9** molecules to form the **MAC (poly-C9 pore)** that inserts into and lyses target membranes.
- ▶ An **amplification loop** (factor D, factor B, properdin generating C3bBb) means a small initial stimulus from *any* pathway is greatly magnified through the alternative pathway.

Biological functions

- ▶ **Opsonisation / phagocytosis**: surface-bound **C3b** and **iC3b** (and C4b) coat microbes and are recognised by complement receptors (CR1/CD35, CR3) on neutrophils and macrophages — the dominant antibacterial role; deficiency predisposes to **encapsulated pyogenic organisms** (*S. pneumoniae*, *H. influenzae*).
- ▶ **Inflammation (anaphylatoxins)**: small cleavage fragments **C3a** and **C5a** trigger mast-cell/basophil mediator release, increase vascular permeability and smooth-muscle contraction; C5a is a powerful **neutrophil chemoattractant** and activator.
- ▶ **Cytolysis**: the **MAC (C5b–9)** lyses bacteria and cells; it is the **only effective defence against *Neisseria*** (thick wall lysed only by MAC).

- **Immune-complex handling:** early components (C1q, C4, C3) **solubilise and clear circulating immune complexes**; C3b-coated complexes bind erythrocyte **CR1** and are transported to liver/spleen — failure causes deposition and **vasculitis / glomerulonephritis**.
- **Clearance of apoptotic cells** and cellular debris (C1q, C3) — important in preventing autoimmunity.
- **Bridge to adaptive immunity:** C3d bound to antigen engages **CR2 (CD21)** on B cells, lowering the threshold for B-cell activation and antibody production.

Regulation of complement

Regulation is essential because activated C3b and the convertases would otherwise deposit indiscriminately on host cells. Control acts at three checkpoints — **initiation, the C3/C5 convertases, and MAC assembly** — by both **fluid-phase** and **membrane-bound** inhibitors. **Properdin** is the only *positive* regulator.

Regulator	Location / type	Action
C1 inhibitor (C1-INH; SERPING1)	Plasma serpin	Inactivates C1r/C1s and MASP-2 ; also inhibits kallikrein and factor XIIa (limits bradykinin)
C4b-binding protein (C4BP)	Plasma	Decays the classical C3 convertase; cofactor for factor I cleavage of C4b
Factor H	Plasma	Decays the alternative C3 convertase; cofactor for factor I cleavage of C3b; discriminates host vs microbial surfaces
Factor I	Plasma serine protease	Cleaves/inactivates C3b and C4b (requires cofactors H, C4BP or MCP)
Decay-accelerating factor (CD55, DAF)	Membrane, GPI-anchored	Accelerates decay of C3 and C5 convertases
Membrane cofactor protein (MCP, CD46)	Membrane	Cofactor for factor I cleavage of surface-bound C3b/C4b
CD59 (protectin / MIRL)	Membrane, GPI-anchored	Blocks incorporation of C9 into C5b-8 → prevents MAC formation
Properdin (factor P)	Plasma — <i>stabiliser</i>	Stabilises the alternative-pathway C3 convertase (C3bBb)

- Two regulators — **CD55 and CD59** — are attached to the membrane through a **glycosylphosphatidylinositol (GPI) anchor**; their loss (PNH) removes host protection from autologous complement.

Diseases of complement deficiency and dysregulation

Defect	Disorder	Mechanism
Classical components C1q, C1r/s, C4, C2	SLE / lupus-like syndromes , immune-complex disease, pyogenic infection	Defective clearance of immune complexes & apoptotic cells (C1q deficiency = strongest genetic link to SLE)

Defect	Disorder	Mechanism
C3, factor I, factor H	Pyogenic infections; factor H → haemolytic-uraemic syndrome	Loss of opsonisation; factor I/H deficiency causes secondary C3 consumption
Alternative pathway factor D, properdin	Recurrent <i>Neisseria</i> (meningococcal) infection	Failure of alternative-pathway amplification
Terminal C5, C6, C7, C8 (±C9)	Recurrent <i>Neisseria</i> infection	Cannot assemble MAC to lyse <i>Neisseria</i>
C1-INH deficiency (<i>SERPING1</i>)	Hereditary angioedema (HAE)	Unopposed C1/kallikrein activation → excess bradykinin ; ↓C4, ↓C2
PIGA mutation → loss of CD55 + CD59	Paroxysmal nocturnal haemoglobinuria (PNH)	Complement-mediated intravascular haemolysis + thrombosis
Alternative-pathway dysregulation — CFH, CFI, CD46, C3, CFB, THBD	Atypical HUS (aHUS)	Endothelial complement injury → thrombotic microangiopathy + AKI
C3 nephritic factor / CFHR mutations	C3 glomerulopathy (dense-deposit disease, C3GN)	Persistent alternative-pathway activation; glomerular C3 deposition with low C3

- **Hereditary angioedema**: autosomal dominant, fully penetrant; **Type 1** (~85%) low C1-INH antigen, **Type 2** dysfunctional protein, **Type 3** normal complement (often factor XII mutation). Features — non-pruritic, non-urticarial angioedema, recurrent **GI colic**, **laryngeal oedema**; **chronically low C4** is the best screening clue. Treatment: acute — C1-INH concentrate, **icatibant** (B2-receptor antagonist), **ecallantide** (kallikrein inhibitor); prophylaxis — C1-INH, **lanadelumab**, **berotralstat**, attenuated androgens (danazol).
- **PNH**: somatic **PIGA** mutation in a haematopoietic clone → GPI-anchor deficiency → red cells lacking CD55/CD59 are exquisitely sensitive to complement; intravascular haemolysis, haemoglobinuria, **thrombosis**, and marrow failure (links with aplastic anaemia). Diagnosis — **flow cytometry** showing CD55/CD59-negative cells (Ham acidified-serum test historically).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The three activation pathways converging on the terminal pathway.** Three vertical limbs: (left) **Classical** — labels *Immune complex* → *C1q-C1r-C1s* → *C4, C2* → *C4b2a (C3 convertase)*; (middle) **Lectin** — labels *Mannose on microbe* → *MBL/ficolin* + *MASP-1/MASP-2* → *C4, C2*; (right) **Alternative** — labels *C3(H₂O) / microbial surface* → *factor B + factor D + properdin* → *C3bBb (C3 convertase)*. All converge at a central box **C3** → **C3a + C3b**, then **C5** → **C5a + C5b**, then **C5b-6-7-8-9 (MAC / poly-C9)** → **membrane lysis**. Side arrows label **C3a, C5a = anaphylatoxins** and **C3b = opsonin**.
- ▶ **Diagram 2 — Regulators superimposed on the cascade.** Mark inhibitory points: **C1-INH** on *C1r/C1s* & *MASP*; **C4BP + factor I** on *C4b*; **factor H + factor I** and **CD55 (DAF)** on the *C3 convertase*; **MCP/CD46** as factor-I cofactor; **CD59 (protectin)** blocking *C9/MAC*. Show **properdin** as a green "+" stabilising *C3bBb*.

Clinical / Diagnostic significance

- ▶ **Functional screening:** **CH50** assesses the *classical* + terminal pathway; **AP50 (AH50)** assesses the *alternative* + terminal pathway. A **low CH50 with normal AP50** localises the defect to early classical components, and vice-versa; a profoundly low value prompts measurement of individual components.
- ▶ **C3 and C4 levels** are key serological clues: **low C3 + low C4** indicates **classical-pathway consumption** (active SLE, immune-complex disease); **low C3 with normal C4** indicates **alternative-pathway activation** (post-streptococcal GN, C3 glomerulopathy, aHUS).
- ▶ **Disease-specific tests:** **flow cytometry** for CD55/CD59-deficient clones (PNH); **C1-INH antigen + functional assay with C4 (HAE)**; **anti-factor H antibodies / complement gene panel** (aHUS); **C3 nephritic factor** (dense-deposit disease).
- ▶ **Therapeutics:** terminal-complement blockade with the **anti-C5 monoclonal antibody eculizumab** (and longer-acting **ravulizumab**) is transformative in PNH, aHUS, and C3 glomerulopathy. Because anti-C5 therapy abolishes MAC, patients are at high risk of *Neisseria* and **must receive meningococcal vaccination** (± penicillin prophylaxis) before treatment.
- ▶ **Infection prophylaxis:** patients with classical-, alternative- or terminal-pathway deficiency need appropriate **vaccination (meningococcal, pneumococcal, Hib)** and often **oral penicillin** prophylaxis.

High-yield exam pointers

- ▶ Three activation pathways (classical, lectin, alternative) → **all cleave C3** → common terminal MAC (C5b-9).
- ▶ **C3 convertases:** classical/lectin = **C4b2a**; alternative = **C3bBb**. **C5 convertases:** **C4b2a3b** and **C3bBbC3b**.
- ▶ **C3a + C5a = anaphylatoxins** (C5a chemotactic); **C3b = opsonin**; **MAC = lysis**, the sole defence against *Neisseria*.
- ▶ **Early classical deficiency (C1q/C4/C2)** → SLE & immune-complex disease; **terminal/alternative deficiency** → recurrent *Neisseria*.

- ▶ **Regulators:** C1-INH (HAE), factor H/I & MCP (aHUS), CD55/CD59 GPI-anchored (PNH), C4BP, properdin (only positive regulator).
- ▶ **HAE = C1-INH deficiency**, bradykinin-mediated, **persistently low C4**, no urticaria/pruritus, treat with C1-INH/icatibant/ecallantide.
- ▶ **PNH = PIGA mutation**, loss of CD55/CD59, intravascular haemolysis + thrombosis, diagnosed by **flow cytometry**.
- ▶ **Eculizumab (anti-C5)** for PNH/aHUS/C3G — give **meningococcal vaccine first**.
- ▶ **CH50 (classical) and AP50 (alternative)** are the functional screening tests; combine with **C3/C4** levels.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Introduction to the Immune System" (complement pathways, anaphylatoxins, opsonisation, MAC, Table 360-12 Complement Deficiencies and Associated Diseases); "Primary Immune Deficiency Diseases" (complement deficiency, CH50/AP50, *Neisseria* and SLE associations); "Hemolytic Anemias" (PNH — PIGA/GPI/CD55/CD59, aHUS — CFH/CFI/CD46/C3/CFB/THBD, eculizumab); "Urticaria, Angioedema, and Allergic Rhinitis" (hereditary angioedema, C1-INH/SERPING1, bradykinin, icatibant/ecallantide/lanadelumab/berotralstat); "Glomerular Diseases" (C3 glomerulopathy, dense-deposit disease, C3 nephritic factor, CFHR mutations).
- ▶ **Coverage note:** Harrison provides full pathway, function, deficiency and disease detail and uses the **CD55/CD59/CD46** nomenclature; the synonymous regulator labels **DAF, protectin/MIRL, MCP and C4b-binding protein**, and the convertase composition diagram, are standard, universally accepted immunology added for completeness and are consistent with the cascade as depicted in Harrison's Fig. 360-5 and Fig. 105-10. No dedicated subspecialty immunology text was listed in the spec; grounding is Harrison-based and internally cross-verified.



Cytochrome P450 enzyme system and drug metabolism

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

Definition / Introduction — *Drug metabolism* (biotransformation) is the enzymatic conversion of a drug into more polar, more readily excretable products, occurring predominantly in the liver but also in kidney, intestinal epithelium, lung and plasma. The **cytochrome P450 (CYP)** superfamily is a group of heme-containing **mono-oxygenase** enzymes (named for the 450-nm absorbance peak of their reduced carbon-monoxide complex) that catalyse most **Phase I** oxidative reactions and so determine the clearance, bioavailability and interaction profile of a large fraction of drugs in clinical use. Variability in CYP function — from genetic polymorphism, enzyme induction/inhibition or disease — is a principal source of the wide inter-individual variability seen in drug response and adverse drug reactions (ADRs).

Phases of drug metabolism (biotransformation)

- ▶ **Phase I (functionalisation):** chemical modification — *most often oxidation* — that introduces or unmasks a reactive group (–OH, –NH₂, –SH). This is accomplished chiefly by members of the **cytochrome P450 mono-oxygenase superfamily**; reactions also include reduction and hydrolysis. The product may be active, inactive or toxic.
- ▶ **Phase II (conjugation):** covalent attachment of an endogenous moiety to the drug or its Phase I metabolite, generating a highly polar, usually inactive conjugate. Enzymes include **glucuronyl-, acetyl-, sulfo- and methyl-transferases** (e.g., UGT1A1, N-acetyltransferase, thiopurine S-methyltransferase).
- ▶ **Net effect:** metabolites are *more polar and more readily excreted* than the parent drug (renally or in bile). Drug efflux/uptake **transporters** (e.g., the P-glycoprotein efflux pump, product of the *ABCB1/MDR1* gene, on the apical enterocyte and canalicular hepatocyte membranes) act in concert with metabolism to limit drug delivery to the systemic circulation.
- ▶ **First-pass (presystemic) elimination:** an orally administered drug must traverse the enterocyte, portal vein and hepatocyte before reaching the systemic circulation; CYP-mediated metabolism (especially intestinal/hepatic CYP3A) plus efflux at these sites reduces **bioavailability**.

The cytochrome P450 superfamily — organisation

- ▶ **Nomenclature:** root "CYP", then a **family** number (e.g., 3), a **subfamily** letter (e.g., A) and an **individual gene** number (e.g., 4) → *CYP3A4*; families/subfamilies are grouped by amino-acid sequence homology.
- ▶ The families most important for human drug metabolism are **CYP1, CYP2 and CYP3**.
- ▶ **CYP3A (CYP3A4, CYP3A5)** metabolises the **greatest number of drugs in therapeutic use**; CYP3A4 activity varies up to an order of magnitude between individuals, largely from variation in *regulatory* regions rather than coding mutations.
- ▶ **CYP2D6** is *second to CYP3A4* in the number of commonly used drugs it handles, and is highly polymorphic.
- ▶ CYPs may **bioactivate** procarcinogens and generate **reactive electrophilic metabolites** that covalently bind tissue macromolecules (protein/DNA) close to the site of production (typically the liver), mediating certain ADRs.

Major drug-metabolising CYP isoforms — representative substrates and inhibitors

Isoform	Representative substrates	Representative inhibitors
CYP3A	Calcium-channel blockers; antiarrhythmics (lidocaine, quinidine, mexiletine); HMG-CoA reductase inhibitors (statins); erythromycin, clarithromycin; cyclosporine, tacrolimus; HIV protease inhibitors (indinavir, saquinavir, ritonavir)	Amiodarone; ketoconazole, itraconazole; ritonavir; gemfibrozil/fibrates
CYP2D6	β -blockers (timolol, metoprolol, carvedilol); propafenone, flecainide; tricyclic antidepressants; bupropion; codeine, tamoxifen (prodrugs)	Quinidine (even ultra-low doses); fluoxetine, paroxetine
CYP2C9	Warfarin; phenytoin; glipizide; losartan (prodrug)	Amiodarone; fluconazole; phenytoin
CYP2C19	Omeprazole; mephenytoin; clopidogrel (prodrug)	Omeprazole; ritonavir; fluoxetine, fluvoxamine
CYP2B6	Efavirenz	Ticlopidine

- **Non-CYP pathways also tested in exams:** thiopurine S-methyltransferase (6-mercaptopurine, azathioprine); N-acetyltransferase/NAT2 (isoniazid, procainamide, hydralazine, some sulfonamides); UGT1A1 (irinotecan); pseudocholinesterase (succinylcholine); xanthine oxidase (azathioprine/6-MP — inhibited by allopurinol). Transporters: P-glycoprotein (digoxin, HIV protease inhibitors) and SLCO1B1/OATP1B1 (simvastatin and some statins).

Enzyme induction and inhibition — basis of drug–drug interactions

- **Induction** (increased synthesis/activity → *reduced* drug levels and effect, or increased toxic-metabolite formation): classic inducers are **rifampin**, **carbamazepine**, **phenytoin**, **St John's wort** and **glutethimide**, plus *smoking*, *chlorinated insecticides* and *chronic alcohol ingestion*. Induction lowers concentrations of warfarin, quinidine, cyclosporine, losartan, **oral contraceptives** (→ contraceptive failure), methadone and dabigatran.
- **Inhibition** (→ *increased* drug levels and dose-related toxicity): **cimetidine** inhibits many CYPs (raises warfarin, theophylline, phenytoin); **amiodarone** inhibits multiple CYPs and P-glycoprotein (raises warfarin, digoxin, dabigatran); CYP3A inhibitors precipitate statin and colchicine toxicity; CYP2D6 inhibitors potentiate β -blockade.
- **Clinical sentinels:** prescribers must be especially alert when *starting or stopping* **CYP2D6**, **CYP3A** or **P-glycoprotein inhibitors** and **CYP3A/P-glycoprotein inducers**, e.g., a stable warfarin patient who bleeds after **amiodarone** is added (warfarin metabolism inhibited), not a direct amiodarone reaction.
- **Reactive-metabolite toxicity (acetaminophen/paracetamol):** CYP-generated reactive metabolite is normally detoxified by hepatic **glutathione**; once glutathione is depleted it binds hepatic protein → hepatocyte necrosis. Risk is *increased* by enzyme inducers (phenobarbital, phenytoin) and by ethanol (which exhausts glutathione stores). Antidote: **N-acetylcysteine** (IV 140 mg/kg loading, then 70 mg/kg every 4 h), which replenishes sulfhydryl/glutathione.

Pharmacogenomics of CYP — metaboliser phenotypes

- ▶ Polymorphism produces a **multimodal population distribution** of enzyme activity (classically demonstrated for CYP2D6):
 - **Poor metabolisers (PM)**: two loss-of-function alleles → slow clearance, higher steady-state levels, longer time to steady state.
 - **Intermediate metabolisers (IM)**: one functional / reduced-function allele.
 - **Extensive (normal) metabolisers (EM)**: one or two functional alleles.
 - **Ultra-rapid metabolisers (UM)**: gene duplication (2–12 active copies) → very low parent-drug levels.
- ▶ **CYP2D6**: PM phenotype in 5–10% of European- and African-derived populations (few Asians); UMs frequent in East Africa, the Middle East and Oceania. **Codeine** is bioactivated to **morphine** by CYP2D6 — analgesia is *blunted in PMs* and *dangerous (respiratory depression) in UMs*; deaths in children after tonsillectomy led the FDA to a black-box warning and to **forbid codeine in children <12 years**. PMs show exaggerated β -blockade (metoprolol, carvedilol, timolol, propafenone).
- ▶ **CYP2C19**: PM common (~20%) in Asians, ~2–3% in others, >50% in Oceania. Reduced bioactivation of **clopidogrel** → less antiplatelet effect and more stent thrombosis/ischaemic events; omeprazole both is a substrate and phenocopies the defect by inhibition.
- ▶ **CYP2C9 + VKORC1**: together account for up to 50% of variability in stable **warfarin** dose; CYP2C9 variants also cause phenytoin neurotoxicity and glipizide hypoglycaemia, and impair bioactivation of the prodrug **losartan**.
- ▶ **CYP3A5**: a splicing polymorphism (common in Europeans/Asians) reduces activity; African-origin "expressers" clear **tacrolimus** faster (reduced efficacy at standard dose).
- ▶ **Implementation**: the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** and the **Dutch Pharmacogenetics Working Group** publish drug–gene dosing guidance; "point-of-care" vs "pre-emptive" genotyping models are in use.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Two-phase hepatocyte metabolism schema:** *Lipophilic drug* → arrow into a box labelled "Phase I: CYP450 oxidation (–OH/–NH₂/–SH added)" → *intermediate metabolite* → arrow into a box labelled "Phase II: conjugation (glucuronyl-/sulfo-/acetyl-/methyl-transferase)" → *polar conjugate* → arrows to "Bile" and "Urine." Side label: "P-glycoprotein (ABCB1) efflux." Annotate the CYP box with "Inducers: rifampin, carbamazepine, phenytoin, St John's wort" and "Inhibitors: amiodarone, ketoconazole, cimetidine, fluoxetine."
- ▶ **Diagram 2 — Population distribution of CYP2D6 activity:** x-axis "enzyme activity (low → high)", y-axis "population frequency", with labelled peaks "Poor metaboliser (2 LOF alleles)", "Extensive/normal metaboliser," "Ultra-rapid metaboliser (gene duplication)" and a vertical "antimode" line separating PMs.

Clinical / Diagnostic significance

- ▶ **Prodrugs requiring CYP bioactivation:** codeine (→morphine, CYP2D6), clopidogrel (CYP2C19), losartan (CYP2C9), tamoxifen (CYP2D6), many ACE inhibitors, irinotecan — failure of activation = therapeutic failure.
- ▶ **"High-risk pharmacokinetics":** when an active drug depends on a *single* CYP pathway, any inhibitor (drug, gene or disease) causes large swings in concentration — dangerous for narrow-therapeutic-index drugs (warfarin, phenytoin, ciclosporin, theophylline, digoxin).
- ▶ **Therapeutic drug monitoring & genotyping:** anticonvulsants, antiarrhythmics, immunosuppressants and some antibiotics benefit from level monitoring; targeted CYP2C19/CYP2D6/CYP2C9 genotyping guides clopidogrel, codeine and warfarin use.
- ▶ **Disease modifiers:** in cirrhosis, oral bioavailability of high first-pass drugs (morphine, meperidine, midazolam, nifedipine) is nearly *doubled* — reduce oral doses. In the **porphyrias**, CYP inducers can precipitate acute attacks.
- ▶ **Special groups:** neonates have immature CYP pathways; the elderly on polypharmacy are prone to CYP-mediated interactions and ADRs.

High-yield exam pointers

- ▶ CYP = heme-thiolate **mono-oxygenase**; named for **450-nm** CO-complex absorbance; chiefly hepatic endoplasmic reticulum.
- ▶ **CYP3A4** metabolises the most drugs; **CYP2D6** is second and highly polymorphic.
- ▶ **Inducers** (Rifampin, Carbamazepine, Phenytoin, St John's wort, chronic alcohol, smoking) ↓ drug levels → e.g., **OCP failure, warfarin resistance**.
- ▶ **Inhibitors** (amiodarone, azole antifungals, macrolides, cimetidine, grapefruit-type CYP3A inhibition, fluoxetine/paroxetine) ↑ drug levels → toxicity (statin myopathy, colchicine, warfarin bleeding).
- ▶ Metaboliser phenotypes: PM / IM / EM / UM; UM + codeine = **fatal respiratory depression** (FDA bans codeine <12 y after tonsillectomy).

- ▶ **Clopidogrel** = CYP2C19 (loss-of-function → stent thrombosis); **warfarin** = CYP2C9 + VKORC1 (≈50% of dose variance).
- ▶ **Paracetamol** reactive metabolite detoxified by **glutathione**; antidote **N-acetylcysteine**; alcohol/inducers raise risk.
- ▶ Phase II = **conjugation** (glucuronidation by UGT1A1 → Gilbert's/irinotecan; acetylation by NAT2 → slow acetylators → INH hepatitis, drug-induced lupus).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Clinical Pharmacology" (drug metabolism, Phase I/II, CYP substrate–inhibitor–inducer tables, first-pass effect, high-risk pharmacokinetics, drug interactions, reactive-metabolite/acetaminophen toxicity) and "Pharmacogenomics" (CYP3A/2D6/2C19/2C9 polymorphisms, PM/IM/EM/UM phenotypes, codeine/clopidogrel/warfarin/tacrolimus pharmacogenetics, CPIC).
- ▶ **Harrison's 22e** — "Toxic and Drug-Induced Hepatitis" (acetaminophen reactive-metabolite mechanism, glutathione, N-acetylcysteine dosing; CYP-inducer enhancement of toxicity).
- ▶ *Coverage note:* This is a pharmacology topic with no dedicated subspecialty textbook in the spec (specialty_books empty; CMDT not flagged); the answer is grounded entirely in the two Harrison clinical-pharmacology chapters plus the drug-induced hepatitis chapter. CYP nomenclature convention (family/subfamily/gene) and the 450-nm naming are stated as universally accepted standard pharmacology, as exact homology thresholds are not specified in the corpus.



Cytokines, physiology and clinical implications

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

Definition / Introduction — Cytokines are soluble, low-molecular-weight proteins produced by a wide variety of cell types that act through specific cell-surface receptors to regulate the **growth, development, and activation** of immune cells and to mediate the **inflammatory response**. They are pivotal to both **innate and adaptive immunity**, and their expression is perturbed in most immune, inflammatory, and infectious disease states. Functionally overlapping molecules that primarily attract and direct leukocyte movement are called **chemokines**. The cytokine system is the molecular target of an expanding class of "biologic" therapies, making its physiology directly relevant to internal-medicine practice.

General properties (physiology)

- ▶ **Mode of action** — cytokines act (1) in an **autocrine** manner when the target cell is the same cell that secreted it, (2) in a **paracrine** manner when the target is a nearby cell, and (3) in an **endocrine** manner when secreted into the circulation to act on distant tissue.
- ▶ **Pleiotropy** — a single cytokine acts on many different cell types, because receptors for it are expressed on multiple lineages.

- ▶ **Redundancy** — different cytokines exert similar (overlapping) biologic functions.
- ▶ **Synergy / antagonism and networks** — one cytokine commonly induces another, producing interlinked "**cytokine networks**"; effects may be additive (synergy) or opposing (antagonism).
- ▶ **Nomenclature** — cytokines thought primarily to target leukocytes were named **interleukins** (IL-1, IL-2, IL-3 ...); those described by an original function retained that name (e.g., **granulocyte colony-stimulating factor** [G-CSF], interferons, tumour necrosis factor).
- ▶ **Mechanism** — they alter **gene activation**, producing cellular activation, growth, differentiation, surface-molecule expression, and effector function. The **TH1/TH2/TH17** classification of helper T cells is itself defined by the *pattern of cytokines* the cell secretes (TH1 → cell-mediated immunity; TH2 → humoral immunity; TH17 → mucosal defence against extracellular bacteria/fungi).

Structural classification of cytokines and their receptors

- ▶ Cytokines fall into **three major structural families**: the **hematopoietin family**; the **TNF / IL-1 / PDGF / TGF- β family**; and the **CXC and C-C chemokine families** (chemokines have a distinctive 3-D structure and act via G-protein-coupled receptors).
- ▶ Cytokine **receptors** are grouped into **five families** by their conserved extracellular domains:

Receptor family	Representative members	Note
Immunoglobulin (Ig) superfamily	IL-1 receptors (type I, type II)	Extracellular Ig domains
Hematopoietic growth-factor (type I) receptor family	Receptors sharing the common γ chain (γ_c) — IL-2, IL-4, IL-7, IL-9, IL-15, IL-21; gp130-using receptors (IL-6, IL-11)	γ_c mutation causes X-linked SCID (X-SCID)
Interferon (type II) receptor family	Receptors for IFN- γ and IFN- β	Conserved cysteine-paired ~210-aa binding domain
TNF (type III) receptor family	TNF-R1 (p55), TNF-R2 (p75), CD40, Fas/Apo-1, CD27, CD30, NGF receptor	Cysteine-rich repeats; Fas triggers apoptosis
Seven-transmembrane (G-protein-coupled) family	Chemokine receptors (e.g., CXCR4, CCR5)	CXCR4 & CCR5 are the major HIV-1 co-receptors

Major cytokines and their physiological actions

Cytokine	Principal source	Key biologic action
IL-1 α/β	Monocytes-macrophages, endothelium	Upregulates adhesion molecules, fever, shock , hepatic acute-phase protein production, hematopoiesis
IL-2	T cells	T-cell activation & proliferation, B-cell growth, NK proliferation/activation
IL-4	T cells, mast cells, basophils	Drives TH2 differentiation; B-cell Ig class-switch to IgG1 and IgE ; anti-inflammatory
IL-5	T cells, mast cells, eosinophils	Regulates eosinophil migration and activation
IL-6	Monocytes-macrophages, fibroblasts	Acute-phase protein induction, T/B differentiation, myeloma & osteoclast growth

Cytokine	Principal source	Key biologic action
IL-8 (CXCL8)	Monocytes, neutrophils, endothelium	Neutrophil chemotaxis and adhesion (via CXCR1/CXCR2)
IL-10	Monocytes-macrophages, T cells	Anti-inflammatory — inhibits macrophage proinflammatory cytokine production, downregulates MHC class II
IL-12	Activated macrophages, dendritic cells	Induces TH1 formation; ↑IFN- γ , ↓IL-17; ↑CD8 CTL activity
IL-17	CD4 ⁺ (TH17) T cells	Enhances cytokine/chemokine secretion; promotes delayed-type reactions
IL-23	Macrophages	Opposite of IL-12 — ↑IL-17, ↑IFN- γ ; sustains TH17
IFN- α / IFN- β	All cells (type I IFN)	Antiviral ; activate T cells/macrophages/NK; upregulate MHC class I ; antitumour
IFN- γ	T cells, NK cells (type II)	Activates macrophages & NK ; induces MHC class II ; drives TH1
TNF- α	Monocytes-macrophages, mast cells	Fever, anorexia, shock, capillary-leak syndrome , proinflammatory cytokine induction
G-CSF / GM-CSF	Macrophages, fibroblasts, T cells	Regulate myelopoiesis ; reverse chemotherapy-induced neutropenia ; GM-CSF aids DC maturation
TGF- β	Most cell types	Immunosuppressive — downregulates T-cell/macrophage/granulocyte responses; stimulates matrix synthesis & angiogenesis

Cytokine signalling — the JAK-STAT pathway

- ▶ Hematopoietin-receptor signalling uses the **Janus kinase (JAK) family** — JAK1, JAK2, JAK3, and Tyk2, which preferentially associate with different receptor subunits.
- ▶ Cytokine binding **juxtaposes receptor subunits**, allowing paired JAKs to **transphosphorylate** and activate one another; JAKs then phosphorylate receptor tyrosines.
- ▶ STAT (signal transducer and activator of transcription) factors dock via **SH2 domains**, are phosphorylated by JAKs, dissociate, **translocate to the nucleus**, and bind specific DNA motifs to regulate gene transcription.
- ▶ **Clinical correlate** — JAK3 mutation produces an X-SCID-like phenotype (but affects both sexes, as JAK3 is on chromosome 19). **JAK inhibitors** (small molecules) are approved for **rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, atopic dermatitis, and alopecia areata**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Modes of cytokine action.** Draw three cells with arrows: *Autocrine* (cytokine loops back to its own secreting cell), *Paracrine* (acts on an adjacent cell), *Endocrine* (enters a blood vessel to act on a distant cell). Labels: **Secreting cell, Cytokine, Receptor, Autocrine, Paracrine, Endocrine, Bloodstream, Distant target cell.**
- **Diagram 2 — JAK-STAT signalling.** Draw a transmembrane cytokine receptor dimer. Labels: **Cytokine (ligand), Receptor subunits, JAK1/JAK2/JAK3/Tyk2, Transphosphorylation, Tyrosine-P residues, STAT with SH2 domain, STAT phosphorylation, STAT dimer, Nucleus, DNA/gene transcription.**

Clinical / Diagnostic significance

- Anti-cytokine biologic therapy is a mainstay for autoimmune/inflammatory disease:

Target	Agent(s)	Main indication(s)
TNF- α	Adalimumab, infliximab, golimumab, certolizumab pegol (mAbs); etanercept (soluble Fc:TNF-receptor trap)	RA, psoriasis/psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis
IL-1	Anakinra (IL-1 receptor antagonist), canakinumab, rilonacept (IL-1 trap)	Cryopyrin-associated/auto-inflammatory syndromes, gouty arthritis, juvenile arthritis
IL-6 / IL-6R	Tocilizumab (anti-IL-6R); siltuximab (anti-IL-6)	RA, juvenile idiopathic arthritis; Castleman's disease
IL-12 / IL-23	Anti-IL-12/IL-23 (p40) mAb (e.g., ustekinumab)	Psoriasis, inflammatory bowel disease (block TH17 differentiation)
IL-17	Anti-IL-17 mAb (e.g., secukinumab)	Psoriasis, psoriatic arthritis
IL-4R α	Dupilumab	Atopic dermatitis, steroid-dependent asthma
IgE	Omalizumab	Allergic asthma
BAFF	Belimumab	Systemic lupus erythematosus
VEGF	Bevacizumab, ramucirumab, ranibizumab, aflibercept	Tumour angiogenesis; macular degeneration/diabetic macular edema

- **Therapeutic cytokines (replacement/augmentation):** IFN- α/β in viral and autoimmune disease; IFN- γ corrects the phagocyte defect of **chronic granulomatous disease**; G-CSF/GM-CSF reverse chemotherapy-induced neutropenia; IFN- β and IL-11 lower IL-1/TNF- α and are used as inhibitory agents in inflammation.
- **Cytokine excess (cytokine release syndrome, CRS):** uncontrolled cytokine release with systemic inflammation is the dose-limiting toxicity of **CAR T-cell therapy**; IL-6/IL-6R blockade (tocilizumab) is a key antidote — illustrating the "cytokine storm" concept.
- **Autoantibodies to cytokines** cause distinctive disease: anti-IFN- γ $\rightarrow$ disseminated mycobacterial/bacterial infection and VZV reactivation; anti-GM-CSF $\rightarrow$ **pulmonary alveolar proteinosis** and fungal infection; anti-IL-17A/IL-17F $\rightarrow$ **chronic mucocutaneous candidiasis**;

anti-IL-6 → severe bacterial infections; anti-IL-1/TNF autoantibodies seen in RA, systemic sclerosis, SLE.

- ▶ **Diagnostic use:** acute-phase reactants (CRP, driven by IL-6) and the febrile/inflammatory response are downstream cytokine readouts; chemokine receptors CXCR4/CCR5 are exploited for HIV tropism testing and CCR5-antagonist therapy.

High-yield exam pointers

- ▶ Three cytokine actions: **autocrine, paracrine, endocrine**; two cardinal properties: **pleiotropy** and **redundancy**, forming **cytokine networks**.
- ▶ **Five cytokine-receptor families:** Ig superfamily, hematopoietic (type I), interferon (type II), TNF (type III), and 7-transmembrane (GPCR/chemokine).
- ▶ **Common γ -chain cytokines** = IL-2, -4, -7, -9, -15, -21; **γ c or JAK3 mutation = SCID**.
- ▶ **Pro-inflammatory triad:** IL-1, IL-6, TNF- α (fever, shock, acute-phase response). **Anti-inflammatory:** IL-10, TGF- β .
- ▶ **TH1** = IFN- γ /IL-2 (cell-mediated); **TH2** = IL-4/IL-5/IL-13 (humoral, IgE/eosinophils); **TH17** = IL-17/IL-23 axis (mucosal, psoriasis/IBD).
- ▶ **IFN type I** (α , β) → MHC class I & antiviral; **IFN- γ (type II)** → MHC class II & macrophage activation.
- ▶ Signalling = JAK-STAT; targeted by oral **JAK inhibitors** (RA, UC, atopic dermatitis, alopecia areata).
- ▶ Know the biologic targets: TNF (**etanercept/infliximab**), IL-1 (**anakinra**), IL-6R (**tocilizumab**), IL-17/IL-23 (psoriasis), IL-4R α (**dupilumab**), IgE (**omalizumab**), BAFF (**belimumab**).
- ▶ IFN- γ is therapeutic in **chronic granulomatous disease**; CRS is the cytokine-storm toxicity of CAR T-cell therapy.

SOURCE & COVERAGE

Harrison 22e — Ch 360 "Introduction to the Immune System" (cytokine biology, Table 360-7 Cytokines and Cytokine Receptors, Table 360-8 chemokine families, receptor families and JAK-STAT signalling) and Ch 361 "Mechanisms of Regulation and Dysregulation of the Immune System" (anti-cytokine biologics — Table 361-5, cytokine autoantibodies, cytokine release syndrome). **Coverage note:** Both chapters fully support the physiology and the biologic-target list. Brand/generic names *ustekinumab* and *secukinumab* are not spelled out in the provided text (which states only "anti-IL-12/IL-23" and "anti-IL-17" antibodies) — they are added as universally accepted standard internal medicine and flagged in *italics*. The term "cytokine storm" is standard terminology; the source explicitly describes **cytokine release syndrome** with CAR T-cell therapy.



Smoking-related health hazards and nicotine de-addiction

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

Definition / Introduction — *Nicotine addiction* is a chronic, relapsing disorder in which reversible binding of nicotine to **nicotinic acetylcholine receptors (nAChRs)** in brain reward circuits produces compulsive, repetitive use and a withdrawal syndrome on abstinence. While nicotine itself drives the dependence (and some pregnancy harm), the **vast majority of tobacco-attributable disease results from repeated exposure to the carcinogens and toxicants in combusted tobacco smoke**, not nicotine per se. Approximately **40% of cigarette smokers die prematurely** of smoking-related disease unless they quit, and globally tobacco accounts for ~13.6% of all deaths. Tobacco dependence is a treatable medical condition: structured counselling plus pharmacotherapy can roughly **triple** cessation success.

Mechanism of Nicotine Addiction (basis of de-addiction)

- ▶ Inhaled/absorbed nicotine reaches the brain within seconds and **reversibly attaches to nicotinic ACh receptors** active in networks subserving mood, reward, joy and excitement; chronic high exposure causes **upregulation of nicotinic receptors**.
- ▶ As blood nicotine falls between doses, nicotine detaches from receptors; the addicted user no longer feels "normal", generating a **compulsive need for the next dose** — the diagnostic hallmark is *loss of control over the next use*.
- ▶ **Withdrawal symptoms** (irritability, craving, anxiety, restlessness) appear within a day of cessation and may persist **4–6 weeks**.
- ▶ Addictiveness is driven by **speed and arterial concentration** of nicotine reaching the brain. Mildly acidic aerosols (cigarettes, nicotine-salt vapes) reduce airway irritation, permitting deep inhalation; lung pH (~7.4) then converts nicotine to the rapidly absorbed **unprotonated (freebase)** form — explaining why cigarettes and nicotine-salt devices are the most addictive forms.
- ▶ **Genetic susceptibility** (genes reducing nicotine clearance or increasing dependence/depression risk) influences whether adolescent experimentation progresses to adult addiction.

Smoking-Related Health Hazards (system-wise)

- ▶ **Cardiovascular** — promotes both large-vessel atherosclerosis and small-vessel disease, and raises MI/sudden cardiac death risk by enhancing **platelet aggregation and vascular occlusion**. Attributable fractions: **~90% of peripheral vascular disease** (non-diabetic), **~50% of aortic aneurysms**, **~24% of coronary artery disease**, **~11% of ischaemic and haemorrhagic strokes**. There is a **multiplicative interaction** with hypertension and dyslipidaemia.
- ▶ **Cancer** — causes cancers of lung; lip, oral cavity, naso-/oro-/hypopharynx; nasal cavity/paranasal sinuses; larynx; oesophagus; stomach; pancreas; liver (HCC); colon and rectum; kidney and renal pelvis; ureter; urinary bladder; uterine cervix; and **acute myeloid leukaemia**. Risk rises **linearly with cigarettes/day** and **logarithmically with duration**. Synergy occurs with **alcohol** (oral cavity, oesophagus) and with **asbestos/radon** (lung).
- ▶ **Respiratory** — responsible for **~80% of COPD**; chronic mucous hyperplasia causes productive cough in up to 80% of smokers >60 yr; **~15–25%** develop clinically significant airflow obstruction (chronic bronchitis/emphysema).

- ▶ **Pregnancy** — premature rupture of membranes, abruptio placentae, placenta praevia, spontaneous abortion; offspring show preterm delivery, **small-for-gestational-age**, higher perinatal mortality, infant respiratory distress, **SIDS** and developmental lag.
- ▶ **Other** — delayed peptic-ulcer healing; periodontal disease; diabetes; active tuberculosis; rheumatoid arthritis; osteoporosis; senile cataract; macular degeneration; premature menopause; skin wrinkling; gallstones/cholecystitis (women); male impotence; and **poorer chemo-/radiotherapy outcomes**.
- ▶ **Environmental tobacco smoke (passive smoking)** — increases lung cancer and CAD in non-smokers; in children causes respiratory infections, chronic otitis media and asthma (incidence and exacerbation).
- ▶ **"Low-tar/low-nicotine" and filtered cigarettes confer no real benefit** — smokers compensate by deeper/more frequent puffing; design changes have driven the rise in **lung adenocarcinoma**.

Relative Risks for Current Smokers (Harrison Table 465-1)

Disease (current vs never smoker)	Male	Female
Lung cancer (age 45–64)	19.0	19.0
COPD (age 35–44)	29.7	38.9
Coronary heart disease (35–44)	3.9	5.0
Cerebrovascular disease (35–44)	2.2	2.3
Larynx cancer	14.6	13.0
Lip/oral cavity/pharynx	10.9	5.1
Oesophagus	6.8	7.8
Bladder	3.3	2.2

Relative risk for most cancers and COPD rises with age; for CVD the relative risk falls with age but the absolute excess death rate keeps rising (cumulative injury).

Benefits of Cessation (motivational pearls)

- ▶ Risk of a **second coronary event falls within 6–12 months**; rates of first MI and CHD death decline within 2–4 years.
- ▶ After **15 years** of abstinence, risk of stroke, MI and CHD death approaches that of a never-smoker.
- ▶ Cancer risk begins to fall after ~4 years, but a residual **3- to 4-fold lung cancer risk persists even 20 years** after quitting.
- ▶ Small-airway changes in young smokers reverse within 1–2 years; in established COPD, cessation mainly **slows the rate of decline** in lung function.

Nicotine De-addiction — Behavioural Framework ("5 A's")

- ▶ Cessation is typically **cyclical** — ~70–80% of smokers want to quit and >50% attempt yearly, but only ~6% remain abstinent at 6 months and ~3% at 2 years (CMDT: 5–10% unaided success). Repeated, structured intervention is therefore essential.
- ▶ **Ask** — systematically identify all tobacco/nicotine use at every visit (record cumulative daily episodes across *all* products — cigarettes, cigars, roll-your-own, vapes, oral nicotine).
- ▶ **Advise** — give a clear, strong, personalised message to quit; brief clinician advice at the time of an acute illness triggers a quit attempt in up to half of patients and makes quitting **1.6×** more likely.
- ▶ **Assess** — gauge readiness to change and intensity of addiction (uses/day, use within ~30 min of waking, prior quit history, craving on abstinence).
- ▶ **Assist** — negotiate a **quit date** (usually within a few weeks, not the visit day); offer pharmacotherapy to all who accept plus counselling; address anticipated **weight gain** (~80% gain, average ~2 kg; 10–15% gain >13 kg).
- ▶ **Arrange** — schedule follow-up contact around the quit date; system-wide tracking/outreach can raise 12-month abstinence to ~25%.
- ▶ *Counselling formats*: individual or group sessions (≥4–7 sessions of 20–30 min), telephone **quitlines** and text-messaging are all proven and highly cost-effective.

Pharmacotherapy for Nicotine De-addiction

Offer to all quit attempters **except** those with medical contraindications, pregnant/breastfeeding women and adolescents. Numbers in parentheses are the **multiple of cessation success vs no intervention** (Harrison Table 465-2).

Agent	Mechanism	Regimen	Efficacy (* vs none)
Nicotine patch	Transdermal NRT	7/14/21 mg per 24 h, 1 patch/day	1.9
Nicotine gum	Oral mucosal NRT	2 or 4 mg, 8–24 pieces/day	1.5
Nicotine lozenge	Oral mucosal NRT	2 mg (2.0) / 4 mg (2.8), up to 20/day	2.0–2.8
Nicotine nasal spray	Rapid NRT (Rx)	1–2 sprays, max 10/h	2.3
Nicotine oral inhaler	NRT (Rx)	4–16 cartridges/day	2.1
Bupropion SR	Dopamine–noradrenaline reuptake inhibitor	150 mg OD ×3 days → 150 mg BID; up to 6 months; start 1–2 wk before quit date	2.0
Varenicline	Partial agonist at nicotinic ACh receptor	0.5 mg OD ×3 days → 0.5 mg BID days 4–7 → 1 mg BID ; up to 6 months; start 1–2 wk pre-quit	3.1
Exclusive e-cigarette	Nicotine-salt aerosol (harm reduction)	Caution: avoid dual use	3.0

- ▶ NRT roughly **doubles** quit success; usual course **3–6 months**, higher doses for heavier smokers, with longer maintenance for those who relapse. Combining a **patch (basal) plus gum/lozenge (acute craving)** improves outcomes.
- ▶ **Bupropion** boosts dopamine/noradrenaline (mimicking nicotine), causes minimal weight gain, but is **contraindicated in seizure disorders**; especially useful where depression coexists.
- ▶ **Varenicline** is the single most effective monotherapy (partial agonism reduces craving while blunting reward); start 1–2 weeks before the quit date.
- ▶ **Combination therapy > single agent**. Pre-treatment (NRT, bupropion or varenicline) before the quit date improves results. The best outcomes (nearly **3-fold**) come from **advice + pharmacotherapy + counselling** together.
- ▶ **Harm reduction**: switching completely from combusted cigarettes to exclusive nicotine-salt e-cigarettes is at least as effective as FDA-approved drugs and markedly lowers toxicant biomarkers, but must avoid **dual use** (which negates benefit) — reserved chiefly for those failing or refusing approved therapy; never recommended to never-smokers.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Reward-pathway / addiction cycle**: Inhaled nicotine → arterial blood → brain → **nicotinic ACh receptor** binding on VTA dopaminergic neurons → dopamine release in **nucleus accumbens** (pleasure/reward) → receptor upregulation → falling nicotine → **withdrawal/craving** → next dose. Labels: *nicotine, nAChR, ventral tegmental area, nucleus accumbens, dopamine, reward, withdrawal/craving, compulsive use*.
- ▶ **Body-map of smoking hazards (whole-body schematic)**: label *brain/stroke; oral cavity–larynx–pharynx cancer; lung cancer & COPD; coronary artery disease; aortic aneurysm; peripheral vascular disease; oesophagus/stomach/pancreas/liver/colorectal cancer; kidney & bladder cancer; cervix & AML; pregnancy complications; passive-smoke effects in children*.

Clinical / Diagnostic significance

- ▶ **Diagnosis is clinical** — loss of control over next nicotine use; quantify via uses/day, time-to-first-use after waking, craving on abstinence and prior failed quits.
- ▶ Smoking **induces hepatic CYP450**, lowering levels of drugs such as **warfarin** (anticoagulation may destabilise on admission/discharge), increases first-pass clearance of **lidocaine/theophylline**, and blunts effects of **benzodiazepines and beta-blockers** — review doses when patients are hospitalised and abstinent.
- ▶ Continued smoking during cancer chemotherapy/radiotherapy worsens survival — cessation is part of oncologic care.
- ▶ Counsel about **screening** (low-dose CT lung-cancer screening for eligible heavy smokers) and aggressive control of co-existing CVD risk factors given multiplicative interaction.

High-yield exam pointers

- ▶ **~40% of smokers die prematurely**; tobacco ≈ 13.6% of global deaths; ~480,000 US deaths/year.
- ▶ Top three killers: **cancer, cardiovascular disease, COPD** (~80% of COPD).
- ▶ Attributable fractions: **90% PVD, 50% aortic aneurysm, 24% CAD, 11% stroke**.

- ▶ Cancer risk: **linear** with cigarettes/day, **logarithmic** with duration; lung-adenocarcinoma rise linked to filter/design changes.
- ▶ Withdrawal lasts **4–6 weeks**; nicotine-salt/cigarette acidic aerosols → fast **freebase** absorption → high addictiveness.
- ▶ **5 A's**: Ask–Advise–Assess–Assist–Arrange; brief advice makes quitting **1.6×** more likely.
- ▶ **Varenicline** (partial nicotinic agonist) is most effective monotherapy (**3.1×**); **NRT doubles** success; **bupropion** contraindicated in seizures.
- ▶ Cessation benefits: coronary risk falls in **6–12 months**; risk approaches never-smoker by **15 years**; residual 3–4× lung-cancer risk persists.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Nicotine Addiction" (mechanism, relative-risk table, disease manifestations, environmental tobacco smoke, cessation framework, pharmacologic efficacy multipliers and dosing); "Promoting Good Health" (preventive context).
- ▶ **CMDT 2026** — "Disease Prevention & Health Promotion" (smoking-cessation counselling, Table 1–4 inquiries, Table 1–5 medication doses for NRT/bupropion/varenicline, weight gain, e-cigarette/EVALI caution).

Coverage note: The spec lists no dedicated subspecialty textbook (specialty = GENERAL); the answer is fully grounded in Harrison 22e and CMDT 2026. The "5 A's" labelling follows the standard ATS/USPHS clinical-practice framework — Harrison's Table 465-2 lists the same actions (Ask, Advise, Identify-those-willing/Assess, Assist, Arrange).



Delayed hypersensitivity reaction

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

Definition / Introduction — *Hypersensitivity* denotes an exaggerated or inappropriate adaptive immune response to an antigen that causes tissue injury. In the **Gell and Coombs classification** (Types I–IV), **Type IV (delayed, cell-mediated) hypersensitivity** is the only type that is *antibody-independent*: it is mediated by **antigen-specific T lymphocytes** (CD4⁺ T-helper and CD8⁺ cytotoxic T cells) and the macrophages/eosinophils/neutrophils they recruit. It is termed "delayed" because the reaction develops **48–72 hours** after antigen exposure in a sensitised host — the time required to recruit and activate effector T cells — in contrast to the immediate (minutes) reaction of Type I. The classic prototypes are the **tuberculin (Mantoux) skin reaction**, **allergic contact dermatitis**, **granuloma formation**, and **severe cutaneous adverse drug reactions (SJS/TEN, DRESS)**.

Gell and Coombs classification — placing Type IV in context

Type	Eponym / name	Principal mediator	Onset	Representative examples
I	Immediate / anaphylactic	IgE on mast cells & basophils (TH2/ILC2: IL-4, IL-5, IL-13)	Minutes	Anaphylaxis, urticaria, angioedema, allergic asthma/rhinitis
II	Cytotoxic (antibody-mediated)	IgG/IgM + complement; ADCC by NK cells/phagocytes	Variable	Autoimmune haemolytic anaemia, drug-induced cytopenias, Goodpasture, Graves
III	Immune-complex	Antigen–antibody (IgG/IgM) complexes → complement, neutrophils	Hours–days	Serum sickness, Arthus reaction, SLE, post-streptococcal glomerulonephritis, drug-induced vasculitis
IV	Delayed / cell-mediated	T cells (CD4 TH1/TH2/TH17, CD8 CTL) + macrophages/eosinophils/neutrophils	48–72 h	Tuberculin reaction, contact dermatitis, granulomas, SJS/TEN, DRESS, allograft rejection

- Types I–III are **antibody (humoral)-mediated and transferable by serum**; Type IV is **cell-mediated and transferable only by sensitised T cells/lymphocytes, not by serum**.

Mechanism — two sequential phases

1. Sensitisation (afferent/induction) phase — occurs on *first* contact, evolving over ~10–14 days, and is clinically silent:

- The antigen is often a **low-molecular-weight hapten** (e.g., nickel, urushiol of poison ivy, a drug or its metabolite) that must **covalently bind a self carrier-protein** to become immunogenic (*hapten–prohapten model*); some drugs bind **non-covalently** to the HLA molecule or T-cell receptor (the **pharmacological interaction "p-i" model**, e.g., abacavir within HLA-B*57:01).
- **Antigen-presenting cells** — cutaneous **Langerhans/dendritic cells** — process the antigen and migrate to regional lymph nodes, presenting peptide on **MHC class II to naïve CD4⁺ T cells** and on **MHC class I to CD8⁺ T cells**.

- Under IL-12/IFN- γ this drives **clonal expansion and differentiation into effector and memory TH1 (also TH2, TH17) and cytotoxic CD8⁺ T cells**.

2. Effector (elicitation) phase — occurs on *re-exposure*, peaking at 48–72 h:

- Sensitised CD4⁺ TH1 cells recognise antigen and secrete IFN- γ , TNF- α and IL-2, which **recruit and activate macrophages**, increasing their microbicidal and tissue-damaging capacity.
- CD8⁺ cytotoxic T cells kill target cells directly via **perforin, granzyme B and granulysin** (the dominant cytolytic mediator of keratinocyte death in SJS/TEN).
- Persistent, indigestible antigen → chronic macrophage activation → transformation into **epithelioid and multinucleate giant cells** → **granuloma** formation (e.g., tuberculosis, leprosy, sarcoidosis, fungal infection).

Subclassification of Type IV (Pichler) — by effector cell and cytokine

Harrison (adapted from Jutel *et al*, *Allergy* 2023) subdivides cell-mediated reactions by the dominant effector arm:

Subtype	Effector cells	Key cytokines/mediators	Final effector	Clinical correlate
IVa (T1)	TH1, ILC1, Tc1, NK	IFN- γ , TNF- α , granzyme B, perforin, granulysin	Macrophage activation → granuloma	Tuberculin reaction, granulomatous disease, allergic contact dermatitis
IVb (T2)	TH2, ILC2, Tc2, NK-T	IL-4, IL-5, IL-9, IL-13, IL-31	Eosinophil inflammation	DRESS/DIHS, maculopapular exanthem with eosinophilia
IVc (T3)	TH17, ILC3, Tc17	IL-17, IL-22, IL-23, CXCL8 (IL-8), GM-CSF	Neutrophil inflammation	AGEP, neutrophilic drug eruptions

- The *classic four-part Pichler scheme* additionally separates **Type IVc = CD8⁺ cytotoxic** reactions (SJS/TEN, fixed drug eruption) and **Type IVd = neutrophil-rich** reactions (AGEP) — both are universally taught and worth naming.

Clinical examples — organised by category

- **Diagnostic skin tests (in-vivo DTH):**
 - **Tuberculin / Mantoux (TST):** intradermal PPD (purified protein derivative, standard PPD-S/RT23); reaction read at **48–72 h** as induration. Cellular basis = previously sensitised CD4⁺ T cells attracted to the skin site producing cytokines. CDC cut-offs: **≥5 mm** (HIV, recent TB contacts, organ-transplant/immunosuppressed, fibrotic CXR), **≥10 mm** (recent immigrants, injection drug users, lab/congregate-setting staff, children <5 y), **≥15 mm** (low-risk persons). Modern equivalents — **TBST** and **IGRAs** (QuantiFERON-TB Gold Plus, T-SPOT.TB) use TB-specific antigens **ESAT-6 and CFP-10**.
 - **Lepromin test** (tuberculoid leprosy), **Candida**, **mumps**, **trichophyton** (anergy panel) — assess intact cell-mediated immunity; *anergy* indicates impaired DTH (HIV, sarcoid, malnutrition, overwhelming TB).

- ▶ **Infective / granulomatous DTH:** tuberculosis (caseating granuloma; the tissue damage and cavitation are largely DTH-mediated), tuberculoid leprosy, leishmaniasis, deep fungal infection, schistosome-egg granuloma.
- ▶ **Allergic contact dermatitis (prototype skin DTH):** sensitisers include **nickel**, **urushiol** (poison ivy/oak), **potassium dichromate**, **neomycin/bacitracin/polymyxin B**, **formaldehyde**, **paraphenylenediamine**, **adhesive tape**. *Allergic contact dermatitis* (a DTH, lag ~48 h on re-challenge) is distinguished from *irritant dermatitis* (non-immune, onset within hours); confirmed by **patch testing**. *Systemic contact dermatitis/SDRIFE* follows systemic exposure to a previously contact-sensitising drug.
- ▶ **Drug-induced delayed hypersensitivity (T-cell-mediated):** **morbilliform/maculopapular exanthem** (commonest), **fixed drug eruption** (sulfonamides, NSAIDs, tetracyclines), **DRESS/DIHS** (eosinophilia, facial oedema, hepatitis; aromatic anticonvulsants, allopurinol, vancomycin, sulfonamides), **AGEP** (sterile pustules), **SJS/TEN** (full-thickness epidermal necrosis; granulysin-mediated). Strong **HLA-restricted pharmacogenomic associations:** **HLA-B*57:01–abacavir** (100% negative predictive value; PREDICT-1), **HLA-B*15:02–carbamazepine** SJS/TEN (Han Chinese), **HLA-B*58:01–allopurinol** DRESS/SJS-TEN, **HLA-A*32:01–vancomycin** DRESS, **HLA-B*13:01–dapson**; **CYP2C9*3** slow metabolism predisposes to phenytoin reactions.
- ▶ **Transplantation:** **acute cellular allograft rejection** and **graft-versus-host disease** are T-cell-mediated (Type IV).
- ▶ **Cell-mediated autoimmunity (DTH component):** type 1 diabetes mellitus, Hashimoto thyroiditis, multiple sclerosis, rheumatoid arthritis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Two-phase mechanism of Type IV hypersensitivity.** Labels: *Hapten + carrier protein; Langerhans/dendritic cell (APC); MHC II → naïve CD4⁺ T cell; MHC I → CD8⁺ T cell; regional lymph node — clonal expansion; Sensitisation phase (10–14 days); Memory/effector TH1 + cytotoxic CD8⁺ T cells; Re-exposure; Effector phase (48–72 h); IFN- γ , TNF- α → macrophage activation; Perforin/granzyme/granulysin → target-cell death; epithelioid & giant cells → granuloma.*
- ▶ **Diagram 2 — Tuberculin (Mantoux) reaction.** Labels: *Intradermal PPD (forearm); Read at 48–72 h; measure induration (not erythema) in mm; cut-offs ≥ 5 / ≥ 10 / ≥ 15 mm.*

Clinical / Diagnostic significance

- ▶ **Diagnostic use:** DTH skin tests (tuberculin, lepromin, anergy panel) detect prior sensitisation and gauge intact cell-mediated immunity; *anergy* flags immunodeficiency.
- ▶ **Granuloma = protective yet pathogenic:** the same DTH that walls off intracellular organisms (*M. tuberculosis*, *M. leprae*) also causes the caseation, cavitation and tissue destruction of disease.
- ▶ **Management of contact dermatitis:** identify and remove the allergen; **patch testing** to confirm; topical (or short systemic) glucocorticoids; emollients.

- ▶ **Severe cutaneous adverse drug reactions (SCARs):** SJS/TEN, DRESS and AGEP are dermatological emergencies — **immediate withdrawal of the culprit drug**, supportive/burns-unit care, and monitoring for late autoimmune sequelae (thyroiditis, diabetes) in DRESS.
- ▶ **Pharmacogenomic screening prevents disease:** pre-prescription **HLA-B*57:01** testing before abacavir, and **HLA-B*15:02** before carbamazepine (and **HLA-B*58:01** before allopurinol in at-risk groups) avert life-threatening reactions.
- ▶ DTH underlies the efficacy read-out of **BCG vaccination** and the **immunology of granulomatous diseases** (sarcoidosis, Crohn's, berylliosis).

High-yield exam pointers

- ▶ Type IV is the **only antibody-independent** Gell–Coombs type — **T-cell mediated, transferable by lymphocytes, not serum**.
- ▶ Reaction is "**delayed**" — **peaks at 48–72 h**; two phases: **sensitisation (10–14 d)** then **elicitation (48–72 h)**.
- ▶ Effector arms: CD4 TH1 → IFN-γ → **macrophage activation/granuloma**; CD8 CTL → **perforin, granzyme, granulysin** → **cytotoxicity**.
- ▶ **Tuberculin test** read at 48–72 h; measure **induration in mm** (not erythema); cut-offs 5/10/15 mm; modern IGRA uses **ESAT-6 & CFP-10**.
- ▶ **Allergic contact dermatitis** (nickel, poison ivy/urushiol, chromate, neomycin) — diagnosed by **patch test**; *irritant* type is non-immune and faster.
- ▶ **SCARs are Type IV:** SJS/TEN, DRESS, AGEP, morbilliform, fixed drug eruption — first step is **stop the drug**.
- ▶ Memorise **HLA links**: B*57:01–abacavir, B*15:02–carbamazepine, B*58:01–allopurinol, A*32:01–vancomycin, B*13:01–dapsone.
- ▶ **Acute cellular allograft rejection and GVHD** are clinically important Type IV reactions.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Introduction to the Immune System" (T-cell subsets, TH1/TH17, granuloma/macrophage activation); "Cutaneous Drug Reactions" (Revised immune-pathway classification Table 63-1 with Type IVa/IVb/IVc, HLA-pharmacogenomic associations, SJS/TEN/DRESS/AGEP); "Eczema, Psoriasis... (dermatitis)" (allergic vs irritant contact dermatitis, patch testing); "Tuberculosis" (skin-test reactivity as delayed-type hypersensitivity, PPD, TST cut-offs Table 183-5, IGRA/ESAT-6/CFP-10).
- ▶ **Coverage note:** The Gell–Coombs four-type framework is presented across the immunology, allergy/pulmonary-diagnostics and drug-reaction chapters rather than as a single dedicated table; the classic two-phase DTH mechanism, the 10–14-day sensitisation interval, the Pichler IVc/IVd cytotoxic-vs-neutrophil subdivision, and standard contact allergens/anergy-panel antigens are universally accepted textbook immunology used to complete the answer.



Nucleotide repeat expansion disorders

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

Definition / Introduction — Nucleotide (most commonly *trinucleotide* / *triplet*) repeat expansion disorders are a distinct class of human genetic disease caused by **dynamic mutations** — tandemly repeated short DNA sequences that are intrinsically unstable and **expand beyond a critical threshold copy number**, with progressive lengthening of the repeat both across generations (germline) and within tissues (somatic). They were first recognised as the cause of *fragile X syndrome*, and now encompass several common neurological diseases (Huntington's disease, myotonic dystrophy, Friedreich's ataxia, spinocerebellar ataxias). Their hallmark clinical signature is **genetic anticipation** — earlier onset and greater severity in successive generations.

Molecular basis and key concepts

- ▶ **Mechanism of expansion** — repeats expand through **unequal recombination (crossing-over)** and **slipped-strand mispairing** during DNA replication; once an expansion is present the DNA fragment is unstable and tends to expand further during cell division.
- ▶ **Premutation → full mutation** — a *premutation* is a small increase in repeat copy number; the carrier may be phenotypically normal or mildly affected, but in subsequent generations the expanded repeat may increase further in length, producing an increasingly severe phenotype — the essence of a **dynamic mutation**.
- ▶ **Anticipation** — when repeat length increases from one generation to the next, disease manifests earlier and more severely. In Huntington's disease there is a direct correlation between age of onset and triplet-codon length; documented across many repeat disorders.
- ▶ **Repeat length–phenotype correlation** — larger expansions → younger onset and more aggressive disease (well shown in SCA1, SCA7, DRPLA, SBMA).
- ▶ **Somatic / tissue-specific instability** — repeat number can vary between tissues; e.g., in myotonic dystrophy the CTG repeat may be ~10-fold larger in muscle than in lymphocytes.
- ▶ **Parent-of-origin effect** — paternal transmission tends to cause greater expansion (HD, SCA7, DRPLA), whereas the severe **congenital form of myotonic dystrophy** occurs almost exclusively with maternal transmission.

Classification by repeat location and pathogenic mechanism

Repeat disorders are best grouped by *where* the repeat lies and *how* it injures the cell:

Group	Repeat / location	Pathogenic mechanism	Examples
Coding (exonic) CAG	CAG in coding exon → polyglutamine (polyQ) tract	Toxic gain-of-function of mutant protein; β-pleated aggregates form neuronal intranuclear inclusions	Huntington's disease, SBMA (Kennedy), SCA1/2/3/6/7/12/17, DRPLA
Non-coding — loss of function	CGG in 5'UTR; GAA in intron	Hypermethylation/ gene silencing or reduced gene expression	Fragile X (FMR1), Friedreich's ataxia (frataxin)

Group	Repeat / location	Pathogenic mechanism	Examples
Non-coding — RNA toxic gain	CTG/CCTG in untranslated region/intron	Mutant RNA forms nuclear foci that sequester splicing proteins	Myotonic dystrophy DM1 (DMPK), DM2 (CNBP)
Larger/other repeats (non-coding)	Hexanucleotide GGGGCC; pentanucleotide AAGGG; intronic GAA	RNA foci, dipeptide-repeat proteins, haploinsufficiency	C9orf72 ALS/FTD, RFC1-CANVAS, SCA27B (FGF14)

- **Polyglutamine (polyQ) diseases** share a unifying biology: expanded CAG encodes glutamine; ataxins/huntingtin with >~40 glutamines undergo conformational change to a β -pleated structure, accumulate in neuronal nuclei, bind and impair the TATA-binding protein and CREB-binding protein, overwhelm the **ubiquitin–proteasome system**, impair autophagy, and induce neuronal apoptosis.

Representative disorders (with genetic detail)

Selected trinucleotide repeat disorders (Harrison *Table 479-5*):

Disease	Locus	Repeat	Normal / Disease range	Inheritance	Gene product
Spinobulbar muscular atrophy (Kennedy, SBMA)	Xq12	CAG	11–34 / 40–62	XR	Androgen receptor
Fragile X (FRAXA)	Xq27.3	CGG	6–50 / 200–300	XR	FMR-1 protein (FMRP)
Fragile X (FRAXE)	Xq28	GCC	6–25 / >200	XR	FMR-2 protein
Myotonic dystrophy (DM1)	19q13.32	CTG	5–30 / 200–1000	AD	Myotonin protein kinase (DMPK)
Huntington's disease (HD)	4p16.3	CAG	6–34 / 37–180	AD	Huntingtin
SCA1	6p22.3	CAG	6–39 / 40–88	AD	Ataxin-1
SCA2	12q24.12	CAG	15–31 / 34–400	AD	Ataxin-2
SCA3 / Machado-Joseph disease	14q32.12	CAG	13–36 / 55–86	AD	Ataxin-3
SCA6	19p13	CAG	4–16 / 20–33	AD	α 1A voltage-gated Ca^{2+} channel (CACNA1A)
SCA7	3p14.1	CAG	4–19 / 37 to >300	AD	Ataxin-7
SCA12	5q32	CAG	6–26 / 66–78	AD	Protein phosphatase 2A
DRPLA	12p13.31	CAG	7–23 / 49–75	AD	Atrophin-1

Disease	Locus	Repeat	Normal / Disease range	Inheritance	Gene product
Friedreich's ataxia (FRDA1)	9q21.11	GAA	7–22 / 200–900	AR	Frataxin

- ▶ **Huntington's disease** — AD, *huntingtin* on 4p16.3, CAG >40 fully penetrant (intermediate 36–39 with reduced penetrance). Onset 25–45 yr; chorea early, evolving to dystonia, rigidity, bradykinesia and myoclonus; behavioural disturbance, depression with suicidality, and dementia. The **Westphal variant** (akinetic-rigid) affects ~10%, usually juvenile-onset. MRI shows **caudate (head) and putamen atrophy** with enlarged frontal horns; intranuclear ubiquitin + huntingtin inclusions. Expansion is greater with **paternal** transmission. Tetrabenazine, **deutetrabenazine** and valbenazine treat chorea; antisense oligonucleotide trials ongoing.
- ▶ **Myotonic dystrophy** — commonest adult muscular dystrophy. **DM1** = unstable CTG repeat in 3' untranslated region of *DMPK* (chr 19); "hatchet face", frontal balding, grip/percussion myotonia, posterior subcapsular cataracts, cardiac conduction block (sudden death), insulin resistance, hypersomnia, testicular atrophy. **Congenital DM1** in ~25% of infants of affected mothers. **DM2 / PROMM** = CCTG repeat in intron 1 of *CNBP* (*ZNF9*), predominantly proximal. Both act by an **RNA toxic gain-of-function** — mutant RNA forms intranuclear inclusions that sequester splicing proteins, causing mis-splicing of multiple transcripts. Mexiletine for myotonia; pacemaker/ICD for conduction disease.
- ▶ **Friedreich's ataxia** — most common inherited ataxia (AR); homozygous GAA expansion in intron 1 of *frataxin* (chr 9) in >95%; **loss of frataxin expression**. Onset <25 yr: progressive gait ataxia, **areflexia with extensor plantar responses**, loss of vibration/position sense, dysarthria, pes cavus, scoliosis; **hypertrophic cardiomyopathy in 90%** and **diabetes in 20%**. Frataxin is a mitochondrial iron-homeostasis protein; its loss causes mitochondrial iron accumulation and oxidative injury. **Omaveloxolone** (NRF2 agonist) is the first FDA-approved drug.
- ▶ **Spinocerebellar ataxias** — polyQ "ataxins"; **SCA3/MJD** is the most common AD ataxia worldwide; **SCA7** is uniquely associated with **retinal pigmentary/macular degeneration** (blue-yellow colour blindness). Genotype is the diagnostic gold standard.
- ▶ **SBMA (Kennedy's disease)** — XR, CAG in exon 1 of the **androgen receptor**; lower-motor-neuron bulbar and limb weakness with **androgen insensitivity** (gynaecomastia, reduced fertility); inverse correlation between repeat number and age of onset.
- ▶ **Fragile X syndrome** — commonest inherited cause of intellectual disability; CGG in 5'UTR of *FMRI*; **full mutation (>200)** triggers promoter **hypermethylation and gene silencing**, loss of FMRP.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Dynamic mutation and anticipation (pedigree):** A three-generation pedigree (I → II → III) with the repeat tract drawn beside each affected member showing increasing length. Labels: *Normal (stable allele) → Premutation → Full mutation; Slipped-strand mispairing / unequal crossing-over; Increasing CAG repeat number; Anticipation = earlier onset + increasing severity; Paternal vs maternal transmission bias.*
- ▶ **Diagram 2 — Classification tree by repeat location/mechanism:** Root "Repeat expansion disorders" branching to (a) *Coding CAG → polyglutamine → toxic protein gain-of-function* (HD, SCA1/2/3/6/7, SBMA, DRPLA — neuronal intranuclear inclusions); (b) *Non-coding loss-of-function* (CGG–FMR1 fragile X; GAA–frataxin Friedreich's); (c) *Non-coding RNA toxic gain* (CTG–DMPK DM1; CCTG–CNBP DM2 — RNA nuclear foci). Label each branch with repeat type, gene and mechanism.

Clinical / Diagnostic significance

- ▶ **Diagnosis** — repeat sizing by PCR (small alleles) and Southern blot (large expansions); genotype is the gold standard for SCAs and confirms HD, DM, FRDA. Triplet-repeat sizing also enables **prenatal diagnosis** (e.g., myotonic dystrophy).
- ▶ **Genetic counselling is mandatory** — presymptomatic/predictive HD testing must be done with trained counsellors because disclosure can precipitate depression and suicide; anticipation and parent-of-origin effects must be explained to families.
- ▶ **Phenotype prediction** — repeat length broadly predicts severity and age of onset and helps anticipate the more severe congenital DM1 in offspring of affected mothers.
- ▶ **Therapeutics** — symptomatic for most (tetrabenazine/deutetrabenazine for HD chorea; mexiletine + cardiac pacing for DM); **omaveloxolone** for Friedreich's ataxia; **antisense oligonucleotide / RNA-lowering and gene-editing (CRISPR)** strategies are in trials for HD and others.

High-yield exam pointers

- ▶ **Dynamic mutation** = unstable repeat expanding beyond a threshold; **first described in fragile X.**
- ▶ **Anticipation** = earlier onset + worse disease in successive generations with longer repeats — the defining clue.
- ▶ **CAG = polyglutamine** diseases (HD, SCA1/2/3/6/7/17, SBMA, DRPLA) → **toxic gain-of-function**, neuronal **intranuclear inclusions**, threshold **~40 glutamines**.
- ▶ **HD:** chr 4p16.3, CAG >40 (36–39 reduced penetrance); caudate atrophy; Westphal variant; paternal anticipation.
- ▶ **Myotonic dystrophy:** DM1 = CTG in DMPK 3'UTR (chr 19); DM2 = CCTG in CNBP/ZNF9; RNA gain-of-function; congenital form via affected mother.
- ▶ **Friedreich's ataxia:** GAA in intron 1 of frataxin, AR, **loss of function**; areflexia + upgoing plantars, HCM, diabetes; omaveloxolone.
- ▶ **Fragile X (CGG, FMR1) and Friedreich's (GAA) = loss-of-function**; remember they are the non-coding exceptions to the polyQ rule.

- ▶ SCA7 = ataxia + **retinal degeneration**; SCA3/MJD = commonest AD ataxia.
- ▶ Newer **non-triplet** repeats: C9orf72 GGGGCC hexanucleotide (commonest familial ALS/FTD), RFC1 AAGGG (CANVAS), FGF14 GAA (SCA27B).

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — "Principles of Human Genetics" (Jameson & Kopp; unstable DNA sequences, dynamic mutation, anticipation, *Table 479-5* Selected Trinucleotide Repeat Disorders); "Ataxic Disorders" (SCAs, Machado-Joseph, Friedreich's ataxia, DRPLA, polyglutamine biology); "Tremor, Chorea, and Other Movement Disorders" (Huntington's disease genetics, MRI, treatment, HDL disorders); "Muscular Dystrophies and Other Muscle Diseases" (myotonic dystrophy DM1/DM2, DMPK/CNBP, RNA toxicity); plus the motor neuron disease chapter (Kennedy's/SBMA) and the ALS/frontotemporal dementia chapters (C9orf72 GGGGCC hexanucleotide expansion).
- ▶ Coverage note: The corpus covers this topic well. Fragile X is detailed mainly through *Table 479-5* genetics (gene, locus, repeat ranges, loss-of-function silencing) rather than a dedicated clinical fragile-X chapter; FXTAS (the premutation-associated tremor/ataxia syndrome) is not separately described in the searched chapters, so it is not emphasised here.



Problems of old age

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

Definition / Introduction — *Geriatric medicine* addresses the health of older adults (conventionally ≥ 65 years), in whom illness is shaped less by single organ disease than by *multimorbidity*, diminished physiologic reserve and impaired function. Ageing itself is not a disease: normal ageing changes do not cause symptoms but increase susceptibility to disease. The characteristic clinical problems of old age — the *geriatric syndromes* (falls, incontinence, delirium/dementia, frailty, polypharmacy) — are multifactorial, often atypical in presentation, under-diagnosed and frequently reversible. Their management is *person-centred*: function, comfort, quality of life and what "matters most" to the patient supersede cure.

Principles of care — the "5 M's" and comprehensive geriatric assessment

- ▶ The modern framework for caring for older adults is the 5 M's of geriatrics: **Mentation** (cognition, mood, delirium), **Mobility** (gait, falls), **Medication** (polypharmacy, deprescribing), **Multicomplexity** (multimorbidity, geriatric syndromes) and **Matters Most** (goals of care). This reframes care from a disease-driven to a person-centred paradigm.
- ▶ **Comprehensive Geriatric Assessment (CGA)** is the cornerstone — a multidimensional, interdisciplinary evaluation of medical conditions, functional status (basic and instrumental *Activities of Daily Living*), cognition/affect, social support, nutrition and a "geriatric review of systems" using validated screens.

- ▶ Key principles: conditions are multiple and multifactorial; iatrogenic illness (adverse drug reactions, immobility, deconditioning) is common; many treatable problems (fall risk, incontinence, elder abuse) are missed; and care is mostly delivered outside hospital with vulnerable *care transitions*.

Falls and immobility

- ▶ **Epidemiology:** about *one in three* community-dwelling older people and *one in two* long-term-care residents fall annually; complications (hip/wrist fracture, subdural haematoma) are a leading cause of injury death after 65.
- ▶ **Causes are multifactorial** — intrinsic (postural hypotension, arrhythmia, aortic stenosis, Parkinson's disease, neuropathy, visual impairment, cognitive impairment, muscle weakness, foot disorders) and extrinsic (sedatives, antihypertensives, environmental hazards). Up to half of "unexplained falls" in dementia are due to near-syncope from postural hypotension. Always exclude *syncope* and *seizure*.
- ▶ **Screen** every older person: "Have you fallen in the past year?", "Are you afraid of falling?", "Trouble rising from a chair?" Assess with the **Get Up and Go test**.
- ▶ **Management** is multifactorial: physical therapy for strength and balance, *Tai Chi* (proven in trials), medication review/withdrawal, treat postural hypotension and arrhythmia, correct vision, podiatry/footwear, home-hazard modification, fall-alert system and hip protectors in selected patients. **Vitamin D ≥ 800 IU/day** is reasonable, but *high-dose vitamin D (60,000 IU monthly) increases falls* and should be avoided. Patients fracturing after a fall must be evaluated and treated for **osteoporosis**.
- ▶ **Immobility** and hospital bed-rest cause deconditioning, muscle loss, pressure injury, venous thromboembolism and functional decline — early mobilisation is preventive.

Polypharmacy and prescribing

- ▶ **Polypharmacy** (commonly ≥ 5 simultaneous drugs): ~40% of those ≥ 65 take 5–9 drugs and ~20% take ≥ 10 . It magnifies adverse drug events ($>100,000$ hospitalisations/year), chiefly from *warfarin/antiplatelets*, *insulin/hypoglycaemics* and cardiovascular drugs.
- ▶ **Evaluation:** medication reconciliation at every visit and especially at care transitions; match each drug to an indication; watch for the **prescribing cascade** (e.g. treating amlodipine-induced oedema with a diuretic).
- ▶ **Deprescribing tools:** the *AGS Beers criteria* (**potentially inappropriate medications**) and the **STOPP**** (Screening Tool of Older Persons' Prescriptions) criteria. Common deprescribing targets: benzodiazepines/hypnotics, anticholinergics, PPIs without indication, hypoglycaemics causing tight control, and statins near end of life.
- ▶ **Safe geriatric prescribing:** "start low, go slow"; minimise drug number; estimate renal function (Cockcroft–Gault, which safely under-estimates clearance) and adjust renally-cleared drugs; simplify regimens and use adherence aids.

Cognitive disorders — delirium and dementia

Feature	Delirium	Dementia
Onset	Acute, <i>fluctuating</i>	Insidious, progressive
Attention	Impaired (hallmark)	Preserved early
Course	Usually reversible	Chronic, often irreversible
Consciousness	Often altered	Clear until late

- **Delirium** occurs in up to **40% of hospitalised** older patients; it is a *medical emergency* signalling underlying illness. Diagnose with the **Confusion Assessment Method (CAM)**: acute onset + fluctuating course **and** inattention **plus** disorganised thinking *or* altered consciousness. Identify precipitants (drugs, infection, electrolytes, hypoxia, pain, retention, impaction). Manage by treating the cause, reorientation, sensory aids, mobilisation, sleep hygiene; reserve low-dose **risperidone (0.25–0.5 mg)** or **quetiapine (12.5–50 mg)** for danger or psychosis. Avoid benzodiazepines (except alcohol withdrawal).
- **Dementia**: by age 85, **30–40%** have dementia; **>20%** of those over 70 have mild cognitive impairment (MCI), **15–20%/year** of whom progress. Alzheimer's and vascular dementia (often coexisting) predominate; *dementia with Lewy bodies* (~25%) features early parkinsonism, fluctuating attention and visual hallucinations. Screen with the **Mini-Cog** (3-item recall + clock draw); confirm with MoCA/MMSE plus neuroimaging and reversible-cause labs (B12, TSH, metabolic). Manage with non-pharmacological measures, cholinesterase inhibitors/memantine (modest benefit, GI and bradycardia effects), treat depression, and avoid antipsychotics for behavioural symptoms unless dangerous.

Urinary incontinence, sleep, frailty and other syndromes

- **Urinary incontinence/overactive bladder**: affects ~1 in 3 older women and 15–20% of men; precipitates falls, social isolation and institutionalisation. Types: **stress, urge, mixed, overflow, functional**; distinguish with the **3 Incontinence Questions (3IQ)**. Exclude reversible causes (UTI, atrophic vaginitis, drugs, impaction, hyperglycaemia, CHF). Check **post-void residual** (>200 mL abnormal). Treat with pelvic-floor (*Kegel*) and behavioural therapy, **antimuscarinics** or **β₃-agonists** for urge, α-blockers ± 5α-reductase inhibitor in men.
- **Sleep disorders**: insomnia (~30%), obstructive sleep apnoea (~10%), restless legs (5–10%) and periodic limb movements. Treat with sleep hygiene/stimulus-control first; if needed use **melatonin** or **low-dose trazodone** — avoid chronic benzodiazepine hypnotics (hangover, falls).
- **Frailty**: a syndrome of reduced physiologic reserve. The **Fried phenotype** requires ≥3 of five criteria — *unintentional weight loss, weakness (grip), exhaustion, slowness (gait speed), low physical activity*; the **Rockwood Frailty Index** is a deficit-accumulation measure. Prevalence ~10–14% in the community, rising with age. Manage with structured **exercise (resistance + aerobic)**, protein/nutritional supplementation, polypharmacy reduction and treatment of comorbidity.
- **Pressure injuries, malnutrition/weight loss, sensory (vision, hearing) impairment** and **chronic pain** (commonly osteoarthritis) round out the syndromes. For pain, prefer **acetaminophen 1 g 2–3 times daily**, topical NSAIDs/lidocaine, and *duloxetine*; avoid systemic NSAIDs (GI bleed, renal, CHF) in the multimorbid.

- ▶ **Elder abuse and neglect** (incidence $\geq 8\text{--}10\%$ /year, under-reported): physical, psychological, financial, sexual and neglect/self-neglect. Screen privately ("Do you feel unsafe?", "Has anyone taken your money?"); treat injuries and report to adult protective services.

Management of common chronic diseases — geriatric tailoring

- ▶ **Hypertension**: treat to individualised targets; *HYVET* (≥ 80 years, target ≤ 150 mmHg) reduced stroke, heart failure and mortality; *SPRINT* supported lower systolic targets in selected fit elderly — but beware postural hypotension, falls and syncope.
- ▶ **Diabetes**: relax control — **HbA1c target** $\sim 7.5\%$ in most older adults; **metformin** first line; *avoid glyburide* (hypoglycaemia); avoid sliding-scale insulin. SGLT2 inhibitors aid heart-failure/renal outcomes.
- ▶ **Prevention**: individualise cancer screening to life expectancy; vaccinate against **influenza**, **pneumococcus**, **herpes zoster**, **COVID-19** and **RSV**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The 5 M's of geriatrics** — a central hub "Matters Most" with four spokes labelled *Mentation, Mobility, Medication, Multicomplexity*.
- ▶ **Multifactorial falls model** — a circle "FALL" with arrows from labelled risk factors: *Postural hypotension, Medications (sedatives/antihypertensives), Visual impairment, Gait/balance & muscle weakness, Cognitive impairment, Foot/footwear problems, Environmental hazards* → leading to outcomes *Hip/wrist fracture, Subdural haematoma, Fear of falling, Loss of function*.

Clinical / Diagnostic significance

- ▶ Atypical disease presentation is the rule — infection may present as delirium or a fall rather than fever; myocardial infarction may be painless.
- ▶ A new **fall, delirium or incontinence** should trigger a search for acute illness, not be dismissed as "ageing".
- ▶ CGA-based, interdisciplinary models — **Acute Care for the Elderly (ACE) units**, co-management (e.g. ortho-geriatric hip-fracture care) and structured **care-transition programmes** — reduce complications, length of stay and readmission.
- ▶ End-of-life planning matters: **CPR survival is $<20\%$** in hospitalised patients ≥ 65 and near-zero in nursing-home residents; advance directives (living will, POLST, durable power of attorney) and avoidance of feeding tubes in advanced dementia are person-centred standards.

High-yield exam pointers

- ▶ **Geriatric giants/syndromes**: Falls, Incontinence, Delirium/Dementia, Frailty, Polypharmacy (plus immobility, pressure injury, malnutrition, sensory loss).
- ▶ **5 M's**: Mentation, Mobility, Medication, Multicomplexity, Matters Most.
- ▶ **CAM** = acute/fluctuating + inattention + (disorganised thinking *or* altered consciousness).
- ▶ **Fried frailty phenotype** = weight loss, weakness, exhaustion, slowness, low activity (≥ 3 of 5).

- ▶ **Beers and STOPP** criteria identify potentially inappropriate medications; use **Cockcroft–Gault** for renal dosing.
- ▶ Falls: screen ("fallen in past year?"), **Get-Up-and-Go**, Tai Chi, vitamin D 800 IU (avoid high-dose monthly).
- ▶ Older-adult targets: **HbA1c** ~7.5%, metformin first line, avoid glyburide; HTN — **HYVET/SPRINT**.
- ▶ Avoid benzodiazepines for insomnia/delirium; prefer melatonin or low-dose trazodone.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Caring for the Geriatric Patient" (5 M's, CGA, falls, polypharmacy/Beers–STOPP, delirium and dementia, incontinence, sleep, frailty, elder abuse, hypertension/diabetes/pain in older adults, models of care) and "Biology of Aging" (hallmarks of ageing — genomic instability, telomere attrition, cellular senescence, stem-cell exhaustion).
- ▶ **CMDT 2026** — "Geriatric Disorders" (functional screening, delirium work-up, falls risk-factor table and targeted interventions, immobility).



Thermoregulation

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

Definition / Introduction — Thermoregulation is the homeostatic process by which the body maintains its **core temperature within a narrow range of 36.5–37.5°C (97.7–99.5°F)** despite wide swings in environmental temperature and in metabolic heat production. It is a classic negative-feedback control system with a central integrator (the **hypothalamic thermoregulatory centre**), afferent thermosensors, and efferent autonomic, somatic, endocrine and behavioural effectors that continuously balance heat production/gain against heat loss. In a thermoneutral environment the resting metabolic rate generates *more* heat than is needed to hold the core temperature, so the system is biased toward controlled heat dissipation. Disturbance of this loop underlies fever, hyperthermia/heatstroke and hypothermia.

The thermoregulatory control loop — afferent, central, efferent

- ▶ **Central integrator (the "thermostat")**: the **preoptic anterior hypothalamus (POAH)** is the central thermostat; the posterior hypothalamus also participates. Neurons here receive **two kinds of input** which they integrate against a regulated **set point** (~37°C):
 - signals from **peripheral warmth/cold receptors in the skin** (cutaneous thermoreception), carried by peripheral nerves; and
 - the temperature of the **blood bathing the hypothalamus** itself (central/core thermoreception).
- ▶ **Comparator action**: if integrated temperature exceeds the set point, heat-loss effectors are driven; if it falls below, heat-conservation and heat-production effectors are driven — until blood temperature again matches the set point.
- ▶ **Efferent (output) limbs**:

- **Autonomic (immediate defence):** sympathetic control of **cutaneous vasomotor tone** (vasoconstriction to conserve / vasodilation to dissipate heat), **sudomotor (sweating)** activity, and release of **norepinephrine** with increased muscle tone. The autonomic limb is the rapid first responder.
- **Somatic: shivering** thermogenesis via skeletal muscle.
- **Endocrine (delayed defence):** prolonged cold stimulates the **thyroid axis**, raising basal metabolic rate; antidiuretic hormone and aldosterone also rise with heat stress.
- **Behavioural:** adding/removing clothing, seeking shade or warmth, altering posture and activity — quantitatively the most powerful and the cheapest defence.

Heat production (thermogenesis) and heat gain

- ▶ **Obligatory (basal) heat:** generated continuously by metabolism in **muscle and liver**; even at rest this exceeds the heat needed to maintain core temperature.
- ▶ **Shivering thermogenesis:** rhythmic involuntary skeletal-muscle contraction; the principal acute mechanism to raise core temperature in cold.
- ▶ **Non-shivering thermogenesis:** heat from the **liver** and metabolic tissues, augmented by sympathetic/thyroid drive, contributing to the rise in core temperature without shivering.
- ▶ **Exercise / exertion:** strenuous exercise can increase heat generation up to **twentyfold**, making exertional heat illness possible even in cool conditions.
- ▶ **Exogenous heat gain:** by **radiation** (a major source of gain in hot climates) and by conduction/convection when ambient temperature exceeds skin temperature.

Heat loss (dissipation) — the four/five physical mechanisms

The skin surface acts as the **radiator** and is the principal site of heat loss; cutaneous **skin blood flow can increase 25–30 times** above basal rate to deliver core heat to the surface, with **compensatory vasoconstriction of the splanchnic and renal beds** to support blood pressure.

Mechanism	Definition	Key quantitative / clinical points
Radiation	Emission of infrared electromagnetic energy to surroundings	~55–65% of heat loss at rest; <i>reverses</i> to become a major heat gain in hot climates
Conduction	Direct transfer of heat to a cooler contacting object	~10–15%; greatly increased in cold water (thermal conductivity of water is 25× that of air); ineffective once ambient > skin temperature
Convection	Loss of heat to moving air currents	Increased in wind ; ineffective once ambient > skin temperature
Evaporation	Latent heat lost as sweat/skin moisture vaporises	The single most efficient mechanism in heat; becomes progressively ineffective when relative humidity > 70%
Respiration	Heat lost in expired air (and respiratory water)	Listed as a fifth mechanism in cold-injury physiology; depends on ambient temperature and humidity

- ▶ The **wet-bulb globe temperature (WBGT)** integrates air temperature, humidity, radiant heat and wind speed, and is superior to the simple "heat index" for assessing environmental heat load.

Normal core temperature and its physiological variation

- ▶ **Mean oral temperature** $\approx 36.6^{\circ}\text{C}$ (95% CI $35.7\text{--}37.3^{\circ}\text{C}$); a temperature $>37.7^{\circ}\text{C}$ (99.9°F) — the 99th percentile of healthy individuals — defines fever.
- ▶ **Diurnal rhythm**: lowest around **8 a.m.**, highest around **4 p.m.**; seasonal variation (lower in summer, higher in winter).
- ▶ **Site differences**: **rectal** temperature is $\sim 0.4^{\circ}\text{C}$ (0.7°F) **higher** than oral; **lower-oesophageal** temperature best reflects core; unadjusted-mode **tympenic** readings run $\sim 0.8^{\circ}\text{C}$ (1.6°F) **lower** than rectal.
- ▶ **Menstrual cycle**: at ovulation temperature rises by $\sim 0.6^{\circ}\text{C}$ (1°F) and stays elevated through the luteal phase (progesterone effect).
- ▶ **Modifiers**: temperature falls slightly with **age** ($\sim 0.02^{\circ}\text{C}$ lower per decade), and varies with demographics and comorbidity (e.g., higher in cancer, lower in hypothyroidism).

Integrated responses to cold and heat stress; acclimatisation

Stimulus	Heat conservation/production response	Heat dissipation response
Cold exposure	Cutaneous reflex vasoconstriction (conserves heat); shivering + raised muscle tone; norepinephrine release and non-shivering thermogenesis; delayed thyroid-axis activation; behavioural warming	Suppressed
Heat exposure	Suppressed	Cutaneous vasodilation (skin blood flow up 25–30 $\times$) + diaphoresis/evaporation ; splanchnic–renal vasoconstriction to defend BP; behavioural cooling

- ▶ **Heat acclimatisation** is a set of adaptations developing over **1 to several weeks** of work in the heat: the **sweating threshold is lowered**, sweat **volume increases** with a **lower salt concentration**, **plasma volume expands** (better cutaneous flow), and the heart rate falls with a higher stroke volume. Sweating rates reach **1–2 L/h** in acclimatised individuals. Acclimatisation is lost ("de-acclimatisation") within weeks of leaving the hot environment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Thermoregulatory negative-feedback loop (block diagram).** Labels: *Cutaneous warmth/cold receptors* and *temperature of blood* → afferent input → **Preoptic anterior hypothalamus (set point / comparator)** → efferent limbs: (1) Sympathetic — cutaneous vasoconstriction/vasodilation; (2) Sudomotor — sweating; (3) Somatic — shivering; (4) Endocrine — thyroid axis / norepinephrine; (5) Behavioural responses → effectors alter *Heat production vs Heat loss (radiation, conduction, convection, evaporation, respiration)* → **Core temperature** → feedback arrow back to hypothalamus.
- ▶ **Set-point diagram — fever vs hyperthermia.** Draw a horizontal "thermostat" line at 37°C. *Fever*: set point **raised** (e.g., 37→39°C) by PGE2 → body actively conserves/produces heat to reach it (vasoconstriction, shivering, "feels cold"). *Hyperthermia/heatstroke*: set point **unchanged** at 37°C but core temperature overshoots because heat load exceeds dissipation. Label the OVLT/PGE2 input on the fever side.

Clinical / Diagnostic significance

- ▶ **Fever vs hyperthermia (a must-distinguish):**

Feature	Fever	Hyperthermia (e.g., heatstroke)
Hypothalamic set point	Raised (PGE2-mediated)	Normal / unchanged
Mechanism	Pyrogens → IL-1, IL-6, TNF, IFN → PGE2 (via EP-3 receptor, near the OVLT — organum vasculosum of lamina terminalis) → cAMP → raised set point	Heat load (exogenous + endogenous) overwhelms dissipation; no pyrogens
Skin	Often cold (vasoconstriction), shivering	Hot, dry (classic heatstroke) or sweaty (exertional)
Response to antipyretics	Responds (aspirin/acetaminophen/NSAID lower set point by ↓brain PGE2)	No response — dangerous; needs rapid physical cooling

- ▶ **Pyrogen pathway (fever):** exogenous pyrogens (e.g., **lipopolysaccharide/endotoxin**) → myeloid/endothelial cells release **pyrogenic cytokines** (IL-1, IL-6, TNF) → hypothalamic endothelial PGE2 → glial cAMP → set point reset upward; antipyretics (cyclooxygenase inhibitors) reverse this.
- ▶ **Hyperthermia/heatstroke:** core >40.5°C with **CNS dysfunction**; above 42°C thermosensitive enzymes fail and there is **uncoupling of oxidative phosphorylation**, endothelial injury, heat-shock-protein/cytokine-mediated SIRS, DIC and multiorgan failure. Antipyretics are useless and potentially harmful; treat by rapid cooling (evaporative/immersion) to ~38–39°C.
- ▶ **Hypothermia (core <35°C):** failure of heat conservation; the **autonomic limb** (vasoconstriction, shivering) is the immediate defence and the **endocrine** (thyroid) limb the delayed one. The **Osborn (J) wave**, cold diuresis, coagulopathy and "paradoxical undressing" are classic; rewarming risks **core-temperature afterdrop**.

- ▶ **Drugs/conditions that impair thermoregulation:** anticholinergics, phenothiazines, tricyclics (impair sweating, depress POAH dopamine), **beta-blockers, calcium-channel blockers and stimulants** (reduce cutaneous perfusion), and ethanol/anaesthetics (block shivering, cause vasodilation) — all raise heat- or cold-illness risk. Useful differentials of disordered thermoregulation: **malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm.**
- ▶ **Metabolic cost of temperature change:** oxygen consumption rises ~13% for every 1°C above 37°C, explaining why fever stresses cardiac/pulmonary/CNS-compromised patients.

High-yield exam pointers

- ▶ Central thermostat = **preoptic anterior hypothalamus**; integrates **skin thermoreceptor** input + **blood temperature**; regulated set point ~37°C.
- ▶ Normal core 36.5–37.5°C; mean oral 36.6°C; fever defined as >37.7°C (99th percentile).
- ▶ Four/five heat-loss routes: **radiation (55–65%), conduction (10–15%), convection, evaporation (most efficient, fails if humidity >70%), respiration.**
- ▶ **Skin blood flow can rise 25–30×**; evaporative sweating up to 1–2 L/h when acclimatised; water conducts heat 25× faster than air.
- ▶ **Fever = raised set point (pyrogen→PGE₂→EP-3, near OVLT); hyperthermia = normal set point overwhelmed** — only fever responds to antipyretics.
- ▶ Efferent limbs: **autonomic (immediate) + endocrine/thyroid (delayed) + somatic shivering + behavioural.**
- ▶ **Acclimatisation** (1–several weeks): lower sweat threshold, more sweat with **less salt**, plasma-volume expansion, lower HR.
- ▶ **O₂ consumption ↑13% per 1°C rise**; ovulation raises core by ~0.6°C; rectal is 0.4°C > oral.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Fever" (Dinarello & Surana; thermoregulatory centre, set point, normal temperatures and variation, fever vs hyperthermia, pyrogen/PGE2 pathway, antipyretic mechanism); "Heat-Related Illnesses" (Danzl; thermoregulation, heat-dissipation mechanisms, skin blood flow, acclimatisation, heatstroke); "Hypothermia and Peripheral Cold Injuries" (Danzl; five heat-loss mechanisms with percentages, autonomic vs endocrine defence of thermoneutrality).
- ▶ **Coverage note:** This is a basic-physiology (anatomy/physiology) question; the RGUHS spec lists **no dedicated specialty textbook**, and Harrison covers thermoregulation only as it is embedded within the Fever, Heat-Related-Illness and Hypothermia chapters (spec flagged as a thin/"gap" topic). The answer therefore synthesises these three chapters; the underlying control-loop framework (afferent–integrator–efferent limbs, shivering/non-shivering thermogenesis, behavioural responses) is universally accepted standard physiology and is stated only where consistent with the cited Harrison text. Cell-physiology depth (e.g., brown-adipose-tissue UCP-1 mechanism, TRP-channel thermoreceptors) is not elaborated in this corpus and has been omitted rather than fabricated.

**DNA replication**

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

Definition / Introduction — **DNA replication** is the enzymatically catalysed, **semiconservative** process by which a cell duplicates its entire double-stranded genome so that each daughter cell receives an identical copy during division. It exploits the strict **base-pair complementarity** of the double helix (A–T, G–C): the two parental strands separate and each acts as a **template** for synthesis of a new complementary strand, so every daughter duplex contains one old (parental) and one newly made strand. In humans, ~3 billion base pairs per haploid genome are copied with extraordinary fidelity during the **S phase** of the cell cycle, the accuracy of which is essential to prevent mutation, cancer and inherited disease.

Structure of DNA — the template that makes replication possible

- ▶ DNA is a **double-stranded right-handed helix** of four bases — **adenine (A), thymine (T), guanine (G), cytosine (C)** — with **A pairing T** (2 hydrogen bonds) and **G pairing C** (3 hydrogen bonds) across the helix.
- ▶ The two strands are **antiparallel**: one runs 5'→3', its partner 3'→5'; the sugar–phosphate (deoxyribose–phosphodiester) backbone is on the outside, bases inside.
- ▶ This **complementarity and double-stranded nature permit faithful replication during cell division** and underlie the flow of information DNA → RNA → protein.
- ▶ In the eukaryotic nucleus DNA is packaged with **histones** into **nucleosomes** (core octamer of H2A, H2B, H3, H4; H1 is the linker histone), coiled into **solenoid** fibres and **supercoiled**

chromatin, ending in **centromeres** and **telomeres** — all of which must be transiently unpacked and re-assembled as the replication fork passes.

Key enzymes and proteins of the replication machinery

Protein / enzyme	Function
DNA helicase	Unwinds and separates the parental duplex at the fork (ATP-dependent)
Topoisomerase / DNA gyrase	Relieves torsional strain (positive supercoils) ahead of the fork
Single-strand binding (SSB) proteins	Coat and stabilise unwound single strands; prevent re-annealing
Primase (an RNA polymerase)	Synthesises short RNA primers providing a free 3'-OH to start synthesis
DNA polymerase	Adds dNTPs to the 3'-OH; synthesises only 5'→3', reads template 3'→5'; has 3'→5' exonuclease proofreading
Sliding clamp / clamp loader	Tethers polymerase to template for high processivity
DNA ligase	Seals nicks (phosphodiester bonds) between adjacent fragments
Telomerase	Reverse transcriptase that extends 3' chromosome ends (germ/stem/cancer cells)

- **Polymerase specialisation:** in bacteria, **Pol III** is the main replicase and **Pol I** removes RNA primers and fills the gaps; in eukaryotes, **Pol α/primase** initiates, **Pol δ** extends the lagging strand and **Pol ε** the leading strand, while **Pol γ** replicates mitochondrial DNA.

Stages of replication — initiation, elongation, termination

- **Initiation:** Begins at specific **origins of replication** — a single *oriC* in bacteria but **thousands of origins** along the large eukaryotic chromosomes (permitting timely S-phase completion). Origins are "**licensed**" once per cycle by the **origin recognition complex (ORC)** and loading of the **MCM helicase**, ensuring DNA is copied **exactly once** per cell cycle. Helicase opens the duplex to form two **replication forks** moving in opposite directions (a **replication bubble**).
- **Elongation:** Helicase unwinds; SSB and topoisomerase keep the template open and untangled. Primase lays an RNA primer; DNA polymerase extends it 5'→3', incorporating the correct complementary dNTP. Because the two template strands are antiparallel and polymerase works in only one direction, the two new strands are made differently (see below).
- **Termination:** Forks converge; in eukaryotes adjacent **replicons** merge, RNA primers are excised and replaced with DNA, and ligase joins all fragments into two continuous daughter duplexes. Histones reassemble nucleosomes on the new DNA.

Leading vs lagging strand and Okazaki fragments

Feature	Leading strand	Lagging strand
Direction relative to fork	Same as fork movement	Opposite to fork movement
Synthesis	Continuous	Discontinuous

Feature	Leading strand	Lagging strand
Primers needed	One (single)	Many (one per fragment)
Product	One long strand	Short Okazaki fragments later ligated
Eukaryotic polymerase	Pol ϵ	Pol δ

- ▶ The lagging strand is built as short segments called **Okazaki fragments** (~100–200 nucleotides in eukaryotes; ~1000–2000 in bacteria), each begun with its own RNA primer; primers are then removed, gaps filled and nicks sealed by **DNA ligase**.

Fidelity, proofreading and DNA repair

- ▶ Replication is remarkably accurate (~ 1 error per 10^9 – 10^{10} bp) because of (1) correct base selection, (2) **3'→5' exonuclease proofreading** by polymerase, and (3) post-replication **mismatch repair**.
- ▶ Certain sites are mutation "hot spots": adjacent pyrimidines (T-T, C-C) form **UV-induced photoadducts/pyrimidine dimers**; methylated CpG cytosines deaminate to thymine causing recurrent **C→T (G→A) transitions**.
- ▶ Repair pathways correcting replication/damage errors — and the diseases caused by their failure:

Repair pathway	Corrects	Disease if defective
Nucleotide excision repair (NER)	Bulky lesions / pyrimidine dimers	Xeroderma pigmentosum
Mismatch repair (MMR) — <i>MutS/MSH2, MLH1</i>	Base mismatches & slippage from replication	HNPCC / Lynch syndrome (colon, endometrial, ovarian cancer)
Homologous recombination — <i>BRCA1/2, Fanconi pathway</i>	Double-strand breaks, inter-strand crosslinks	Hereditary breast/ovarian cancer; Fanconi anaemia

Telomeres, telomerase and the "end-replication problem"

- ▶ Because lagging-strand synthesis needs a primer, the extreme 3' end of a linear chromosome cannot be fully copied, so chromosomes **shorten with each division** (telomere attrition) — a marker of replicative ageing/senescence.
- ▶ **Telomerase**, a ribonucleoprotein **reverse transcriptase** carrying its own RNA template, adds tandem **TTAGGG** repeats to chromosome ends, counteracting shortening.
- ▶ Telomerase is active in germline, stem and most **cancer** cells (conferring replicative immortality) but largely silent in mature somatic tissue — a key link between replication biology and oncogenesis and ageing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled replication fork:** show parental duplex opened into a "Y". Label — *parental DNA* (3' and 5' template strands), *helicase* (at fork), *single-strand binding proteins*, *topoisomerase/gyrase* (ahead of fork), *RNA primer*, *primase*, *leading strand* (continuous, 5'→3'), *lagging strand with Okazaki fragments*, *DNA polymerase*, *DNA ligase*, *direction of fork movement*.
- ▶ **Semiconservative replication (Meselson–Stahl) schematic:** one parental double helix → two daughter duplexes, each with one *old (parental)* strand (shaded) and one *new* strand. Label *parental strand*, *newly synthesised strand*, *origin of replication*, *replication bubble/two forks*.

Clinical / Diagnostic significance

- ▶ **Cancer:** loss of replication fidelity / repair drives carcinogenesis — MMR defects produce **microsatellite instability** in Lynch syndrome; **BRCA1/2** and Fanconi-pathway defects give breast/ovarian cancer; reactivated **telomerase** sustains tumour growth.
- ▶ **Pharmacology:** replication is the target of cytotoxic and antimicrobial drugs — antimetabolites and **fluoropyrimidines/cytarabine/gemcitabine** (block dNTP supply/incorporation), **topoisomerase inhibitors** (irinotecan, etoposide), **alkylating agents** and **fluoroquinolones** (inhibit bacterial gyrase/topoisomerase) and antiretroviral/antiviral **reverse-transcriptase and polymerase inhibitors**.
- ▶ **Inherited disease:** replication-slippage at unstable repeats causes **trinucleotide-repeat expansion disorders** (e.g., Huntington, fragile X, myotonic dystrophy); unequal crossing-over of tandem repeats causes CMT1A (PMP22 duplication).
- ▶ **Diagnostics:** the same complementarity and polymerase chemistry underpin **PCR**, **next-generation sequencing** and molecular cytogenetics used across modern internal medicine.

High-yield exam pointers

- ▶ DNA replication is **semiconservative** — proven by **Meselson & Stahl**; each daughter duplex = one old + one new strand.
- ▶ DNA polymerase synthesises only 5'→3' and **needs an RNA primer** made by primase (cannot start de novo).
- ▶ **Leading strand** = continuous; **lagging strand** = discontinuous (**Okazaki fragments**) later joined by DNA ligase.
- ▶ Fork proteins: **helicase** (unwinds), **SSB** (stabilises), **topoisomerase/gyrase** (relieves supercoils), **primase**, **polymerase**, **ligase**.
- ▶ **Bacteria** = one origin (**oriC**); **eukaryotes** = many origins; replication confined to **S phase** and licensed (**ORC/MCM**) to occur **once per cycle**.
- ▶ Fidelity = base selection + 3'→5' **proofreading** + **mismatch repair**; MMR failure → **Lynch syndrome / microsatellite instability**.
- ▶ **NER defect** → **xeroderma pigmentosum**; **BRCA/Fanconi defect** → **breast/ovarian cancer**, **Fanconi anaemia**.

- ▶ **Telomerase** (RNP reverse transcriptase) adds TTAGGG repeats, solves the end-replication problem; reactivated in cancers.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Principles of Human Genetics*" (DNA double-helix structure and base-pair complementarity, faithful semiconservative replication, chromatin/nucleosome/telomere organisation, the cell cycle and replication of chromosomes at mitosis, replication-error mutational hot spots, and the DNA-repair pathways with their disease correlations — nucleotide excision repair/xeroderma pigmentosum, mismatch repair/HNPCC–Lynch, BRCA1 and the Fanconi pathway, and trinucleotide-repeat expansion).

Coverage note: Harrison 22e (and the cited chapter) treat DNA structure, chromatin, the cell cycle, replication fidelity and DNA-repair/cancer correlations, but do **not** detail the enzymatic replication-fork machinery. The mechanistic specifics in this answer — helicase/topoisomerase/SSB/primase/polymerase/ligase, leading- versus lagging-strand synthesis, Okazaki fragments, polymerase subtypes, origin licensing (ORC/MCM) and telomerase chemistry — are drawn from universally-accepted standard molecular biology and are stated to satisfy the full scope of the question; they are not unique claims of the corpus.



Down's syndrome — genetics and clinical features

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

Definition / Introduction — Down syndrome is the commonest **autosomal chromosomal (aneuploidy) disorder** compatible with survival and the leading genetic cause of **intellectual disability**. It results from the presence of **three copies of chromosome 21 (trisomy 21)**, or of a rearrangement that produces three copies of the critical long-arm segment of chromosome 21. Nearly **0.5% of all human conceptions are trisomic for chromosome 21**; because of high fetal loss the birth incidence is about **1 in 700**, varying from ~1 in 1000 in young mothers to more than three-fold higher with advanced maternal age. The phenotype reflects a *gene-dosage effect* — over-expression of the genes on the supernumerary chromosome 21.

Cytogenetic basis — three genetic mechanisms

Chromosomal disorders are caused by **numerical (aneuploidy) or structural (translocation, deletion, duplication) aberrations**; such disorders occur in ~1% of the general population, ~8% of stillbirths and close to **50% of spontaneously aborted fetuses** (Harrison). Trisomy 21 arises by three distinct mechanisms:

Mechanism	Karyotype	Approx. share	Origin / key point
Free (standard) trisomy 21	47,XX,+21 or 47,XY,+21	~95%	Meiotic non-disjunction , predominantly in maternal meiosis I; <i>strongly maternal-age dependent</i> ; recurrence risk low (~1%)
Robertsonian translocation	e.g. 46,XX,der(14;21) or der(21;21) — <i>translocation Down syndrome</i>	~4%	Fusion of long arms of an acrocentric chromosome (commonly 14, or 21;21) with chromosome 21; <i>not</i> age-related; ~1/3 inherited from a phenotypically normal balanced-translocation carrier parent , giving a substantial recurrence risk
Mosaicism	46,N/47,+21	~1–2%	Post-zygotic non-disjunction at an early mitotic division → two cell lines; phenotype usually milder and variable

- ▶ *Cytogenomic (karyotype/chromosomal microarray) analysis should always be performed* — even though most patients have simple trisomy — to detect **unbalanced translocations**, because such a child may have a parent carrying a **balanced translocation** with a high recurrence risk in future offspring and in that parent's relatives (CMDT).

Mechanism of non-disjunction and gene dosage

- ▶ **Non-disjunction** = failure of paired homologous chromosomes (meiosis I) or sister chromatids (meiosis II) to segregate, so one gamete receives **two copies of chromosome 21** and, after fertilisation by a normal gamete, the zygote is trisomic.
- ▶ The error occurs most often in the **maternal oocyte at meiosis I**; the oocyte pool is arrested from fetal life and only completes meiosis at ovulation, so prolonged arrest predisposes to mis-segregation — the biological basis of the maternal-age effect (rates of **aneuploidy are increased in the female germline**; by contrast new *point* mutations increase with paternal age).
- ▶ Mosaic trisomy reflects **mitotic non-disjunction** in the early embryo, producing a normal and a trisomic cell line.
- ▶ The phenotype is a **gene-dosage (over-expression) effect** of the *Down syndrome critical region* on the distal long arm (**21q22**); triplication of genes here (including *APP*) accounts for the major features and for the near-universal Alzheimer pathology.

Risk factors

- ▶ **Advanced maternal age** — the single most important factor. The risk rises *exponentially* and accelerates markedly after **age 35**; by **age 45 the risk is as high as ~1 in 40**, because older oocytes are predisposed to non-disjunction during meiosis (CMDT).
- ▶ **Previous child with trisomy 21** — recurrence in free trisomy is ~1% (age-related risk plus a small increment).
- ▶ **Parental balanced (Robertsonian) translocation carrier** — confers the highest recurrence risk: a *der(21;21)* carrier parent has an effectively ~100% risk, and a *der(14;21)* carrier mother ~10–15% (lower if the father is the carrier).
- ▶ **Parental germline mosaicism** for trisomy 21.

- *Paternal age does NOT increase the risk of trisomy 21 (CMDT)* — a high-yield discriminator.

Clinical features (multisystem)

Diagnosis is usually made **at birth** on the basis of typical craniofacial features, **hypotonia** and a **single transverse palmar crease** (CMDT).

System	Features
Craniofacial / dysmorphic	Brachycephaly with flat occiput , up-slanting palpebral fissures with epicanthal folds , <i>Brushfield spots</i> (speckled iris), small ears, flat nasal bridge, large/protruding tongue (relative macroglossia), short neck
Musculoskeletal / limbs	Hypotonia , single transverse palmar (simian) crease, clinodactyly of the 5th finger , wide "sandal gap" between 1st–2nd toes, joint laxity, atlanto-axial instability
Neurodevelopment	Intellectual disability of variable degree; developmental delay; early-onset Alzheimer-type dementia in the 4th–5th decade
Cardiac	Congenital heart disease in ~50%, classically atrioventricular (endocardial) canal / AV septal defect , also VSD, ASD, tetralogy
Gastrointestinal	Duodenal atresia , Hirschsprung disease, celiac disease (immune-related)
Haematologic	Transient abnormal myelopoiesis (transient neonatal leukaemia) that usually resolves with conservative care; increased childhood acute lymphoblastic and especially myeloid leukaemia (ML-DS)
Endocrine / immune	Hypothyroidism , diabetes mellitus, immune deficiency with frequent infections

- **Leukaemia** in Down syndrome typically responds to *reduced-dose chemotherapy*, but relapse carries a poor outcome (CMDT).
- **Alzheimer disease**: adults with trisomy 21 *consistently* develop the neuropathologic hallmarks of AD if they survive beyond ~40 years; the **extra dose of the APP gene on chromosome 21 is the initiating cause**, producing excess cerebral amyloid (Harrison). Average life expectancy of those surviving childhood who develop dementia is ~55 years.

Diagnosis and screening

- **Prenatal screening (first/early-second trimester)**: maternal serum **multiple-marker screen** (α -fetoprotein and other biomarkers), increased **nuchal translucency/thickness** and **under-development of the nasal bone** on ultrasonography.
- **Cell-free fetal DNA (cffDNA / NIPT)** in maternal blood gives high-sensitivity, high-specificity non-invasive detection.
- **Confirmatory diagnosis**: fetal **karyotype/cytogenomic analysis** by **chorionic villus sampling** or **amniocentesis** prenatally, and **postnatal karyotype** — mandatory to define the mechanism (free trisomy vs translocation) for **recurrence-risk counselling**.
- *Indications for cytogenetic analysis* (Harrison Table 479-4) include advanced maternal age, abnormal ultrasound, a positive maternal serum screen, multiple congenital anomalies, intellectual disability and developmental delay.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Non-disjunction in meiosis:** normal vs abnormal segregation of chromosome 21. Label: *homologous pair of chromosome 21, meiosis I — failure of homologue separation (non-disjunction), meiosis II, gametes — one with 2 copies of 21 and one with 0, fertilisation by normal gamete → 47,+21 trisomic zygote.*
- ▶ **Robertsonian translocation karyogram:** label *acrocentric chromosomes 14 and 21, fusion at centromere → der(14;21), balanced carrier parent (45 chromosomes, normal phenotype), unbalanced offspring with translocation Down syndrome (46 chromosomes, 3 copies of 21q).*

Clinical / Diagnostic significance

- ▶ **Always karyotype** the child (and parents if a translocation is found) — distinguishes the ~95% sporadic free trisomy (low recurrence) from translocation Down syndrome (potentially very high familial recurrence).
- ▶ **Multisystem surveillance** at diagnosis: echocardiography for AV canal/CHD, evaluation for duodenal atresia, baseline blood count for transient myelopoiesis/leukaemia, **thyroid function**, screening for **celiac disease**, hearing/vision, and caution regarding **atlanto-axial instability** (cervical-spine assessment before anaesthesia or sport).
- ▶ **Management is largely supportive:** surgical correction of duodenal atresia and congenital heart disease as in any patient; no medical therapy alters the neurodevelopmental or neurodegenerative course, and **antioxidant supplementation has shown no benefit** (CMDT).
- ▶ **Genetic counselling** for parents on recurrence risk and prenatal options in future pregnancies is essential.

High-yield exam pointers

- ▶ Commonest **autosomal aneuploidy**; birth incidence ~1/700; ~0.5% of conceptions are trisomic for 21.
- ▶ Three mechanisms: **free trisomy ~95% (meiotic non-disjunction, maternal age-dependent)**, **Robertsonian translocation ~4% (familial, age-independent)**, **mosaic ~1–2%**.
- ▶ **Advanced maternal age** is the key risk factor; by age 45 ≈ 1 in 40; **paternal age does not increase risk**.
- ▶ **CHD** in ~50%, classically AV (endocardial) canal defect; GI: **duodenal atresia** ("double-bubble").
- ▶ Haematology: **transient abnormal myelopoiesis** in neonates; increased **ALL and AML (ML-DS)** in childhood.
- ▶ Classic signs: hypotonia, **single palmar crease**, epicanthal folds, Brushfield spots, protruding tongue, clinodactyly, sandal gap.
- ▶ **Tripllicated APP gene (chromosome 21)** → **early Alzheimer dementia** by the 4th–5th decade; life expectancy ~55 years.
- ▶ **Cytogenomic/karyotype analysis is mandatory** to detect unbalanced translocation and guide recurrence-risk counselling.

- Prenatal: **multiple-marker serum screen + nuchal translucency + nasal bone**, confirmed by **cffDNA (NIPT)** and **amniocentesis/CVS karyotype**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (chromosomal/cytogenetic disorders: aneuploidy, non-disjunction, Robertsonian translocation, mosaicism, indications for cytogenetic analysis); "The Integration of Inherited Genetics into Clinical Practice"; "Alzheimer's Disease and Other Dementias" (*APP*/chromosome-21 mechanism); "Myelodysplastic Syndromes" (Down syndrome predisposition).
- **CMDT 2026** — "Genetic & Genomic Disorders: Down Syndrome" (incidence, maternal-age risk, screening, clinical features, leukaemia, dementia, karyotype/counselling, management).

Coverage note: Harrison 22e treats chromosomal-syndrome clinical detail sparingly (chromosome-disorder specifics are condensed from earlier editions), so the clinical and screening depth here is drawn mainly from CMDT 2026. The exact mechanism percentages (~95% free trisomy / ~4% translocation / ~1–2% mosaic), the specific translocation recurrence-risk figures, the "21q22 Down syndrome critical region", and several classic dysmorphic eponyms (Brushfield spots, clinodactyly, sandal gap) are universally accepted standard genetics not all stated verbatim in the available corpus; CMDT confirms the translocation/recurrence principle, the single palmar crease, flat occiput, epicanthal folds, large tongue and 50% CHD/AV-canal figure.



Effects of disease on drug concentration and response

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

Definition / Introduction — The response to a drug is the product of two linked processes: **pharmacokinetics** (the relationship between dose and plasma/tissue concentration, governed by absorption, distribution, metabolism and excretion — ADME) and **pharmacodynamics** (the relationship between concentration and effect at the molecular target). Concurrent disease can perturb *either* arm, shifting the position of the dose–response curve relative to the **therapeutic window** and thereby causing toxicity or loss of efficacy at conventional doses. A useful unifying idea is that disease modulates drug action by altering the **expression or function of the genes whose products determine PK and PD** — the same framework underlying pharmacogenomics. The clinically dominant disease states are **renal failure, hepatic disease, heart failure/shock, altered protein-binding (acute illness)**, and the physiologically "disease-like" extremes of **age**.

Conceptual framework — why disease matters

- **The therapeutic ratio (index/window):** the separation between the dose–concentration curve for the *desired* effect and that for *toxicity* (Fig. 71-1). Disease that raises free drug concentration or sensitises the target effectively *narrows* this window; the danger is greatest for drugs with an

intrinsically **narrow therapeutic index** (digoxin, phenytoin, aminoglycosides, vancomycin, warfarin, lithium, antiarrhythmics).

- ▶ **"High-risk pharmacokinetics"**: when active drug concentration depends on a **single** elimination pathway, any disease (or genetic/drug-interaction) inhibiting that pathway produces large, often dangerous swings in concentration. Drugs cleared by **multiple** pathways are relatively protected.
- ▶ **Free vs total drug**: only **unbound** drug is pharmacologically active. Because response tracks free concentration, disease-induced changes in protein binding can dissociate the *total* (measured) level from the *active* level — pivotal for highly bound drugs.
- ▶ **Both PK and PD shift**: disease may change concentration (PK) *and* independently alter target sensitivity (PD), e.g. receptor up-/down-regulation, ion-channel modulation by ischaemia/electrolytes.

Disease → mechanism → consequence (master table)

Disease state	Dominant PK/PD change	Net effect on drug	Illustrative drugs
Renal failure	↓ renal excretion of drug/active metabolite; altered binding in uraemia	↑ levels, accumulation, ADR	Digoxin; dofetilide, sotalol (QT/arrhythmia); normeperidine (seizures); edoxaban
Hepatic disease (cirrhosis)	↓ first-pass metabolism, portacaval shunting, ↓ hepatocyte function; ↓ albumin	↑ oral bioavailability; ↑ free drug	Morphine, meperidine, midazolam, nifedipine (bioavailability ~doubled)
Heart failure / shock	Redistribution of CO; ↓ V _d ; ↓ hepatic & renal perfusion; ↓ gut perfusion	↑ plasma & CNS/cardiac levels; ↓ clearance; ↓ oral absorption	Lidocaine, digoxin; orally administered drugs (reduced effect)
Acute illness (MI, infection, surgery)	↑ acute-phase reactant binding (transient)	↓ free drug → ↓ efficacy	Drugs bound to α ₁ -acid glycoprotein
Chronic kidney/liver disease	↓ albumin → ↓ binding	↑ free drug → ↑ effect/toxicity	Phenytoin (monitor <i>free</i> level)
Elderly / children	Altered organ maturity/decline, body-compartment size, polypharmacy	Variable; ↑ ADRs	Long-t _{1/2} benzodiazepines (falls/hip fracture)

Renal disease

- ▶ If a drug or its active metabolite is **mainly renally excreted** and high levels cause ADRs ("high-risk pharmacokinetics"), the **dose or dosing interval must be reduced** in renal dysfunction to avoid toxicity.
- ▶ **Digoxin** is the classic example. **Dofetilide and sotalol** undergo predominant renal excretion and risk **QT prolongation and torsades** if not dose-reduced.

- ▶ **Active/toxic metabolites accumulate** even when the parent is hepatically cleared: **meperidine (pethidine)** is largely metabolised by the liver, but its metabolite **normeperidine** is renally excreted and accumulates in renal failure, producing **CNS excitation** — **irritability, twitching, seizures**.
- ▶ **Anticoagulants**: at approved doses **edoxaban** appears *more* effective in mild renal dysfunction, possibly reflecting higher drug levels — a caution against assuming "lower function is always safer."
- ▶ **Binding: uraemia alters protein binding** of some drugs (e.g. **phenytoin**), so measuring the **free concentration** is preferable.
- ▶ **Practical dose adjustment** is based on the severity of dysfunction indexed by **creatinine clearance** (estimated in standard practice by the *Cockcroft–Gault* equation); published dose/interval tables give only a **first approximation** that must be refined with plasma-level data (where available) and clinical observation.

Hepatic disease

- ▶ **Standard liver-function tests do NOT predict** the need for dose adjustment in hepatitis or cirrhosis (a key exam point) — there is no hepatic equivalent of creatinine clearance; severity tools such as the *Child–Pugh* score are used clinically but no test reliably quantifies metabolic capacity.
- ▶ **Loss of first-pass (presystemic) metabolism** is the central effect: disrupted hepatocyte function, altered liver architecture and portacaval shunts mean orally administered drug bypasses hepatic extraction.
- ▶ For high first-pass drugs — **morphine, meperidine, midazolam, nifedipine** — **oral bioavailability is almost doubled** in cirrhosis versus normal liver. Therefore the **oral dose should be reduced**.
- ▶ Reduced albumin synthesis further **lowers protein binding**, raising free drug.

Heart failure and shock (circulatory failure)

- ▶ With **reduced tissue perfusion**, cardiac output is **redistributed** to protect heart and brain at the expense of other tissues.
- ▶ Consequences: drug distributes into a **smaller volume of distribution** → **higher plasma concentrations**, and the well-perfused **brain and heart are exposed to these higher levels** → exaggerated **CNS or cardiac effects** (e.g. lidocaine, digoxin toxicity).
- ▶ **Reduced renal and hepatic perfusion impairs clearance**; **reduced gut perfusion impairs absorption**, so orally administered drugs may have **reduced or absent effect** — favour the IV route in shock.

Altered protein binding and acute-phase states

- ▶ Many drugs circulate **partly bound to plasma proteins**; only free drug acts.
- ▶ In **chronic kidney or liver disease**, binding falls and **drug action increases**; in **MI, infection or surgery**, acute-phase reactants **transiently increase binding** and **decrease efficacy**.

- ▶ The effect is greatest for **highly bound drugs**: a fall in binding from 99% to 98% **doubles the free fraction** (1% → 2%) — a quantitative pearl. Hence for **phenytoin**, monitor **free** rather than total concentration.

Disease-modified pharmacodynamics (same concentration, different effect)

- ▶ A drug may produce **no action or a different spectrum** in disease versus health, and disease can confound interpretation of ADRs (e.g. worsening dyspnoea on **amiodarone** in chronic lung disease may be drug, disease, or intercurrent illness — favour alternative antiarrhythmics).
- ▶ The drug–receptor interaction sits in a **dynamic biologic milieu**: **ion-channel blockade** (anticonvulsant/antiarrhythmic) is modulated by **membrane potential**, itself altered by **extracellular potassium** and **local ischaemia**.
- ▶ Receptors are **up-/down-regulated** by disease or by the drug: chronic β -blockade **up-regulates** β -receptor density, so **abrupt withdrawal** can precipitate **rebound hypertension/tachycardia**.

Extremes of age (physiologically "disease-like")

- ▶ **Elderly**: multiple pathologies, **polypharmacy**, and decline of disposition organs → more interactions and ADRs. **Start below the usual adult dose and titrate slowly**; minimise drug number and doses/day. Long- $t_{1/2}$ **benzodiazepines** are linked to **hip fractures** (falls from sedation plus osteoporosis).
- ▶ **Children**: metabolism and response pathways **mature at different rates**; body-compartment sizes change. With limited evidence, doses are scaled to **weight or body surface area** as a first approximation unless age-specific data exist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Therapeutic-ratio dose–response curves** (Fig. 71-1): two panels, x-axis *Dose or concentration*, y-axis *Probability of drug response (0–100%)*; plot a *Desired effect* curve and an *Adverse effect* curve. Label **Top = wide therapeutic ratio** (well-separated curves) and **Bottom = narrow therapeutic ratio** (overlapping curves); annotate the gap as the **therapeutic window**, and show how disease "shifts the adverse curve left."
- ▶ **Presystemic (first-pass) elimination schematic** (Fig. 71-3): *Orally administered drug* → *Intestinal lumen* → *Enterocyte* (with **P-glycoprotein efflux** back to lumen and **metabolite** formation) → *Portal vein* → *Hepatocyte* (with **biliary canaliculus/bile** excretion and **metabolism**) → *Systemic circulation*. Annotate "**cirrhosis/portacaval shunt** → **first-pass lost** → **↑ oral bioavailability**."

Clinical / Diagnostic significance

- ▶ **Therapeutic drug monitoring (TDM)** is the practical tool when disease distorts PK — useful for **anticonvulsants**, **antiarrhythmics**, **antirejection agents**, **aminoglycosides/vancomycin**, **digoxin**, **lithium**; measure **trough** for efficacy/toxicity (e.g. vancomycin nephrotoxicity) and **peak** (1–2 h) when targeting a peak effect (e.g. QT on sotalol/dofetilide).
- ▶ Prefer **free-drug levels** in hypoalbuminaemia/uraemia (phenytoin).

- ▶ Recognise **reactive-metabolite toxicity** amplified by disease/co-medication: **acetaminophen** hepatotoxicity follows glutathione depletion — risk ↑ with **enzyme inducers** (**phenobarbital**, **phenytoin**) and **ethanol**; treat with **N-acetylcysteine**.
- ▶ **Classify the ADR:** *Type A* (dose-dependent extension of pharmacology — bleeding on anticoagulants) versus *Type B* (dose-independent, often immunologic — SJS/TEN, DRESS, anaphylaxis).
- ▶ In shock/HF, **give drugs IV**, reduce loading where V_d is contracted, and re-check renal/hepatic function as perfusion changes.

High-yield exam pointers

- ▶ Response tracks **free, not total drug**; **99%→98% binding doubles free drug**.
- ▶ **Renal disease:** dose-reduce renally cleared, narrow-window drugs — **digoxin**, **dofetilide**, **sotalol**; beware **normeperidine** seizures.
- ▶ **Liver disease:** LFTs don't guide dosing; **first-pass falls**, so **oral bioavailability of morphine/meperidine/midazolam/nifedipine ~doubles** → cut the oral dose.
- ▶ **Heart failure/shock:** ↓ V_d + ↓ clearance → **higher plasma & CNS/cardiac levels**; gut hypoperfusion blunts oral absorption.
- ▶ **Acute-phase states** (MI, infection, surgery) transiently ↑ **binding** → ↓ **efficacy**.
- ▶ "**High-risk pharmacokinetics**" = single-pathway elimination + narrow window = dramatic disease-related toxicity.
- ▶ **β-blocker withdrawal** rebound reflects disease/drug **receptor up-regulation** (a PD effect).
- ▶ **Elderly:** "**start low, go slow**", minimise polypharmacy; long- $t_{1/2}$ benzodiazepines → hip fractures.
- ▶ Adjust by **creatinine clearance (Cockcroft–Gault)**, then confirm with **TDM** and clinical response.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Principles of Clinical Pharmacology*" (sections: Effects of Disease on Drug Concentration and Response — Renal disease, Liver disease, Heart failure and shock, Drug use in the elderly/children; Principles of Pharmacokinetics — protein binding, clearance, half-life, high-risk pharmacokinetics; Principles of Pharmacodynamics; Adverse Drug Reactions; Tables 71-1 and 71-2) and adjacent "*Pharmacogenomics*" for the gene-function framework.
- ▶ **Coverage note:** This is a single-chapter clinical-pharmacology topic and is covered well by Harrison 22e; the spec lists no dedicated subspecialty text and no CMDT chapter. *Cockcroft–Gault* (for creatinine-clearance estimation) and *Child–Pugh* (as the clinical hepatic-severity tool) are added as universally accepted standard internal medicine — Harrison here specifies "creatinine clearance"-based renal dose adjustment and explicitly states that standard liver-function tests do **not** guide hepatic dose adjustment.



ELISA — principle, methods and applications

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

Definition / Introduction — The **Enzyme-Linked Immunosorbent Assay (ELISA)** is a *solid-phase immunoassay* that detects and quantifies an antigen or antibody by exploiting the highly specific antigen–antibody reaction, using an **enzyme-labelled reagent (conjugate)** that converts a colourless **chromogenic substrate** into a coloured product. The intensity of colour, read as **optical density (OD)** in a spectrophotometer, is proportional to the quantity of analyte. First described by *Engvall and Perlmann* and independently by *Van Weemen and Schuurs* (1971), ELISA replaced radioimmunoassay (RIA) because it gives comparable sensitivity without radioactive hazard. It is the workhorse screening and quantitative assay of clinical immunology, serology and endocrinology.

Immunological basis (the principle)

- ▶ ELISA depends entirely on the **specificity of the antibody–antigen bond**. Each B cell makes a **single antibody specificity**, and the **variable regions (VL and VH) form the antigen-binding (Fab) site**; within these are *hypervariable regions* that constitute the unique antigen-combining site (the *idiotype*) — this is what confers assay specificity.
- ▶ An antigen presents distinct **antigenic determinants (epitopes)**; an antibody is directed against one such epitope. *Sandwich* assays require an antigen large enough to carry **≥2 epitopes** so that capture and detector antibodies bind simultaneously.
- ▶ High assay sensitivity reflects **high-affinity antibodies** generated in vivo by *somatic hypermutation and affinity maturation*; reagent antibodies are often **monoclonal antibodies** (hybridoma technology), which provide a single, reproducible, well-defined specificity.
- ▶ The **enzyme label amplifies the signal**: one bound enzyme molecule turns over many substrate molecules, magnifying a small number of antigen–antibody complexes into a visible/measurable colour.

Components / reagents

- ▶ **Solid phase** — 96-well polystyrene microtitre plate (also beads, membranes) that adsorbs protein.
- ▶ **Capture reagent** — antigen (to detect antibody) or antibody (to detect antigen) coated on the well.
- ▶ **Enzyme conjugate** — antibody covalently linked to an enzyme.
- ▶ **Substrate / chromogen** — converted by the enzyme into a coloured product.
- ▶ **Blocking agent** — bovine serum albumin (BSA), casein or non-fat milk to saturate free sites and prevent non-specific binding.
- ▶ **Wash buffer** — phosphate-buffered saline with Tween-20 (PBS-T) to remove unbound reagents between steps.
- ▶ **Stop solution** — e.g., dilute sulphuric acid to halt the colour reaction.
- ▶ **Read-out** — ELISA plate reader (spectrophotometer) measuring OD at a defined wavelength.

Enzyme label	Common substrate / chromogen	Colour & read wavelength
Horseradish peroxidase (HRP)	TMB (tetramethylbenzidine); OPD; ABTS	blue → yellow on acid stop, read ~450 nm
Alkaline phosphatase (ALP)	p-nitrophenyl phosphate (pNPP)	yellow, read ~405 nm
β-galactosidase	ONPG / fluorogenic substrates	yellow / fluorescent

Types of ELISA

Type	What is coated	Detection step	Main use / notes
Direct	Antigen	Enzyme-labelled <i>primary</i> antibody binds antigen directly	Fewest steps, low cross-reactivity; less sensitive, each antibody must be labelled
Indirect	Antigen	Unlabelled primary (test) antibody, then enzyme-labelled anti-Ig secondary	Detects/quantifies antibody in serum (e.g., HIV, viral serology); signal amplified, one conjugate serves many tests
Sandwich (capture)	Capture antibody	Antigen bound, then enzyme-labelled detector antibody to a second epitope	Quantifies antigen ; needs multivalent antigen (≥2 epitopes); high sensitivity & specificity
Competitive / inhibition	Antibody (or antigen)	Sample analyte competes with labelled analyte for limited binding sites	For small antigens/haptens (single epitope: drugs, steroid hormones); signal is inversely proportional to analyte

- ▶ **Related variant — ELISPOT:** detects individual cytokine-secreting cells (e.g., IFN-γ-releasing T cells); the basis of some interferon-gamma release assays for tuberculosis.

Methodology (sandwich ELISA, stepwise)

- ▶ **1. Coating** — adsorb capture antibody onto wells; incubate.
- ▶ **2. Wash** — remove unbound antibody.
- ▶ **3. Block** — add BSA to saturate remaining binding sites.
- ▶ **4. Add sample** — patient serum/plasma; target antigen is captured; incubate, then wash off unbound material.
- ▶ **5. Add conjugate** — enzyme-labelled detector antibody binds a second epitope of the captured antigen; incubate, wash.
- ▶ **6. Add substrate/chromogen** — enzyme generates a coloured product over a timed interval.
- ▶ **7. Stop** — add acid stop solution.
- ▶ **8. Read & interpret** — measure OD in a plate reader; **quantitative** assays read against a *standard curve*; **qualitative** assays compare OD against a pre-set *cut-off* (positive vs negative). Each run includes positive, negative and blank controls.

Applications

- ▶ **Infectious-disease serology / screening:** HIV (modern *4th-generation combo* assays detect **p24 antigen + anti-HIV antibody**), hepatitis B (HBsAg, anti-HBc, anti-HBs), hepatitis C antibody, dengue (NS1 antigen, IgM/IgG), leptospirosis, syphilis, *H. pylori*, SARS-CoV-2 antibody.
- ▶ **Acute vs past infection:** IgM-capture (MAC-) ELISA detects recent infection because **IgM is the first antibody of the primary response**; IgG reflects past infection or immunity (*secondary antibody response*).
- ▶ **Endocrine / hormone assays:** hCG (pregnancy test), TSH, insulin, cortisol, thyroid hormones.
- ▶ **Tumour markers:** PSA, CEA, AFP, CA-125.
- ▶ **Autoantibodies:** ANA, anti-dsDNA, anti-CCP, ANCA, anti-TPO.
- ▶ **Allergy:** allergen-specific IgE.
- ▶ **Others:** cytokines, cardiac troponin, D-dimer, therapeutic-drug and toxicology monitoring, food/veterinary testing.

Advantages and limitations

- ▶ **Advantages:** high sensitivity and specificity; **safe** (no radioisotopes, unlike RIA); inexpensive and rapid; **high-throughput and automatable** (96-well plates, plate readers); both **qualitative and quantitative**; stable reagents and long enzyme-conjugate shelf life.
- ▶ **Limitations:** **false positives** from cross-reactivity/non-specific binding (mandating confirmatory testing); **false negatives** in the pre-seroconversion *window period*; the **hook/prozone effect** in sandwich assays; sensitive to technical error (inadequate washing, pipetting, incubation timing); a positive antibody result indicates exposure but **does not by itself distinguish active from past infection** (resolved by IgM-capture format or antigen/NAT testing).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Sandwich ELISA schematic** — labels: *microtitre well (solid phase), capture antibody, antigen (analyte), enzyme-labelled detector antibody, enzyme, chromogenic substrate, coloured product, read OD in plate reader.*
- ▶ **Indirect ELISA schematic** — labels: *well coated with antigen, patient serum antibody (primary), enzyme-conjugated anti-human Ig (secondary), substrate → colour;* alongside a small bar of the **4 ELISA types** (direct, indirect, sandwich, competitive).

Clinical / Diagnostic significance

- ▶ **Screening tool:** because of its **high sensitivity**, ELISA is the first-line *screening* test (e.g., HIV); reactive results are confirmed by a more specific assay (Western blot / line immunoassay / NAT) to exclude false positives.
- ▶ **Window period:** antibody-based ELISA can be falsely negative early in infection before seroconversion; **antigen detection** (HIV p24, dengue NS1) or nucleic-acid testing covers this gap — the rationale for combined Ag/Ab assays.
- ▶ **Quantitation & monitoring:** quantitative ELISA against a standard curve allows titres/levels to be followed (hormones, tumour markers, antibody titres).

- ▶ **Hook (prozone) effect:** in sandwich assays a *very high* antigen concentration can paradoxically lower the signal and give a falsely low/negative result — suspect when the clinical picture mismatches the result; re-test with dilution.
- ▶ **Confirmation principle:** a sensitive screen (ELISA) followed by a specific confirmatory test minimises both false negatives (missed disease) and false positives (mislabelling).

High-yield exam pointers

- ▶ **ELISA = Enzyme-Linked Immunosorbent Assay**, a *solid-phase immunoassay*; Engvall & Perlmann, 1971; replaced RIA (no radioactivity).
- ▶ Principle: **antigen–antibody specificity + enzyme-amplified colorimetric read-out** ($OD \propto$ analyte).
- ▶ Four types: **direct, indirect, sandwich, competitive** — *indirect = detect antibody, sandwich = detect/quantify antigen, competitive = small haptens (signal inversely proportional)*.
- ▶ Common enzymes: **HRP** (substrate **TMB**, read 450 nm) and **ALP** (substrate **pNPP**, read 405 nm).
- ▶ Sandwich ELISA needs an antigen with ≥ 2 **epitopes**; reagent antibodies are often **monoclonal**.
- ▶ Classic use: **HIV screening** (4th-gen combo = p24 Ag + Ab), confirmed by Western blot.
- ▶ **IgM-capture ELISA = acute/recent infection** (IgM is the first antibody); **IgG = past/immune**.
- ▶ Pitfalls: false negative in **window period**; **hook/prozone effect** at very high antigen.
- ▶ Advantages: sensitive, specific, safe, cheap, rapid, **high-throughput/automatable**; ELISPOT detects single cytokine-secreting cells.

SOURCE & COVERAGE

Harrison 22e — Ch 360 "Introduction to the Immune System" (immunological basis: antibody–antigen specificity, Fab/variable-region antigen binding, idiotype, affinity maturation, monoclonal antibody technology, Ig structure, IgM primary vs IgG secondary antibody response). **Coverage note (gap):** Harrison Ch 360 does **not** describe the ELISA technique itself — assay formats (direct/indirect/sandwich/competitive), enzyme–substrate systems (HRP/TMB, ALP/pNPP), the stepwise methodology, the hook effect, and named clinical applications (HIV/HBV/HCV/dengue serology, hormone and tumour-marker assays) are drawn from standard, universally accepted laboratory/clinical-immunology knowledge and are not citable to the provided chapter. Only the underlying immunology is source-grounded.



Epigenetics

Asked in: Paper I Nov 2021 · Paper I May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — The term *epigenetics* (Greek *epi-* = "over, around"), coined by *Conrad Waddington* in 1942, denotes the heritable and reversible mechanisms by which **gene expression and phenotype are altered without any change in the underlying DNA nucleotide sequence**. The *epigenome* is the constellation of covalent modifications of DNA and histones — plus non-coding RNAs — that determine chromatin structure and hence the cell's transcriptome and proteome. Although all somatic cells carry an essentially identical genome, sex-, tissue- and environment-dependent epigenetic marks generate cell-type specificity, and their dysregulation underlies imprinting disorders, cancer, ageing and neuropsychiatric disease.

Biochemical basis — the three core mechanisms

Fundamental to epigenetic regulation is packaging of the genome into **chromatin**. The basic unit is the **nucleosome** — 147 base pairs of DNA wrapped around an octamer of 8 histones (two copies each of the core histones **H2A, H2B, H3, H4**). Compaction governs accessibility to transcription factors and repair machinery: *euchromatin* (open) is transcriptionally active, *heterochromatin* (compacted) is repressed. Three processes regulate compaction:

Mechanism	Key players	Functional output
DNA methylation	Cytosine methylation of CpG dinucleotides (5-mC); written de novo by DNMT3A/3B, maintained after replication by DNMT1; reversed via TET1–3 oxidation (5-mC→5-hmC→5-fC→5-caC)	Promoter CpG-island methylation → gene silencing ; CpG islands normally unmethylated to permit transcription
Histone post-translational modifications (hPTMs)	≥60 covalent marks added by writers , removed by erasers , recognised by readers	Acetylation (KATs/HATs add; HDACs + NAD ⁺ -dependent sirtuins remove) loosens chromatin → activation; lysine methylation (KMTs) gives context-specific output
Nucleosome remodelling	ATP-dependent SWI/SNF, ISWI, INO80 families; histone variants H2AZ (start sites), H3.3 (gene bodies)	Reposition/evict nucleosomes; activate or repress transcription

- ▶ **Acetylation** of H3K9ac and H3K27ac → transcriptional activation (neutralises lysine positive charge, creating a reader-binding surface); dynamic and rapidly reversed by HDACs.
- ▶ **Lysine methylation** gives a "histone code": *activating* marks = H3K4me3, H3K36me3, H3K79me3; *repressive* = H3K27me3; *repeat/centromeric silencing* = H3K9me3. Methylation is more stable than acetylation and its output depends purely on effector (reader) binding.
- ▶ Other marks: phosphorylation of H2A at Ser139 (γH2A.X) flags DNA double-strand breaks; ubiquitination, SUMOylation (repression) and PARP-mediated ADP-ribosylation also signal on chromatin.
- ▶ **RNA epigenetics (epitranscriptomics)**: reversible m6A methylation of mRNA by writers METTL3/METTL14 and demethylases ALKBH5/FTO controls mRNA fate (degradation vs translation).

Physiological epigenetic phenomena

- ▶ **X-chromosome inactivation (Lyonisation):** dosage compensation silencing one of the two X chromosomes in females, mediated by the **Xist** long non-coding RNA; the inactive X is highly methylated with low histone acetylation. Choice of X is random but then stably transmitted through cell division; ~15% of X genes escape inactivation.
- ▶ **Genomic imprinting:** monoallelic, parent-of-origin-specific expression of a small subset of autosomal genes, mediated by allele-specific DNA methylation. The imprint is **reset in the germline** in a sex-specific manner and maintained lifelong.
- ▶ **Bivalent chromatin** in embryonic stem cells: developmental genes carry both activating **H3K4me3** and repressive **H3K27me3** ("poised"), resolving to one mark on differentiation. **H3K9me3** heterochromatin (via SUV39H1) is an epigenetic barrier to reprogramming into iPSCs.
- ▶ **Environmental integration:** diet alters chromatin — acetyl-CoA (from ACLY/ACSS2/PDH) is the best predictor of histone acetylation; **S-adenosylmethionine (SAM)** is the universal methyl donor for DNA/histone methylation, linking folate/methionine status to the epigenome.

Epigenetics in disease

- ▶ **Cancer — a combined genetic + epigenetic disease.** The first epigenetic driver, the remodeller **SMARCB1**, was identified in malignant rhabdoid tumours (1998); TCGA shows **25–30% of cancer driver mutations occur in chromatin-regulatory proteins** (e.g. **MLL3/MLL4**, **EP300/CBP**, **SMARCA4**, **ARID1A** — mostly loss-of-function). **EZH2** (H3K27me3 writer) is an oncogene over-expressed in breast/prostate/melanoma. "**Oncohistones**" — **H3.3 K27M** in paediatric high-grade glioma and **K36M** in chondroblastoma. **MLL1 (KMT2A)** translocations drive AML and ~80% of infant ALL. Metabolic mutations in **IDH1/2**, **FH**, **SDH** generate 2-hydroxyglutarate/fumarate/succinate that inhibit α -KG-dependent demethylases → hypermethylation. Cancer epigenomes show global hypomethylation (genomic instability) with focal CpG-island hypermethylation silencing tumour-suppressors.
- ▶ **Imprinting / uniparental-disomy (UPD) disorders:** **Prader-Willi** (loss of paternal 15q11-13 — deletion, maternal UPD, or imprinting defect) vs **Angelman** (loss of maternal 15q11-13); **Beckwith-Wiedemann syndrome** (overactive **IGF2** / loss of **CDKN1C**; paternal UPD chr 11; overgrowth + Wilms' tumour risk); **GNAS1** imprinting → pseudohypoparathyroidism Ia (maternal) vs pseudopseudohypoparathyroidism (paternal, *Albright hereditary osteodystrophy*). Hydatidiform mole = exclusively paternal genome; ovarian teratoma = maternal.
- ▶ **Neurodevelopmental / neuropsychiatric:** **Rett syndrome** (X-linked, **MECP2** methyl-CpG-binding protein); **Kabuki syndrome** (**MLL4/KMT2D** or **UTX/KDM6A**); **Rubinstein-Taybi syndrome** (**CBP/CREBBP** acetyltransferase); **Fragile-X** (**FMR1/FMR2** promoter hypermethylation). Hypomethylation of **SNCA** (Parkinson's) and **APP** (Alzheimer's), and altered histone acetylation, feature in neurodegeneration; **BDNF** and **REST** are epigenetically regulated in depression/schizophrenia.
- ▶ **Ageing:** progressive heterochromatin loss (reduced **H3K9me3/H3K27me3**), seen severely in **Hutchinson-Gilford progeria** and **Werner syndrome**; the DNA-methylation "**clock**" predicts

chronological age better than telomere length. NAD⁺-dependent **sirtuins** (class III HDACs, e.g. SIRT1/SIRT6) mediate caloric-restriction longevity.

- ▶ **Immunity/inflammation:** corticosteroids recruit **HDAC2** to NF-κB-driven inflammatory promoters in asthma; **FOXP3** and **CTLA4** hypermethylation impairs regulatory T cells in rheumatoid arthritis; "trained immunity" / inflammatory memory is epigenetically encoded.

Tools for studying the epigenome

- ▶ **ChIP-seq** — chromatin immunoprecipitation + sequencing maps genome-wide histone marks and protein-DNA binding.
- ▶ **ATAC-seq** — Tn5 transposase inserts adapters into open chromatin to map accessibility, even single-cell.
- ▶ **CUT&RUN / CUT&Tag** — antibody-tethered MNase or Tn5; fewer cells, lower background, single-cell capable.
- ▶ **Hi-C / 3C and Hi-ChIP** — 3-D genome architecture, enhancer-promoter loops and topologically associated domains (TADs).
- ▶ **CRISPR epigenome editing** — catalytically dead **dCas9** fused to a writer/eraser to activate or repress a target gene without cutting DNA.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Nucleosome & chromatin modifications:** DNA double helix wound around the histone octamer (label H2A, H2B, H3, H4, "147 bp"), with N-terminal **histone tails** carrying **acetylation** (Ac, H3K27ac → active) and **methylation** (Me, H3K27me3 → repressed); mark CpG DNA methylation (5-mC); show transition **euchromatin** (open, active) ↔ **heterochromatin** (compact, silent); annotate **Writers / Erasers / Readers** and DNMT1/3A/3B, TET, HATs/HDACs, KMTs/KDMs.
- ▶ **Imprint-reset schematic** (Fig 479-8 style): maternal germline X both alleles unmethylated, paternal germline methylated → reset each generation; label **Prader-Willi** (paternal loss) vs **Angelman** (maternal loss) at 15q11-13.

Clinical / Diagnostic significance

- ▶ **Diagnosis:** methylation-specific PCR / MS-MLPA for Prader-Willi, Angelman, Beckwith-Wiedemann and Fragile-X; epigenomic "cell-of-origin" profiling identifies cancers of unknown primary better than mutation sequencing; DNA-methylation age as a biomarker of biological ageing.
- ▶ **Therapeutics (epigenetic drugs):** DNMT inhibitors *azacitidine* and *decitabine* (global hypomethylation reactivating tumour-suppressors) for **MDS and AML**; HDAC inhibitors (vorinostat, romidepsin, panobinostat) for **cutaneous T-cell lymphoma and multiple myeloma**; **EZH2 inhibitors** (B-cell lymphoma, sarcoma); **IDH inhibitors** (IDH-mutant AML/glioma); **LSD1, DOT1L and MLL1 inhibitors** in leukaemias; **BET (bromodomain) inhibitors** suppress MYC. Reversibility of epigenetic marks is the key therapeutic rationale.
- ▶ **Pearl:** epigenetic therapy is increasingly combinatorial — re-expressing tumour antigens and IFN responses to potentiate chemotherapy and immunotherapy.

High-yield exam pointers

- ▶ Epigenetics = heritable change in gene expression **without** DNA-sequence change; coined by Waddington (1942).
- ▶ Three mechanisms: DNA methylation (CpG/5-mC), histone PTMs (acetylation/methylation), nucleosome remodelling; plus RNA m6A.
- ▶ DNMT1 = maintenance; DNMT3A/3B = de novo; TET enzymes erase methylation.
- ▶ Active marks: H3K4me3, H3K36me3, acetylation; repressive: H3K27me3, H3K9me3, DNA-CpG methylation.
- ▶ X-inactivation via Xist lncRNA; imprinting reset in germline — Prader-Willi (paternal), Angelman (maternal), Beckwith-Wiedemann (IGF2).
- ▶ Cancer: 25–30% of driver mutations in chromatin regulators; EZH2 oncogene; oncohistones H3K27M/H3K36M; IDH/FH/SDH → hypermethylation.
- ▶ Epigenetic drugs: azacitidine/decitabine (DNMTi), vorinostat/romidepsin (HDACi), EZH2/IDH/BET inhibitors — exploit reversibility.
- ▶ Disease links: Rett (MECP2), Fragile-X (FMR1), Rubinstein-Taybi (CREBBP), Kabuki (KMT2D/KDM6A), ageing methylation clock, progeria H3K9me3 loss.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "The Role of Epigenetics in Disease and Treatment" (biochemical bases, writers/erasers/readers, tools, cancer/ageing/brain/immunity epigenetics, epigenetic drugs).
- ▶ Harrison's Principles of Internal Medicine, 22e — "Principles of Human Genetics" (X-inactivation/Xist, genomic imprinting, imprint reset, uniparental disomy, Prader-Willi/Angelman/Beckwith-Wiedemann, GNAS1, Rett, cancer methylation).

Coverage note: This topic has no dedicated subspecialty textbook in the corpus and is not a CMDT topic; grounding is the two Harrison chapters above, which cover the ask comprehensively. Specific drug indications and disease-gene associations are taken verbatim from those chapters.



Extraocular muscles and superior orbital fissure syndrome

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

Definition / Introduction — Each eye is moved by **six extraocular muscles (EOMs)** — four recti (superior, inferior, medial, lateral) and two obliques (superior, inferior) — supplied by the **oculomotor (III), trochlear (IV) and abducens (VI)** cranial nerves arising from their brainstem nuclei. Their coordinated action keeps the image of a target on the fovea (*foveation*) and maintains binocular single vision. The **superior orbital fissure (SOF)** is the cleft between the greater and lesser wings of the sphenoid through which III, IV, VI and the ophthalmic division (V1) of the trigeminal nerve enter the orbit; its compromise produces a characteristic **painful ophthalmoplegia with V1 sensory loss but preserved vision** — the *superior orbital fissure syndrome*.

Extraocular muscles — innervation and actions

Muscle	Cranial nerve	Primary action	Secondary actions
Medial rectus	III (inferior division)	Adduction	—
Lateral rectus	VI	Abduction	—
Superior rectus	III (superior division)	Elevation (in abduction)	Adduction, intorsion
Inferior rectus	III (inferior division)	Depression (in abduction)	Adduction, extorsion
Superior oblique	IV	Intorsion; depression (in adduction)	Abduction
Inferior oblique	III (inferior division)	Extorsion; elevation (in adduction)	Abduction

- Mnemonic for innervation: **LR6 SO4, rest 3** — Lateral Rectus by VI, Superior Oblique by IV, the remaining four EOMs (plus levator palpebrae superioris and the pupillary sphincter/ciliary muscle) by III.
- The **oculomotor nerve** also supplies the **levator palpebrae superioris** (lid elevation) and, via its parasympathetic component, the **iris sphincter and ciliary muscle** (pupil constriction, accommodation).
- The **vertical recti** act best as pure elevators/depressors when the eye is **abducted**; the **obliques** act best when the eye is **adducted** (superior oblique = main depressor in adduction; inferior oblique = main elevator in adduction). This underlies the *cardinal positions* used to isolate weak muscles.

Movements of the eye and their neural control

- **Terminology:** *ductions* are monocular movements; *versions* are conjugate (both eyes same direction); *vergences* are disjunctive (convergence/divergence). The clinician tests the six **cardinal positions of gaze** to identify a paretic muscle, aided by yoke-muscle pairing (e.g., right lateral rectus pairs with left medial rectus on right gaze).
- **Classes of movement** (Harrison): **saccades** (rapid refixation), **smooth pursuit** (tracking a moving target), and **gaze stabilization / optokinetic reflexes** during head and body movement. These are coordinated by pontine–midbrain centres under descending **supranuclear** input from frontal and parieto-occipital cortex.

- ▶ **Horizontal gaze:** the **paramedian pontine reticular formation (PPRF)** drives the ipsilateral abducens nucleus; abducens interneurons cross via the **medial longitudinal fasciculus (MLF)** to the contralateral medial rectus subnucleus, yoking abduction of one eye with adduction of the other.
- ▶ **Internuclear ophthalmoplegia (INO):** an MLF lesion causes **failure of adduction** of the ipsilateral eye on lateral gaze with nystagmus of the abducting eye; **multiple sclerosis** is the commonest cause. The **frontal eye field** generates contralateral saccades.

Ocular motor nerve palsies — clinical correlation

- ▶ **Oculomotor (III) palsy:** ptosis, a **dilated pupil**, and the eye resting "**down and out**" (unopposed lateral rectus + superior oblique). A **pupil-involving, painful III palsy** suggests a **compressive lesion (posterior communicating artery aneurysm/tumour)** — demands urgent CT/MR angiography. A **pupil-sparing III palsy** is usually **microvascular** (diabetes, hypertension) and recovers spontaneously. *Aberrant regeneration* (lid elevation/pupil constriction on adduction or downgaze) follows trauma/compression, never microvascular infarct.
- ▶ **Trochlear (IV) palsy:** **vertical diplopia** worse on reading/downgaze, with **hypertropia and excyclotorsion**; the **Bielschowsky head-tilt test** (diplopia worse on tilting toward the affected side) is the cardinal sign. The IV nerve is uniquely vulnerable to **closed head trauma**.
- ▶ **Abducens (VI) palsy:** **horizontal diplopia** worse on gaze toward the lesion (failure of abduction). A **classic false-localising sign of raised intracranial pressure**; at the petrous apex, mastoiditis causes deafness, pain and VI palsy (**Gradenigo's syndrome**).
- ▶ **Localising clue:** multiple ocular-motor palsies should never be ascribed to chance microvascular events — neuroimaging must target the **cavernous sinus, superior orbital fissure and orbital apex**, where III, IV, V1 and VI lie in close proximity.

Superior orbital fissure syndrome — anatomy, features and causes

- ▶ **Structures traversing the SOF:** oculomotor nerve (superior and inferior divisions), trochlear (IV), abducens (VI), the three branches of the **ophthalmic division (V1)** — lacrimal, frontal and nasociliary — the **superior ophthalmic vein**, and **sympathetic fibres**. *Crucially, the optic nerve (II) and ophthalmic artery pass through the separate optic canal, not the SOF**.*
- ▶ **Clinical features (Harrison Table 452-2 — "Sphenoid fissure / superior orbital"):** involvement of III, IV, VI and first division of V (V1) producing:
 - **Total external ophthalmoplegia** — globe fixed in central position with diplopia.
 - **Ptosis** (III → levator palpebrae) and a **fixed, dilated, unreactive pupil** (parasympathetic III involvement = internal ophthalmoplegia).
 - **Proptosis** (orbital congestion / superior ophthalmic vein obstruction).
 - **V1 sensory loss** over forehead, upper eyelid and cornea with an **absent corneal reflex**; periorbital pain is common.
 - **Vision is preserved** because the optic nerve is spared — the key sign distinguishing SOF syndrome from **orbital apex syndrome**.
- ▶ **Causes (Harrison):** **invasive tumours of the sphenoid bone and aneurysms**. Other standard causes: **trauma (sphenoid/orbital fractures), neoplasms (meningioma, nasopharyngeal**

carcinoma, metastases), infections (including mucormycosis in diabetics), and idiopathic granulomatous inflammation (Tolosa-Hunt syndrome) — the latter is a painful ophthalmoplegia that is dramatically responsive to glucocorticoids.

Superior orbital fissure vs orbital apex vs cavernous sinus syndromes

Feature	SOF syndrome	Orbital apex syndrome	Cavernous sinus syndrome
Nerves involved	III, IV, V1, VI	III, IV, V1, VI + II	III, IV, VI, V1 (± V2)
Optic nerve / vision	Spared (vision intact)	Involved → visual loss	Usually spared
Pupil / sympathetics	Fixed dilated (III)	Fixed dilated (III)	III palsy ± Horner's (oculosympathetic)
Proptosis / chemosis	Proptosis ±	Proptosis ±	Prominent (venous occlusion), may be bilateral
Typical causes (Harrison)	Sphenoid tumours; aneurysms	Invasive fungal infection, amyloidosis, granuloma	Thrombosis (orbital cellulitis/ <i>S. aureus</i> , sinusitis, mucormycosis), aneurysm, carotid-cavernous fistula, tumour, Tolosa-Hunt

- ▶ The **orbital apex syndrome** is essentially "SOF syndrome plus optic neuropathy" — vision loss is the discriminator.
- ▶ **Cavernous sinus syndrome** adds V2 involvement, possible **postganglionic Horner's** (sympathetic plexus on the carotid), prominent **chemosis/orbital swelling**, and may become **bilateral** via intercavernous channels; a **carotid-cavernous fistula** produces a pulsatile, bruit-positive proptosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1** — Actions of the six EOMs (right eye, "flower" diagram): central circle for the eye with eight radiating arrows labelled **Superior rectus (up & out)**, **Inferior rectus (down & out)**, **Medial rectus (in/adduction)**, **Lateral rectus (out/abduction)**, **Superior oblique (down in adduction)**, **Inferior oblique (up in adduction)**; annotate innervation **III / IV / VI** beside each.
- ▶ **Diagram 2** — Coronal section through the superior orbital fissure / cavernous sinus: label **Oculomotor (III)**, **Trochlear (IV)**, **Ophthalmic (V1)**, **Maxillary (V2)**, **Abducens (VI)**, **Internal carotid artery**, **Superior ophthalmic vein**, **Optic nerve (II) in optic canal (separate)**, **Annulus of Zinn**. Mark that **VI and ICA lie within the sinus** while **III, IV, V1, V2 lie in the lateral wall**.

Clinical / Diagnostic significance

- ▶ **Examination:** test the six cardinal positions, **corneal light reflex (Hirschberg)** and the **cover test** (detects deviations as small as 1°); the **red-glass / diplopia chart** localises the paretic muscle. Always check the **pupil, lid and corneal sensation** in any ophthalmoplegia.

- ▶ A painful ophthalmoplegia with V1 numbness and intact vision = SOF syndrome until proven otherwise — obtain contrast MRI/MRA of the orbital apex, SOF and cavernous sinus; add CT for bony sphenoid lesions/fractures and angiography if aneurysm/fistula suspected.
- ▶ Emergencies to exclude: posterior communicating artery aneurysm (pupil-involving III palsy), cavernous sinus thrombosis (fever, bilateral signs, sepsis source) and rhino-orbital mucormycosis in a diabetic/immunocompromised host (urgent biopsy, antifungals, surgical debridement).
- ▶ Management is cause-directed: glucocorticoids for Tolosa-Hunt, antibiotics/anticoagulation for septic cavernous sinus thrombosis, surgery/embolisation for tumour or fistula. Symptomatic diplopia relief uses occlusion, prisms (Fresnel), or eye-muscle surgery once the deficit stabilises.

High-yield exam pointers

- ▶ 6 EOMs; innervation = LR6 SO4, rest III. III also supplies levator, iris sphincter and ciliary muscle.
- ▶ III palsy = "down and out" + ptosis + dilated pupil; pupil-involving + pain → aneurysm (emergency); pupil-sparing → microvascular.
- ▶ IV palsy = vertical diplopia, head-tilt test positive; commonest nerve injured in head trauma.
- ▶ VI palsy = horizontal diplopia; false-localising sign of raised ICP; Gradenigo's at petrous apex.
- ▶ SOF contents = III, IV, VI, V1, superior ophthalmic vein, sympathetics — NOT the optic nerve (optic canal).
- ▶ SOF syndrome: ophthalmoplegia + ptosis + dilated pupil + V1 loss + vision preserved; orbital apex = SOF + optic neuropathy; cavernous sinus = adds V2 ± Horner's + chemosis, may be bilateral.
- ▶ Tolosa-Hunt = idiopathic granulomatous painful ophthalmoplegia, steroid-responsive (diagnosis of exclusion).
- ▶ Multiple ocular-motor palsies together → image the cavernous sinus / SOF / orbital apex, not "diabetic coincidence."

SOURCE & COVERAGE

Harrison 22e — Ch 34 "Disorders of the Eye" (EOM innervation, eye-movement classes/control, III/IV/VI palsies, INO; Horton) and Ch 452 "Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders" (Table 452-2 cranial-nerve syndromes — superior orbital fissure, orbital apex, cavernous sinus; cavernous sinus syndrome text). **Coverage note:** Harrison covers SOF/orbital-apex/cavernous-sinus syndromes only briefly (Table 452-2) and does not tabulate the detailed primary/secondary actions of individual EOMs or the cardinal-position testing scheme; these, the muscle-action table, the LR6SO4 mnemonic, the precise SOF contents (superior ophthalmic vein, sympathetics) and the optic-canal-vs-SOF distinction are supplied from universally accepted standard anatomy/neuro-ophthalmology (consistent with Brazis, *Localization in Clinical Neurology*, cited in the spec but not provided as text here). The Rochon-Duvigneaud eponym for SOF syndrome is standard but not in the provided Harrison text.



Fabry's disease

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

Definition / Introduction — Fabry disease (*angiokeratoma corporis diffusum universale*) is an **X-linked lysosomal storage disease** caused by deficient activity of the lysosomal hydrolase **α -galactosidase A**, encoded by the **GLA** gene. The enzyme defect leads to progressive intralysosomal accumulation of the neutral glycosphingolipid **globotriaosylceramide (Gb3, also called ceramide trihexoside)**, predominantly within **vascular endothelium**, and in renal, cardiac, neural, corneal and cutaneous cells. It is a multisystem vasculopathy and is regarded as **likely the most prevalent lysosomal storage disease (LSD)**, with manifestations spanning a spectrum from classic early-onset disease in hemizygous males to attenuated, organ-limited late-onset variants.

Etiology, genetics and pathogenesis

- ▶ **Enzyme/substrate:** deficiency of **α -galactosidase A** (a neutral glycosphingolipidosis) → failure to cleave the terminal galactose from **globotriaosylceramide (Gb3)**, causing its lysosomal accumulation. Substrate is in part delivered to lysosomes by **LDL-receptor-mediated uptake**.
- ▶ **Gene/inheritance:** mutations in the **GLA** gene on the X chromosome (Xq22). Inheritance is **X-linked**; Harrison's neuropathy chapter terms it *X-linked dominant* because **heterozygous females can be clinically affected** owing to **Lyonzation** (random X-inactivation).
- ▶ **Epidemiology:** estimated prevalence of **hemizygous males 1 in 40,000 to 1 in 3,500** in selected populations. **Females have a higher prevalence of mutations but far more variable expression**; up to **70% of heterozygous females** show clinical manifestations.
- ▶ **Threshold concept:** disease appears when residual enzyme activity falls below a tissue-specific threshold; small differences in residual activity (and substrate flux) explain the broad phenotypic spectrum, including organ-restricted variants.
- ▶ **Pathology:** progressive Gb3 deposition in **endothelial and smooth-muscle cells of small vessels** produces a generalised vasculopathy with ischaemia/infarction in kidney, heart and brain; deposition in **dorsal-root ganglia/small nerve fibres** produces a painful small-fibre neuropathy.

Clinical features (multisystem)

The **classic triad/quartet** of early disease comprises **acroparesthesias, angiokeratomas, hypohidrosis and corneal opacity**, with later renal, cardiac and cerebrovascular failure.

System	Key manifestations (faithful to source)
Skin	Angiokeratomas — punctate, dark red to blue-black, flat or slightly raised, telangiectatic lesions that do not blanch with pressure ; densest between the umbilicus and knees ("bathing-suit area") , also umbilicus, scrotum, inguinal region, perineum. Easily overlooked.
Sweat glands	Hypohidrosis (heat/exercise intolerance).
Peripheral nerve	Acroparesthesia — debilitating episodic burning/lancinating pain of the hands and feet , lasting minutes to days, precipitated by temperature change, exercise, fatigue or fever ; begins in childhood/early adult life (small-fibre neuropathy).

System	Key manifestations (faithful to source)
Eye	Corneal and lenticular opacities on slit-lamp (classic whorl-like <i>cornea verticillata</i> ; Fabry cataract) — useful diagnostic clue; usually asymptomatic.
GI	Abdominal pain (may mimic appendicitis or renal colic) and recurrent diarrhoea, often from childhood.
Kidney	Proteinuria, isosthenuria and progressive renal dysfunction in the 2nd–4th decades → end-stage renal disease. ~5% of males with "idiopathic renal failure" carry GLA mutations.
Heart	Hypertension, left ventricular hypertrophy, anginal chest pain and congestive heart failure in the 3rd–4th decades; a restrictive / hypertrophic cardiomyopathy picture. ~1–3% of "idiopathic hypertrophic cardiomyopathy" is Fabry.
CNS / vasculature	Premature cerebrovascular disease / stroke and TIA (a noninflammatory vasculopathy); ~2–5% of "idiopathic stroke" at 35–50 years carry GLA mutations.
Other	Leg lymphedema without hypoproteinemia.

Phenotypic variants and sex differences

- ▶ **Classic male (hemizygous) phenotype:** earliest and most severe — childhood acroparesthesias, angiokeratomas, hypohidrosis, GI pain → renal, cardiac and cerebrovascular disease; untreated, death often by the fifth decade from cardiovascular, renal or cerebrovascular disease.
- ▶ **Later-onset / residual-activity variants:** patients with some residual α -galactosidase A activity develop late, often organ-restricted disease — predominantly cardiac (mimicking hypertrophic cardiomyopathy / "cardiac variant"), or predominantly renal or CNS; some present primarily with a dilated cardiomyopathy.
- ▶ **Heterozygous females:** highly variable, from asymptomatic carrier to full classic disease; here heart disease is the most common life-threatening manifestation.
- ▶ **Cause of death / organ hierarchy:** in males, renal disease followed by cardiovascular disease; in females, cardiac disease predominates.

Investigations / Diagnosis

- ▶ **Enzyme assay (males):** markedly reduced or absent α -galactosidase A activity in plasma/leukocytes (dried blood spot) is diagnostic in hemizygous males.
- ▶ **GLA gene sequencing:** required in females, in whom enzyme activity may be normal (Lyonization), and to confirm amenable mutations for chaperone therapy.
- ▶ **Biomarkers:** elevated Gb3 (plasma/urine) and its deacylated form lyso-Gb3 (globotriaosylsphingosine) support diagnosis and monitor treatment (standard practice).
- ▶ **Slit-lamp examination:** corneal/lenticular opacities aid diagnosis.
- ▶ **Tissue biopsy:** renal/cardiac/skin biopsy shows lipid-laden cells; electron microscopy reveals characteristic lamellar ("zebra-body"/myelin-figure) lysosomal inclusions (standard).
- ▶ **Organ surveillance:** urinalysis/proteinuria and eGFR; ECG/echocardiography/cardiac MRI (LVH, late gadolinium enhancement); MRI brain for white-matter/vascular lesions.

Management / Treatment

- ▶ **Disease-specific:**
 - Enzyme replacement therapy (ERT) — intravenous α -galactosidase A (agalsidase) clears stored lipid from many cell types; instituted early to slow progression.
 - Pharmacologic chaperone — oral migalastat — stabilises and enhances the patient's residual mutant enzyme; an oral option only for patients with "amenable" GLA mutations.
- ▶ **Symptomatic / supportive:**
 - Neuropathic pain (acroparesthesia): gabapentin and carbamazepine reduce chronic and episodic pain; avoid known triggers (heat, exertion, fever).
 - Renal failure: chronic haemodialysis or kidney transplantation can be life-saving.
 - Cardiac/cerebrovascular: standard heart-failure/arrhythmia care, antihypertensives, and stroke prophylaxis (antiplatelet/risk-factor control).
- ▶ **Key principle:** renal insufficiency, cardiac fibrosis and stroke are irreversible — therefore early institution of therapy gives the best chance to prevent or slow life-threatening complications.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Multisystem "spoke" diagram of Fabry disease. Centre box: GLA mutation → α -galactosidase A deficiency → Gb3 (ceramide trihexoside) accumulation in vascular endothelium. Radiating labelled spokes: Skin — angiokeratomas (bathing-suit area), hypohidrosis; Eye — cornea verticillata / lenticular opacity; Peripheral nerve — acroparesthesia (burning hands/feet); GI — pain, diarrhoea; Kidney — proteinuria → ESRD; Heart — LVH / HCM-like, heart failure; Brain — premature stroke/TIA; Limbs — lymphedema.
- ▶ Metabolic pathway block. Labels: Globotriaosylceramide (Gb3) → [α -galactosidase A — BLOCKED] → lactosylceramide + galactose; show lysosomal accumulation of Gb3 and downstream lyso-Gb3 biomarker.

Clinical / Diagnostic significance

- ▶ "Hidden" cause of common idiopathic syndromes: consider Fabry in young/middle-aged "idiopathic" stroke, unexplained LVH/hypertrophic cardiomyopathy, and unexplained proteinuric renal failure, especially with a positive family history.
- ▶ Treatable LSD: one of the few LSDs with both ERT and an oral chaperone, making early recognition and family screening (X-linked pedigree, cascade GLA testing) clinically rewarding.
- ▶ Differential of cardiomyopathy: an important storage cause of restrictive/hypertrophic cardiomyopathy (with amyloidosis, haemochromatosis, sarcoidosis, glycogen storage disease).
- ▶ Pain mimicry: acroparesthetic crises and Fabry abdominal pain are frequently misdiagnosed as rheumatic "growing pains", appendicitis or renal colic in childhood, delaying diagnosis.

High-yield exam pointers

- ▶ X-linked deficiency of α -galactosidase A (gene GLA) → accumulation of globotriaosylceramide (Gb3 / ceramide trihexoside); most prevalent LSD.

- ▶ **Classic tetrad:** acroparesthesias + angiokeratomas + hypohidrosis + corneal opacity (cornea verticillata).
- ▶ **Angiokeratomas:** non-blanching, dark red–blue, "bathing-suit" distribution (umbilicus to knees).
- ▶ **Organ timeline:** renal disease 2nd–4th decades, cardiac disease 3rd–4th decades, stroke at 35–50 years, untreated death ~5th decade.
- ▶ **Carrier of "idiopathic" disease:** ~5% idiopathic renal failure, ~1–3% idiopathic HCM, ~2–5% idiopathic young stroke.
- ▶ **Females affected** (Lyonzation); enzyme assay may be normal in females → need GLA sequencing.
- ▶ **Treatment:** IV enzyme replacement (agalsidase) + oral migalastat (chaperone) for amenable mutations; gabapentin/carbamazepine for pain; dialysis/transplant for ESRD.
- ▶ **Mortality:** males — renal then cardiac; females — cardiac predominates.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Lysosomal Storage Diseases*" (Fabry disease: genetics, Gb3 accumulation, multisystem features, diagnosis, ERT/migalastat); "*Peripheral Neuropathy*" (Fabry small-fibre neuropathy, angiokeratoma corporis diffusum, premature atherosclerosis); "*Amyloidosis and Other Restrictive Cardiomyopathies*" (Fabry as a storage restrictive cardiomyopathy); "*Ischemic Stroke / TIA*" (Fabry as a noninflammatory vasculopathic cause of stroke).
- ▶ **CMDT 2026** — "*Heart Failure & Cardiomyopathy*" (Fabry among causes of restrictive cardiomyopathy) and "*Nervous System Disorders*" (Fabry as a vascular cause of TIA).

Coverage note: The corpus is rich on Fabry's phenotype, genetics, organ epidemiology and therapy. A few standard add-ons not stated verbatim in these chapters but universally accepted internal-medicine facts are flagged in text — the **GLA locus (Xq22)**, the eponym **cornea verticillata**, lyso-Gb3 biomarker, agalsidase as the specific ERT, and the **lamellar/zebra-body** ultrastructure; all are standard and accurate.



Factors affecting drug metabolism

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

Definition / Introduction — Drug metabolism (biotransformation) is the enzymatic conversion of a drug into compounds that are usually **more polar and hence more readily excreted** than the parent drug. It occurs predominantly in the **liver**, but also in the kidney, intestinal epithelium, lung and plasma. Metabolism proceeds in two phases — **Phase I** (chemical modification, most often oxidation by the **cytochrome P450 (CYP) mono-oxygenase superfamily**) and **Phase II** (conjugation by glucuronyl-, acetyl-, sulfo- and methyl-transferases). Because metabolism is a principal determinant of plasma drug concentration, the marked **inter-individual variability** in drug response is largely explained by genetic, physiological, pathological and environmental factors that modulate these enzyme systems.

Phases and machinery — orienting framework

- ▶ **Phase I (functionalisation):** oxidation, reduction, hydrolysis; the CYP superfamily dominates. The CYPs most important for drug disposition are **CYP3A4/CYP3A5** (metabolise the greatest number of drugs), **CYP2D6**, **CYP2C9**, **CYP2C19**, **CYP2B6**, **CYP1A2** and **CYP2E1**.
- ▶ **Phase II (conjugation):** glucuronidation (UGT), N-acetylation (NAT1/NAT2), sulfation, methylation and glutathione conjugation — usually inactivating and yielding highly polar, excretable products.
- ▶ **Nature of metabolites:** may be **inactive**, **pharmacologically active**, or **toxic/reactive**. *Prodrugs* require metabolism for activity (ACE inhibitors, the ARB *losartan*, *irinotecan*, *tamoxifen*, *codeine* → morphine, *clopidogrel*). Reactive metabolites (e.g. acetaminophen → NAPQI) can cause tissue toxicity.
- ▶ **High-risk pharmacokinetics:** when an active drug's elimination depends on a **single** metabolic pathway, any factor inhibiting that pathway produces large, clinically important swings in concentration.

Genetic / pharmacogenetic factors (the dominant source of variability)

A **multimodal** population distribution of metabolic activity indicates a single-gene effect, producing **poor (PM)**, **intermediate**, **normal/extensive (EM)** and **ultrarapid (UM)** metaboliser phenotypes (gene duplication causes UM). EMs given an inhibitor can behave like PMs — **phenocopying**.

Enzyme / gene	Variant phenotype	Substrate drug(s)	Clinical consequence
CYP2D6	PM 5–10% (Europeans/Africans; few Asians); UM (gene duplication)	codeine, metoprolol, carvedilol, timolol, propafenone, nortriptyline, tamoxifen	PM: no codeine analgesia, exaggerated β -blockade; UM: codeine→morphine toxicity (child deaths post-tonsillectomy; FDA black-box, banned <12 yr)
CYP2C19	PM ~20% Asians, 2–3% others, >50% Oceania	clopidogrel, omeprazole, mephenytoin	reduced clopidogrel bioactivation → stent thrombosis/stroke; lower ulcer-cure with omeprazole

Enzyme / gene	Variant phenotype	Substrate drug(s)	Clinical consequence
CYP2C9 + VKORC1	loss-of-function alleles	warfarin, phenytoin, glipizide, losartan	low warfarin dose, phenytoin neurotoxicity, glipizide hypoglycaemia; the two genes explain up to 50% of warfarin dose variance
CYP3A5	non-expressor splice variant (most Europeans/Asians)	tacrolimus, vincristine	African "expressers" eliminate tacrolimus faster (reduced efficacy)
NAT2 (acetylation)	slow acetylators ~50% of Europeans/Africans (fewer East Asians)	isoniazid, hydralazine, procainamide, some sulfonamides	INH hepatitis/neuropathy; drug-induced lupus with hydralazine/procainamide
TPMT (+ NUDT15)	homozygous inactive ~1/300	azathioprine, 6-mercaptopurine	severe, potentially fatal myelosuppression
UGT1A1	Gilbert's promoter variant	irinotecan, atazanavir	diarrhoea/marrow depression; unconjugated hyperbilirubinaemia
DPYD	loss-of-function homozygote	5-fluorouracil, capecitabine, tegafur	severe/fatal chemotherapy toxicity
Pseudocholinesterase	atypical variant	succinylcholine	prolonged neuromuscular block / apnoea
G6PD	deficiency (African/Mediterranean/South Asian)	primaquine, rasburicase, dapsone	oxidative haemolytic anaemia

Enzyme induction and inhibition (drug interactions)

The single most modifiable factor: co-administered drugs (and chemicals) that **induce** or **inhibit** metabolising enzymes/transporters.

	Enzyme inducers (↓ effect of substrate)	Enzyme inhibitors (↑ effect/toxicity of substrate)
Agents	Rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort, glutethimide, chronic alcohol , cigarette smoking (CYP1A2), chlorinated insecticides	Cimetidine (many CYPs), ketoconazole/itraconazole/fluconazole, erythromycin/clarithromycin, amiodarone (also P-gp), ritonavir, fluoxetine/paroxetine (CYP2D6), grapefruit juice (intestinal CYP3A4)
Affected drugs	warfarin, quinidine, cyclosporine, losartan, oral contraceptives, methadone, dabigatran	warfarin, theophylline, phenytoin, statins (myopathy), colchicine, cyclosporine, digoxin
Kinetics	Slow onset/offset (days–weeks; needs new enzyme synthesis)	Rapid onset (competition at active site)

- *Special interactions:* **allopurinol** (xanthine oxidase inhibitor) blocks azathioprine/6-MP catabolism → toxicity; **chronic alcohol/phenytoin/phenobarbital** increase acetaminophen hepatotoxicity by inducing reactive-metabolite formation and depleting glutathione.

Physiological factors

- ▶ **Age — neonates/infants:** drug-metabolising pathways **mature at different rates after birth**; immature glucuronidation underlies *chloramphenicol* "gray-baby" syndrome and prolonged neonatal jaundice. Dosing in children is approximated by **weight or body-surface area**.
- ▶ **Age — elderly:** declining hepatic mass, **reduced hepatic clearance** and reduced hepatic blood flow (plus falling GFR and altered body composition) impair metabolism; with polypharmacy and comorbidity this drives ADRs. *Rule:* start low, go slow, minimise drug number.
- ▶ **Sex, pregnancy, nutrition and circadian rhythm** also modulate enzyme activity (e.g. altered CYP activity and volume of distribution in pregnancy); protein-calorie malnutrition reduces enzyme content.

Pathological / disease factors

- ▶ **Liver disease (hepatitis, cirrhosis):** standard liver-function tests do **not** predict dose adjustment. **First-pass metabolism falls** owing to hepatocyte dysfunction, distorted architecture and porto-caval shunting, so oral bioavailability of **high first-pass drugs (morphine, meperidine, midazolam, nifedipine)** is **almost doubled** in cirrhosis — reduce the oral dose.
- ▶ **Heart failure / shock:** redistributed cardiac output and **decreased hepatic (and renal) perfusion** **impair drug clearance**; reduced gut perfusion may also lower absorption. Highest impact on **flow-limited (high-extraction)** drugs.
- ▶ **Renal disease:** although metabolism per se is hepatic, accumulation of **active/toxic metabolites** matters — e.g. **normeperidine** accumulates in renal failure causing CNS excitation/seizures; altered protein binding (uremia) raises free drug (phenytoin).
- ▶ **Thyroid status and acute inflammatory states** alter enzyme expression and acute-phase protein binding.

Other determinants

- ▶ **First-pass (presystemic) elimination & hepatic extraction ratio:** drug crossing gut wall and liver before reaching the systemic circulation. **High-extraction (flow-limited)** drugs (nitroglycerin, verapamil, morphine, lidocaine) have clearance sensitive to **hepatic blood flow**; **low-extraction (capacity-limited)** drugs (warfarin, phenytoin) are sensitive to enzyme activity and protein binding. Nitroglycerin is given sublingual/transdermal to bypass near-complete first-pass extraction.
- ▶ **Drug transporters:** efflux (P-glycoprotein/*ABCB1*) and uptake (*OATP1B1/SLCO1B1*) transporters control delivery of drug to metabolising enzymes; *SLCO1B1* variants raise statin myopathy risk.
- ▶ **Environmental/dietary:** smoking, chronic alcohol, industrial pollutants (induction); grapefruit juice (inhibition).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Bimodal/multimodal population-frequency curve of CYP2D6 activity** — x-axis "enzymatic activity (lesser → greater)", y-axis "population frequency"; label the **antimode**, **Poor metabolisers (PM, 2 loss-of-function alleles)**, **Extensive metabolisers (EM)** and **Ultrarapid metabolisers (UM, gene duplication)**.
- ▶ **Two-phase biotransformation flow diagram:** *Lipophilic parent drug* → **Phase I** (oxidation/reduction/hydrolysis, CYP450) → **Phase II** (glucuronidation / acetylation / sulfation / methylation / glutathione conjugation) → *polar conjugate* → *renal/biliary excretion*; annotate branch points for **inducers (↑)** and **inhibitors (↓)**.

Clinical / Diagnostic significance

- ▶ Explains why **fixed doses give variable effects** and is the basis for **therapeutic drug monitoring** (warfarin, phenytoin, digoxin, immunosuppressants, anticonvulsants).
- ▶ Guides **pre-emptive/point-of-care pharmacogenetic testing** (CPIC and Dutch Pharmacogenetics Working Group guidelines); e.g. TPMT/NUDT15 before thiopurines, DPYD before 5-FU, CYP2C19 before clopidogrel, HLA-B*57:01 before abacavir.
- ▶ Mandates **dose reduction** in hepatic disease, heart failure and the elderly, and **anticipation of interactions** when starting/stopping a known inducer or inhibitor of CYP2D6/CYP3A/P-glycoprotein.
- ▶ A 2023 7-country, 6944-patient trial showed pre-emptive **12-gene panel** genotyping cut serious ADRs by ~30%.

High-yield exam pointers

- ▶ Two phases: **Phase I = oxidation (CYP450)**; **Phase II = conjugation** (glucuronyl/acetyl/sulfo/methyl-transferase).
- ▶ **CYP3A4** metabolises the most drugs; **CYP2D6** is genetically the most polymorphic.
- ▶ **Slow acetylators (NAT2 ~50%)** → INH hepatitis/neuropathy and hydralazine/procainamide lupus.
- ▶ **TPMT deficiency (~1/300)** → fatal azathioprine/6-MP marrow toxicity; **DPYD** → 5-FU toxicity; **UGT1A1 (Gilbert)** → irinotecan toxicity.
- ▶ **CYP2D6 UM + codeine** → fatal opioid toxicity (FDA black box); **CYP2D6 PM** → codeine ineffective.
- ▶ **Inducers (rifampin, carbamazepine, phenytoin, St. John's wort, chronic alcohol, smoking)** act slowly; **inhibitors (cimetidine, azole antifungals, macrolides, amiodarone, grapefruit juice)** act fast.
- ▶ **Cirrhosis doubles** oral bioavailability of high first-pass drugs (morphine, midazolam, nifedipine) → reduce dose.
- ▶ **Pseudocholinesterase deficiency** → suxamethonium apnoea; **G6PD deficiency** → primaquine/rasburicase haemolysis.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Principles of Clinical Pharmacology" (drug metabolism, first-pass effect, enzyme induction/inhibition tables, effects of renal/hepatic/cardiac disease, age) and "Pharmacogenomics" (CYP2D6/2C19/2C9/3A5, NAT2, TPMT/NUDT15, UGT1A1, DPYD, pseudocholinesterase, G6PD; PM/EM/UM phenotypes; CPIC; 12-gene trial).
- ▶ CMDT 2026 — "Geriatric Disorders" (impaired hepatic clearance and ADRs in older adults) and pharmacogenetic/therapeutic-drug-monitoring material for current management framing.
- ▶ Coverage note: the corpus is clinical-pharmacology focused; classic pharmacology specifics not separately tabulated in Harrison (Phase I reduction/hydrolysis sub-types, microsomal CYP1A2/CYP2E1 induction by smoking/alcohol, neonatal "gray-baby" glucuronidation immaturity, high- vs low-extraction/flow- vs capacity-limited classification) are included as **universally accepted standard internal-medicine pharmacology** and are consistent with the inducer/first-pass data Harrison does provide.

**Falls in the elderly**

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

Definition / Introduction — A **fall** is an event in which a person inadvertently comes to rest on the ground, floor, or a lower level, not as a result of a major intrinsic event (e.g., stroke, seizure) or overwhelming external force. Falls are among the most common and most consequential of the **geriatric syndromes**: **over one-third of community-dwelling people aged >65 fall each year**, rising to about **one-half of long-term-care (LTC) residents**, and the rate climbs steeply with age. They are *multifactorial* (rarely a single cause), often labelled "mechanical" yet usually concealing reversible intrinsic factors, and they are the **leading cause of death from injury in persons over 65**. Falls therefore demand a systematic, comprehensive internal-medicine evaluation rather than dismissal as accidents.

Epidemiology and impact

- ▶ **Prevalence**: ≈ 1 in 3 community-dwellers >65 and ≈ 1 in 2 LTC residents fall annually; gait abnormality is present in 15% at >65 and approaches **40% by age ≥ 85** .
- ▶ **Morbidity**: $\sim 10\%$ of falls cause serious injury — most commonly fractures of **wrist, hip, and vertebrae**, plus **subdural haematoma** and soft-tissue trauma.
- ▶ **Mortality**: Complications (hip fracture, subdural haematoma) are the leading injury-related cause of death after 65; **hip-fracture mortality in older women is $\sim 20\%$ at 1 year**, especially if debilitated pre-fracture.
- ▶ **Functional/psychological burden**: Nearly **1 in 5 elderly voluntarily restrict activity from fear of falling**, accelerating deconditioning, loss of independence, and institutionalisation. A *long lie* on the floor risks dehydration, pressure injury, hypothermia, and **rhabdomyolysis**.

Why the elderly fall — physiology of balance

- ▶ Upright bipedal gait needs integration of **postural control + locomotion** across brainstem locomotor centres (pontine tegmentum, midbrain, subthalamic region), cerebellum, basal ganglia, and frontal cortex.
- ▶ Standing balance depends on **three sensory channels** — **visual, vestibular, and proprioceptive** (muscle-spindle/joint). There is healthy redundancy, but **loss of any two of the three** is sufficient to destabilise stance.
- ▶ With ageing: balance mechanisms degrade, reaction time slows, and **postural sway increases**, so any added insult (drug, illness, hazard) precipitates a fall.
- ▶ **Cognitive contribution:** Impaired **executive function** degrades *dual-task walking* (walking while attending to a cognitive task), predisposing demented elders to falls.

Risk factors (intrinsic, extrinsic, modifiable)

The presence of **multiple risk factors** multiplies risk. Harrison and CMDT classify them as below.

Domain	Risk factors
Intrinsic	Previous falls; gait/balance disorder ; visual deficits; muscle weakness/physical disability (incl. knee osteoarthritis); orthostatic hypotension ; cognitive impairment; depression; peripheral neuropathy; foot disorders
Medications	Polypharmacy (≥ 4 prescription drugs); benzodiazepines & sedative-hypnotics, antidepressants, antipsychotics, anticholinergics, antiepileptics, opioids, antihypertensives & diuretics, nitrates, antiarrhythmics, hypoglycaemics
Extrinsic / environmental	Loose rugs, electrical cords, poor lighting, unsafe stairs, slippery/wet floors, lack of grab-bars; inappropriate footwear (slippers, high heels); multifocal/bifocal lenses

- ▶ *Medication is the most common reversible cause* — meta-analysis identifies **sedative-hypnotics, antidepressants, and benzodiazepines** as the highest-risk classes.
- ▶ *Postural hypotension* includes **postprandial** hypotension (nadir 30–60 min after a meal) and is defined by a systolic drop >20 mmHg, diastolic drop >10 mmHg, or standing SBP <90 mmHg.

Classification of fall patterns (mechanism-based clues)

- ▶ **Drop attacks / collapsing falls:** sudden loss of postural tone ("legs gave out"); think syncope, orthostatic hypotension, atonic seizure, myoclonus, cataplexy (emotional trigger), or third-ventricle colloid cyst — *not* to be confused with vertebrobasilar attacks.
- ▶ **Toppling falls:** tone maintained but fall "like a tree trunk," often a consistent direction — cerebellar/vestibular lesions, **thalamic astasia**; an *early* feature of **progressive supranuclear palsy (PSP)** and a *late* feature of Parkinson's disease.
- ▶ **Falls due to gait freezing/festination:** feet stick while centre of mass advances $\rightarrow$ forward fall; Parkinson's disease and related parkinsonian syndromes.
- ▶ **Falls from sensory loss:** somatosensory/visual/vestibular deficits; worse on uneven ground and in poor light.
- ▶ **Falls from weakness:** cannot rise from chair or recover after perturbation; often *cannot get up* afterwards (long lie); frequently due to treatable deconditioning.

Clinical assessment

- ▶ **Screen every older patient annually:** "Have you fallen in the past year?", "Are you afraid of falling?", "Do you have trouble climbing stairs or rising from chairs?"
- ▶ **Timed Up and Go (TUG) test:** time the patient rising from a chair (no hands), walking ~3 m/10 ft, turning, returning, and sitting. **>12 s (Harrison) / ≥12.5 s (CMDT) indicates high fall risk** and mandates fuller assessment.
- ▶ **Targeted history:** circumstances, provoking factors (head turn, standing, post-meal, nocturia, straining), prodrome (dizziness — lightheaded vs vertigo, palpitations, focal neurology, seizure features), and a **collateral witness** account. Crucially **distinguish syncope/seizure** from a mechanical fall (as many as half of "unexplained falls" in demented elders are near-syncope from postural hypotension).
- ▶ **Examination:** supine vs standing BP/pulse at immediate and 3 min (orthostasis); cardiac exam (arrhythmia, aortic stenosis, MR, HF); **visual acuity**; neck range of motion; lower-limb strength (hip abductors/flexors, knee, ankle), tone, **proprioception and vibration**, cerebellar heel–shin, reflexes; **monofilament screen** for neuropathy; inspection of **feet (calluses, hallux valgus, hammertoes) and footwear**; gait/balance observation.
- ▶ **Investigations (history-guided):** CBC and basic metabolic panel; fingerstick glucose; urinalysis (only if UTI symptoms); ECG ± cardiac monitoring if syncope suspected; EEG if seizure suspected; X-rays for fractures; **brain imaging for head trauma, focal signs, anticoagulation, or suspected subdural** — otherwise it is reasonable to observe 48–72 h rather than image reflexively.

Complications

- ▶ **Fractures** — wrist, hip, vertebrae (osteoporosis greatly amplifies risk and is *vastly undertreated* — the "**osteoporosis care gap**," <20% of fragility-fracture patients receive treatment).
- ▶ **Chronic subdural haematoma** — easily missed; suspect in any elder with new neurological or cognitive change *even without* recalled trauma or headache.
- ▶ Hip fracture → hospitalisation, nursing-home admission, high 1-year mortality; head/spinal injury; **rhabdomyolysis/dehydration** from a long lie; and **fear of falling** with loss of confidence and independence.

Management and prevention (multifactorial)

Because causation is multifactorial, effective prevention usually needs **several simultaneous interventions** (AGS/BGS guideline; *World Falls Guidelines, Montero-Odasso 2022*).

Contributor	Intervention
Gait/balance, weakness	Exercise — Tai Chi, balance, gait & resistance/strength training (most consistently effective; benefits even in the 80s–90s); physiotherapy; assistive devices
Orthostatic/postprandial hypotension	Reduce hypotensive drugs; hydration, compression stockings; midodrine, fludrocortisone, droxidopa ; rise slowly; postprandial caution

Contributor	Intervention
Medications	Medication review/deprescribing (Beers & STOPP criteria); withdraw benzodiazepines, sedative-hypnotics, anticholinergics, unnecessary antihypertensives
Vision	Cataract surgery; correct refraction; avoid multifocal/bifocal lenses (extra caution in first weeks of new glasses)
Cardiac	Treat arrhythmia (antiarrhythmic, ablation, pacemaker); aortic-stenosis valve replacement (often transcatheter)
Bone health	Bisphosphonate (e.g., alendronate) for osteoporosis to prevent first/recurrent fracture; calcium
Vitamin D	Replacement ≥ 800 IU/day in deficiency (<i>USPSTF advises against routine vitamin D for fall prevention in community-dwellers; avoid high-dose — 60,000 IU monthly increased falls</i>)
Environment	Home-safety evaluation (occupational therapist): lighting, grab-bars, non-slip surfaces, remove rugs/cords; proper footwear
Recurrent fallers	Fall-alert/medical-alert system to prevent long lie; hip protectors in selected patients
Feet	Podiatric care; properly fitted shoes
Cognition	Supervision; cognitive/dual-task training; hazard-free environment

- ▶ **AF + high fall risk:** the stroke risk outweighs the bleeding risk — **anticoagulation is generally preferred**; consider a **left atrial appendage closure device**.
- ▶ The CDC STEADI programme (*Stopping Elderly Accidents, Deaths and Injuries*) provides screening/assessment/intervention tools.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Multifactorial model of falls (Venn / converging-arrows):** three overlapping circles labelled *Intrinsic factors* (gait/balance disorder, weakness, orthostatic hypotension, visual/sensory loss, cognitive impairment), *Medications* (polypharmacy ≥ 4 , benzodiazepines, sedative-hypnotics, antihypertensives), *Extrinsic/environmental* (poor lighting, loose rugs, footwear, multifocal lenses) — overlap zone labelled **FALL**, with outcome arrows to *Fracture (hip/wrist/vertebra)*, *Subdural haematoma*, *Fear of falling*, *Loss of independence*.
- ▶ **Three-channel balance triangle:** apex **Postural control / Balance**, three feeding inputs labelled **Visual**, **Vestibular**, **Proprioceptive**, with a note "loss of any 2 of 3 $\rightarrow$ imbalance," integrated at **Brainstem–Cerebellum–Frontal cortex**.

Clinical / Diagnostic significance

- ▶ Falls are a **sentinel marker** of occult disease (sepsis, MI, stroke, arrhythmia, dehydration) and of frailty — a presenting "atypical" complaint in the elderly.
- ▶ The single most useful bedside discriminator is **syncopal vs non-syncopal** fall, because it diverts the work-up toward cardiac/neurological evaluation.

- ▶ TUG ≥ 12 s, prior falls, and polypharmacy reliably flag the high-risk patient for prospective intervention *before* injury.
- ▶ Every fragility fracture should trigger **osteoporosis assessment and treatment** (closing the care gap) and a multifactorial falls work-up.

High-yield exam pointers

- ▶ $>1/3$ of community elders and $\sim 1/2$ of LTC residents fall yearly; $\sim 10\%$ cause serious injury; falls are the leading injury-death cause after 65.
- ▶ TUG >12 s (≥ 12.5 s CMDT) = **high fall risk**. Always measure **postural BP** (drop SBP >20 / DBP >10 mmHg).
- ▶ **Polypharmacy** = ≥ 4 prescription drugs; highest-risk classes are **benzodiazepines, sedative-hypnotics, antidepressants**.
- ▶ Fall **patterns**: drop attack (loss of tone), toppling fall (early PSP, late PD), freezing fall (parkinsonism), sensory-loss fall, weakness fall.
- ▶ **Exercise** (Tai Chi, **balance + strength training**) is the most consistently effective single intervention; multifactorial intervention adds modest benefit.
- ▶ **Chronic subdural haematoma** — overlooked; suspect with new cognitive/neurological change even without recalled trauma.
- ▶ **Hip fracture** $\rightarrow \sim 20\%$ 1-year mortality in older women; **osteoporosis care gap** ($<20\%$ treated).
- ▶ Use **Beers** and **STOPP** criteria for deprescribing; CDC **STEADI** for screening.
- ▶ In AF + **high fall risk**, anticoagulate (stroke risk $>$ bleed risk); consider **LAA closure**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Gait Disorders, Imbalance, and Falls" (epidemiology, balance physiology, gait-disorder classification, fall patterns, TUG, risk-factor table, STEADI, treatment) and "Caring for the Geriatric Patient" (geriatric-syndrome framing, AGS/BGS algorithm, immediate post-fall evaluation Table, management-by-cause Table, vitamin D, anticoagulation/AF, Beers/STOPP deprescribing).
- ▶ **CMDT 2026** — "Geriatric Disorders" (current management: fall-risk-factor/intervention table, TUG ≥ 12.5 s, postprandial hypotension, complications, USPSTF vitamin D stance, bisphosphonate/alendronate, assistive devices, World Falls Guidelines 2022).
- ▶ *Coverage note*: No dedicated geriatrics subspecialty text was provided in the spec; the answer is fully grounded in the above Harrison chapters and CMDT, which cover the topic comprehensively.



Gene therapy

Asked in: Paper I Dec 2023 · Paper I Jul 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — **Gene therapy** is a novel area of therapeutics in which the active agent is a **nucleic acid sequence** (DNA or RNA) rather than a protein or small molecule. Because delivery of naked DNA or RNA into a cell is inefficient, most gene therapy uses a **vector** (gene-delivery vehicle), typically engineered from a virus by deleting some or all of the viral genome and replacing it with the therapeutic gene under a suitable promoter. It is one of the most powerful concepts in modern molecular medicine, offering treatment for diseases that previously had no pharmacologic therapy. Clinical trials have run since **1990**; the first licensed product in the US/Europe was approved in **2012** (an AAV vector for lipoprotein lipase deficiency, in Europe).

Basic concepts — essential elements and routes

- ▶ Three essential elements: (1) a **gene-delivery vehicle (vector)**; (2) the **gene to be delivered (the transgene)**; (3) a **physiologically relevant target cell**.
- ▶ **Transduction** = the series of steps by which the vector and donated DNA/RNA enter the target cell and express the transgene.
- ▶ **In vivo gene therapy** — the vector is **injected directly into the patient** (e.g., subretinal, intravenous, intramuscular).
- ▶ **Ex vivo gene therapy** — target cells (hematopoietic, liver, immune) are **removed, gene-modified in the laboratory, and the autologous cells are returned** to the patient; effectively combines gene transfer with cellular therapy.
- ▶ Achieving **durable (long-term) expression** uses one of two strategies:
 - Transduce **stem cells with an integrating vector**, so all progeny carry the donated gene; or
 - Transduce **long-lived, post-mitotic cells** (skeletal muscle, neurons) — here integration is unnecessary; the donated DNA persists in **episomal** form and is expressed for the life of the cell, mitigating insertional-mutagenesis risk.

Gene-delivery vehicles (vectors)

Feature	Retroviral / Lentiviral	Adenoviral	AAV	Lipid nanoparticles (nonviral)
Genome	RNA	DNA	DNA	RNA
Cell-division requirement	G1 phase	No	No	No
Packaging limit	8 kb	8–30 kb	5 kb	10 kb or more
Immune response to vector	—	Extensive	Few	Few
Genome integration	Yes	Poor	Poor	Packages RNA or DNA

Feature	Retroviral / Lentiviral	Adenoviral	AAV	Lipid nanoparticles (nonviral)
Long-term expression	Yes	No	Yes	Transient (for RNA)
Main advantage	Persistent transfer in transduced tissues	Highly effective across many tissues	Few inflammatory responses; non-pathogenic	Can package RNA or DNA
Main disadvantage	May induce oncogenesis; used only <i>ex vivo</i>	Capsid elicits strong immune response	Limited packaging capacity	Immunogenic; mainly targets liver; difficult manufacture

- **Recombinant AAV** is engineered from a small replication-defective virus (~4.7 kb wild-type genome), is devoid of viral coding sequences, transduces non-dividing cells, and stabilises DNA **episomally** — hence its dominance for *in vivo* therapy of genetic disease. Its tropism for liver, skeletal muscle and neurons allows long-term expression without integration.

Strategies — gene addition vs gene editing

- Most approved gene therapies use **gene addition** (supplying a functional copy). Other approaches:
 - A **truncated gene** with comparable activity — *B domain-deleted factor VIII* for hemophilia A; *microdystrophin* for Duchenne muscular dystrophy (DMD).
 - A gene producing a **similar biologic effect via an alternative pathway** — *utrophin* in place of dystrophin for DMD.
 - **Down-regulating** a harmful effect via **small interfering (siRNA)** or **short hairpin (shRNA)** RNA.
- **CRISPR/Cas9 gene editing** uses a bacterial **Cas9** enzyme + a **guide RNA** to create a **double-strand break (DSB)** at a precise locus. Cas9 is complexed with the guide RNA as a **ribonucleoprotein (RNP)**.
 - **Without a targeting vector** — the DSB is repaired by **non-homologous end joining (NHEJ)**, producing small insertions/deletions that **disrupt** the target gene.
 - **With a targeting vector** — repair occurs by **homology-directed repair (HDR)**, giving precise **gene replacement** at the endogenous locus; the correction is heritable to every daughter cell.
 - The **cleavage step is far more efficient than the targeting step**; the only approved editing product and most investigational products require **cleavage only**.

Approved gene & cell therapy products (selected)

Product (generic)	Indication	Vector	Transgene / mechanism	Target tissue
Strimvelis	ADA-SCID	Retroviral	ADA (adenosine deaminase)	Autologous HSCs
Kymriah (tisagenlecleucel)	R/R B-ALL; large B-cell lymphoma	Lentiviral	CAR vs CD19 (4-1BB)	Autologous T cells

Product (generic)	Indication	Vector	Transgene / mechanism	Target tissue
Yescarta (axicabtagene ciloleucel)	Large B-cell lymphoma	Retroviral	CAR vs CD19 (CD28)	Autologous T cells
Luxturna (voretigene neparvovec)	Biallelic <i>RPE65</i> retinal dystrophy	AAV2	RPE65	RPE cells, subretinal injection
Zolgensma (onasemnogene abeparvovec)	SMA type 1 (<i>SMN1</i>)	AAV9	SMN1	Spinal motor neurons, IV
Zynteglo (betibeglogene autotemcel)	Transfusion-dependent β -thalassemia; SCD	Lentiviral	β A-T87Q globin	Autologous HSCs
Libmeldy	Metachromatic leukodystrophy	Lentiviral	ARSA (arylsulfatase A)	Autologous HSCs
Skysona (elivaldogene autotemcel)	Cerebral adrenoleukodystrophy	Lentiviral	ABCD1 transporter	Autologous HSCs
Roctavian (valoctocogene roxaparvovec)	Severe hemophilia A	AAV5	FVIII, B domain-deleted	Hepatocytes, IV
Hemgenix (etranacogene dezaparvovec)	Hemophilia B	AAV5	Factor IX Padua	Hepatocytes, IV
Elevidys (delandistrogene moxeparvovec)	Duchenne muscular dystrophy	AAVrh74	Microdystrophin	Skeletal muscle, IV
Casgevy (exagamglogene autotemcel)	Sickle cell anemia; β -thalassemia	Gene editing	Inactivates BCL11A in RBCs	Autologous HSCs

- **Proof of principle — X-linked SCID** (mutations in *IL2RG* encoding the γ c cytokine-receptor subunit): autologous CD34+ cells transduced with a retroviral γ c vector gave **complete, durable immune reconstitution** — the watershed showing gene therapy can cure. However, **5 of 20 children developed a T-ALL-like leukemia** because the retroviral vector integrated within LMO-2, the long terminal repeat driving its over-expression — proving **insertional mutagenesis** is real. This led to mandatory **15-year monitoring** of insertion sites, "**suicide**" gene cassettes, "**insulator**" elements, and a transition to **lentiviral vectors** (safer integration pattern).
- **Hemoglobinopathies** — lentiviral transfer of an anti-sickling **β A-T87Q globin** into autologous HSCs gives transfusion independence in β -thalassemia and abolishes vaso-occlusive crises in SCD. **Casgevy** edits the **erythroid enhancer of BCL11A** (the repressor of γ -globin in the fetal-to-adult switch) $\rightarrow \uparrow \gamma$ -globin and HbF, $\downarrow$ HbS, preventing sickling.
- **Hemophilia B** chosen first because F9 cDNA is small (2.8 kb); the high-specific-activity **factor IX Padua** variant allowed lower vector doses and durable mild-range FIX levels.

Gene therapy for cancer

- ▶ **Modifying the tumor** — adenoviral transfer of **tumor-suppressor p53**; **prodrug/suicide-gene** strategy (adenoviral **thymidine kinase** + **ganciclovir**, which TK phosphorylates to a toxic nucleoside, with bystander killing).
- ▶ **Modifying the host** — recruiting the immune system (checkpoint blockade of **CTLA-4** and the **PD-1/PD-L1** axis); **vaccination** (a dendritic-cell vaccine is approved for recurrent prostate cancer); and **adoptive cell transfer**.
- ▶ **CAR-T cells** — a **chimeric antigen receptor** combines the **VH/VL antigen-binding region** of a **monoclonal antibody**, a transmembrane domain, the **CD3-ζ chain**, and a **costimulatory domain** (**CD28** or **4-1BB**) — recognising antigen **independent of MHC**. Targets include **CD19** (B-cell malignancies) and **BCMA** (multiple myeloma); infused cells expand thousand-fold and produce **>80% complete-response rates** in refractory B-ALL.

Complications / adverse events

Vector / modality	Adverse event	Mechanism / note
Retroviral / lentiviral	Malignancy	Insertional mutagenesis (less frequent with lentiviral)
AAV	Vector in semen → germline-transmission risk; loss of expression	Anti-capsid memory T cells
AAV (high-dose IV)	Thrombotic microangiopathy	Complement activation; responds to eculizumab
Genome editing	Off-target cleavage → unintended gene silencing; transient transaminase rise	Guide-RNA non-specificity; immune response to bacterial Cas9
CAR-T	Cytokine release syndrome (fever, hypotension, tachycardia, hypoxia, multiorgan failure); neurotoxicity (cerebral edema, encephalopathy); hypogammaglobulinemia ; secondary T-cell malignancy	Standard CRS management; lifelong monitoring for secondary malignancy

- ▶ Conceptual complication categories (Table 483-3): **gene silencing**, **genotoxicity** (insertional mutagenesis), **phenotoxicity** (over-/ectopic expression), **immunotoxicity**, and **horizontal** (environmental shedding) and **vertical** (germline) transmission risks.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CAR vs native T-cell receptor (TCR)** — label: native TCR $\alpha\beta$ chains recognising *antigenic peptide* on MHC I/ β 2-microglobulin; CD3 complex ($\gamma\epsilon$, $\epsilon\delta$, $\zeta\zeta$); CAR components — VH and VL (from monoclonal antibody), **spacer**, **transmembrane (TM) domain**, **costimulatory domain** (CD28 or 4-1BB), and CD3- ζ signalling chain; note CAR recognises antigen **independent of MHC**.
- ▶ **CRISPR/Cas9 editing pathway** — label: Cas9 + guide RNA = RNP → **double-strand break (DSB)** → two arms: NHEJ → **indels/gene disruption** and HDR (with targeting vector) → **precise gene replacement**.

Clinical / Diagnostic significance

- ▶ History-taking in a treated patient must record: **which vector** (integrating — retroviral, lentiviral, herpesvirus, editing — vs non-integrating — plasmid, adenoviral, AAV), **dose and route**, **target tissue**, **which gene**, and **adverse events**.
- ▶ **Long-term follow-up screening** for new **malignancy**, **neurologic/ophthalmologic**, **autoimmune/rheumatologic**, or **hematologic disorders**; integrating-vector protocols mandate **15-year** insertion-site surveillance.
- ▶ **Pre-treatment screening for anti-AAV neutralizing antibodies** selects patients likely to benefit, since pre-existing immunity blocks transduction; the cellular anti-capsid response (asymptomatic transaminase rise + transgene loss) is **dose-dependent** and mitigated by **glucocorticoids** or dose reduction.
- ▶ Editing approaches are **heritable to daughter cells**, so the effect persists even as tissue (e.g., growing liver) divides — attractive for children.

High-yield exam pointers

- ▶ Gene therapy = **nucleic-acid active agent**; three elements = **vector + transgene + target cell**; process = **transduction**.
- ▶ **In vivo** (inject vector) vs **ex vivo** (modify autologous cells, re-infuse).
- ▶ Vector recall: AAV — **episomal, non-integrating, long-term, 5 kb limit**; lentiviral — **integrating, ex vivo, long-term**; adenoviral — **strong immunogenicity, transient**; lipid nanoparticles — RNA, transient, liver-tropic.
- ▶ **CRISPR**: NHEJ → gene knockout; HDR (needs targeting vector) → gene replacement; cleavage step > targeting step in efficiency.
- ▶ **Insertional mutagenesis** — X-SCID retroviral trials, LMO-2 activation → T-cell leukemia → switch to lentiviral + 15-yr monitoring.
- ▶ **Casgevy** = first approved gene-editing product → inactivates **BCL11A** → ↑ HbF in SCD/ β -thalassemia.
- ▶ **Factor IX Padua** = high-activity variant enabling low-dose hemophilia B gene therapy.
- ▶ **CAR-T toxicities** = **cytokine release syndrome + neurotoxicity (ICANS)**; AAV high-dose IV → TMA (complement-mediated, eculizumab).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 483 "Gene and Cell-Based Therapy in Clinical Medicine" (High KA, Maus MV). Coverage note: the provided chapter fully supports this answer; ICANS as a named term and the FINER/ethical-regulatory framework are standard internal-medicine knowledge added only where the chapter implies them.



Genetic counselling

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

Definition / Introduction — Genetic counselling is the communication process by which individuals or families at risk of an inherited disorder are helped to understand the medical facts (diagnosis, natural history, management), the way heredity contributes to the disorder and the **recurrence risk**, the options available for dealing with that risk, and to choose the course of action appropriate to them in keeping with their values. It is intended to be **non-directive, non-coercive and confidential**, respecting patient autonomy. Because genetic information has implications for *entire families*, the physician's role is increasingly to identify at-risk patients, explain the indications, limitations, risks and benefits of testing, and refer appropriately to **trained genetic counselors** while providing risk-based management.

Aims and indications for referral

- ▶ **Aims:** confirm/establish the diagnosis; define the mode of inheritance and calculate recurrence risk; explain prognosis and management; discuss reproductive and testing options; and provide psychosocial support to help informed decision-making.
- ▶ **When to refer / suspect a genetic basis:** two or more first-degree relatives affected (relative risk for common adult diseases rises **two- to fivefold**); *young age of onset* (e.g., a 30-year-old non-smoking woman with myocardial infarction); *unusual disease* (male breast cancer, medullary thyroid cancer); *multiple related diseases in one person* (colon + endometrial cancer); a **proband** (first individual ascertained) with a recognised syndrome; **consanguinity**; recurrent miscarriage, infertility, stillbirth, or a previous child with multiple congenital anomalies/intellectual disability.
- ▶ **Cytogenetic/cytogenomic indications (Table 479-4):** *Prenatal* — advanced maternal age, abnormal ultrasound, abnormal maternal serum screen; *neonatal/childhood* — multiple congenital anomalies, intellectual disability, autism, developmental delay, short stature, disorders of sexual development; *adult* — infertility, recurrent miscarriage, familial cancer.
- ▶ Note: chromosomal disorders occur in ~1% of the general population, 8% of stillbirths, and ~50% of spontaneous abortions — underscoring their importance in reproductive counselling.

The counselling process (sequential steps)

- ▶ **1. Confirm the diagnosis first** — the critical first step before any testing; based on family history, characteristic physical findings, pathology or biochemistry. Careful clinical assessment defines the **phenotype** and avoids unnecessary tests.

- ▶ **2. Construct a pedigree** — record health data on first- and second-degree relatives using **standard pedigree symbols** (proband indicated by arrow; affected = filled symbol; consanguineous union = double line; carrier, deceased, monozygotic/dizygotic twins, spontaneous abortion symbols). Expand the pedigree when inherited disease is suggested. Recall is often inaccurate — confirm reported illnesses from records, pathology reports and death certificates before irreversible decisions.
- ▶ **3. Risk assessment** — assign mode of inheritance and quantify recurrence risk (below), accounting for family size, number of unaffected relatives, ages of onset, ethnicity (e.g., 2.5% of Ashkenazi Jews carry a *BRCA1/2* founder variant) and non-hereditary risk factors.
- ▶ **4. Pretest counselling and informed consent** — explain what the test can and cannot determine, possibility of *uninformative/inconclusive* results, **variants of uncertain significance (VUS)**, unexpected/secondary findings, implications for relatives and insurance.
- ▶ **5. Testing** (where indicated) — ideally begin with an **affected family member**.
- ▶ **6. Posttest counselling** — disclose results, discuss treatment/surveillance implications for patient *and* family, address psychosocial impact, and arrange follow-up/support and return to primary care.

Risk assessment — modes of inheritance and modifiers

About 65% of monogenic disorders are autosomal dominant, 25% autosomal recessive, and 5% X-linked; mode of inheritance is determined by **pedigree analysis**.

Pattern	Key pedigree features	Recurrence risk
Autosomal dominant	Successive generations affected; males = females; affected child usually has an affected parent (unless <i>de novo</i>)	50% to each offspring
Autosomal recessive	Often single generation; ↑ with consanguinity ; carriers usually asymptomatic	25% if both parents carriers (50% carriers, 25% unaffected); pseudodominance if one parent homozygous affected
X-linked	No male-to-male transmission ; all daughters of an affected male are obligate carriers ; males hemizygous → more often affected	Carrier mother → 50% of sons affected, 50% of daughters carriers
Mitochondrial (matrilineal)	Transmitted only through the mother ; affected father transmits to none; heteroplasmy → variable expression	All children of affected mother at risk; variable

- ▶ **Modifiers that complicate counselling:**
 - **Incomplete/reduced penetrance** — not all genotype carriers manifest (e.g., HCM from *MYBPC3*); causes generation skipping; penetrance is *age-dependent* (Huntington's, familial ALS).
 - **Variable expressivity** — same mutation, different severity/organs/age of onset (MEN, cystic fibrosis).

- **Anticipation** — in **nucleotide (trinucleotide) repeat expansion** disorders a *premutation* enlarges in successive generations, producing earlier onset and increasing severity (e.g., myotonic dystrophy, Huntington's, Friedreich's ataxia).
- **Genomic imprinting / uniparental disomy** — parent-of-origin effect: **Prader-Willi** (loss of paternal 15q) vs **Angelman** (loss of maternal 15q).
- **Mosaicism** (somatic/germline), **de novo mutations** (more frequent with **advanced paternal age** — e.g., new Marfan mutations in fathers averaging ~37 yr), **locus heterogeneity** and **phenocopies** all confound pedigree interpretation.

Genetic testing within counselling

- ▶ **Predictive testing has two categories: Presymptomatic testing** — for disorders where a variant confers a **near-100%** likelihood of disease (e.g., Huntington's disease); **predisposition testing** — risk **<100%** (e.g., hereditary colon cancer, *APOE ε4* and Alzheimer's). For most adult-onset disorders, testing is only *predictive* — it cannot reveal whether, when or how disease will manifest.
- ▶ **Optimal strategy: test a disease-affected relative first**; a true-negative result in a relative reassures them and excludes transmission to their children; an *uninformative negative* (no familial variant known) does not lower risk and management stays based on personal/family history.
- ▶ **Informed consent & privacy**: patients must understand long-term medical, psychological, social and insurance implications; **DNA banking** should be offered; in the USA the **Genetic Information Nondiscrimination Act (GINA, 2008)** protects against health-insurance and employment discrimination but **not** life, disability or long-term-care insurance, and does not protect the *symptomatic* individual.
- ▶ **Testing children**: genetic testing for **adult-onset** disorders (e.g., Huntington's) is generally *not* offered in childhood (no childhood intervention; violates the child's future autonomy). It is offered when childhood management exists — **MEN 2** (prophylactic thyroidectomy) and **FAP/APC** (colonoscopy from age 10–15 yr).
- ▶ **Pitfalls to counsel about**: **VUS** (reclassified over time), incidental/secondary findings, and the variable quality of **direct-to-consumer (DTC)** testing (SNP "hot-spots", not definitive; ACMG advises professional ordering, CLIA/CAP-accredited labs, and proper consent).

Prenatal/preimplantation diagnosis and reproductive options

- ▶ **Amniocentesis** — **~16 weeks**; amniotic-fluid cells for karyotype, FISH, mutational analysis. Indications: advanced maternal age (**>35 yr**), fetal anomaly on ultrasound, **abnormal quad test** (*α-fetoprotein, β-hCG, inhibin-A, unconjugated estriol*), family history of chromosomal abnormality, or a testable Mendelian disorder.
- ▶ **Chorionic villus sampling (CVS)** — **weeks 9–12**, transcervical or transabdominal; earlier than amniocentesis, relevant when termination is considered.
- ▶ **Percutaneous umbilical blood sampling (PUBS/cordocentesis)** — from **~18 weeks**, for fetal blood analysis.

- ▶ **Cell-free DNA (cfDNA) screening** — non-invasive analysis of fetal DNA in a *maternal blood sample* to screen for chromosomal abnormalities and fetal sex.
- ▶ **Preimplantation genetic testing (PGT)** — with IVF, a single cell from the 4–8-cell embryo or the first polar body is analysed, allowing selection of unaffected embryos and avoiding therapeutic abortion (costly, labour-intensive).
- ▶ **Key caution:** excluding a specific disorder by any of these methods is **never equivalent to assurance of a normal child**. Other reproductive options to counsel: proceeding with the pregnancy, prenatal diagnosis ± termination, donor gametes, adoption, or remaining childless.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-generation pedigree with standard symbols** — label: *square = male, circle = female, filled = affected, arrow = proband, double horizontal line = consanguineous union, diagonal line = deceased, dot-in-circle = carrier female, vertical line from a horizontal sib-line, monozygotic vs dizygotic twins, small triangle = spontaneous abortion*. Annotate generations I–II–III with Roman numerals.
- ▶ **Inheritance-pattern squares (Punnett) for recurrence risk** — label *Autosomal dominant* ($Aa \times aa \rightarrow 50\% \text{ affected}$), *Autosomal recessive* ($Aa \times Aa \rightarrow 25\% \text{ affected, } 50\% \text{ carrier}$), *X-linked* (*carrier mother* $\rightarrow 50\% \text{ sons affected}$), and *Mitochondrial* (*matrilineal* — *all children of affected mother*).

Clinical / Diagnostic significance

- ▶ Accurate risk assignment guides **reproductive decisions, surveillance and risk-reducing interventions** — e.g., *BRCA1/2* carriers: risk-reducing salpingo-oophorectomy, breast MRI screening, risk-reducing mastectomy, PARP inhibitors; **Lynch syndrome/FAP**: early/frequent colonoscopy, prophylactic surgery, aspirin/chemoprevention; **MEN 2**: prophylactic thyroidectomy.
- ▶ Counselling enables **cascade testing** of relatives once a familial pathogenic variant is identified, and population/founder screening (e.g., Ashkenazi *BRCA*).
- ▶ Recognising **incomplete penetrance and variable expressivity** is essential — one cannot always predict disease course even when the mutation is known; this must be conveyed honestly.
- ▶ Counselling has medical, **psychosocial and ethical** dimensions: anxiety, *survivor guilt* in test-negative relatives, parental despair over transmission risk, genetic discrimination, and management of secondary findings.

High-yield exam pointers

- ▶ Genetic counselling = **non-directive, voluntary, confidential** communication of facts, inheritance, recurrence risk and options.
- ▶ Recurrence risks: **AD 50%, AR 25% (both carriers), XL carrier mother $\rightarrow$ 50% sons affected, mitochondrial = matrilineal**.
- ▶ Monogenic disorders: **AD ~65%, AR ~25%, XL ~5%**.
- ▶ **Always confirm the diagnosis and test an affected relative first.**

- ▶ Key modifiers: **penetrance**, **expressivity**, **anticipation**, **imprinting** (Prader-Willi/Angelman), **mosaicism**, **de novo mutations** (advanced paternal age), **consanguinity** (↑ AR).
- ▶ Prenatal tests: CVS 9–12 wk, amniocentesis ~16 wk, PUBS ~18 wk, cfDNA (non-invasive); **quad test** = AFP + β -hCG + inhibin-A + unconjugated estriol.
- ▶ PGT + IVF selects unaffected embryos; no test guarantees a "normal" child.
- ▶ **Presymptomatic** (Huntington's, ~100%) vs **predisposition** (hereditary cancer, <100%) testing; defer adult-onset testing in children (test MEN 2, FAP).
- ▶ **GINA (2008)** protects health-insurance/employment, not life/disability/long-term-care insurance; offer **informed consent** + **DNA banking**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (pedigree symbols and analysis; modes of inheritance and recurrence risks; penetrance, expressivity, anticipation, imprinting, mosaicism, consanguinity; prenatal diagnosis — amniocentesis, CVS, PUBS, cfDNA, PGT; ethical issues and GINA) and "The Integration of Inherited Genetics into Clinical Practice" (family-history/pedigree-based risk assessment; pretest/posttest counselling and informed consent; presymptomatic vs predisposition testing; testing of children; VUS; direct-to-consumer testing; cascade testing and risk-reducing interventions).
- ▶ **Coverage note:** Harrison 22e covers risk assessment, inheritance, testing strategy and prenatal/preimplantation diagnosis in depth, but does **not** lay out a discrete numbered "steps of genetic counselling" protocol or explicitly emphasise the *non-directive* principle; these standard, universally accepted counselling tenets have been stated as established internal-medicine practice and synthesised from the chapters' content. No dedicated clinical-genetics subspecialty text was listed in the spec for this topic.



HLA antigenic system in health and disease

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

Definition / Introduction — The **human leukocyte antigen (HLA) system** is the human **major histocompatibility complex (MHC)**, a cluster of highly polymorphic, closely linked genes on the short arm of **chromosome 6 (6p21)** that encode cell-surface glycoproteins responsible for **presenting peptide antigens to T lymphocytes**. By dictating what the adaptive immune system "sees" as self versus non-self, the HLA system governs T-cell selection, defence against microbes and tumours, natural-killer (NK)-cell regulation, transplant compatibility, and susceptibility to a large group of immune-mediated and drug-induced diseases. It is the single most polymorphic locus in the human genome, which underlies both its protective versatility and its strong disease associations.

Genomic Organisation and Classification

- ▶ The MHC on **chromosome 6** is conventionally divided into three regions encoding **class I, class II and class III** molecules; the genes are **co-dominantly expressed** (both parental alleles are transcribed) and inherited en bloc as a **haplotype**.
- ▶ Because of strong **linkage disequilibrium**, certain alleles travel together as conserved **extended/ancestral haplotypes** — e.g. the **A1-B8-DR3-DQ2 (AH 8.1)** haplotype linked to high TNF- α production and autoimmunity (Harrison, HIV chapter).

Class	Principal loci (HLA)	Chain structure	Cells expressing	Presents peptide to
Class I (Ia)	HLA-A, -B, -C	Polymorphic heavy (α) chain + invariant β 2-microglobulin; closed groove binds short (~9–13 aa) peptides	All nucleated cells + platelets	CD8+ cytotoxic T cells
Class I (Ib)	HLA-E, -F, -G (+ MIC-A)	Limited polymorphism	Restricted (e.g. HLA-G on trophoblast)	NK cells / regulatory
Class II	HLA-DR, -DQ, -DP	Two chains ($\alpha + \beta$); open groove binds longer peptides	Professional APCs — dendritic cells, macrophages, B cells (inducible on others)	CD4+ helper T cells
Class III	C4, C2, factor B, TNF, HSP	Secreted/soluble effectors (not antigen-presenting)	—	—

Structure, Antigen Processing and Presentation

- ▶ T cells (unlike B cells) **do not recognise native antigen**; the TCR sees only short **peptide fragments** (~9–13 amino acids) embedded in the groove of a self-MHC molecule — the basis of **MHC restriction**.
- ▶ **Endogenous (class I) pathway** — cytosolic proteins (e.g. viral, tumour) are degraded by the **proteasome**, peptides are pumped into the endoplasmic reticulum by **TAP (transporters associated with antigen processing)**, loaded onto class I molecules, and displayed to **CD8+ T cells** (which bind via CD8 to class Ia HLA-A/B/C).

- ▶ **Exogenous (class II) pathway** — extracellular antigens taken up by endocytosis/phagocytosis are degraded in acidified vesicles, fused with class II-containing vesicles, and presented to **CD4+ T cells** (CD4 binds DR/DQ/DP).
- ▶ **Non-classical/lipid presentation** — **CD1 molecules** present microbial **lipid antigens** (e.g. *M. tuberculosis*) to $\gamma\delta$ and some CD8+ T cells, an MHC-independent route.

Physiological Roles of HLA in Health

- ▶ **Initiation of adaptive immunity** — antigen presentation is the obligatory first signal for T-cell activation and downstream antibody and cytotoxic responses.
- ▶ **Thymic T-cell selection** — developing thymocytes that interact appropriately with self-MHC are positively selected, while strongly self-reactive clones are negatively selected, shaping a **self-tolerant repertoire**.
- ▶ **NK-cell regulation ("missing-self" hypothesis)** — NK cells kill host cells expressing **low/absent self class I** (e.g. virus-infected or tumour cells that down-regulate HLA); high self-MHC engages inhibitory **killer-cell immunoglobulin-like receptors (KIRs)** and switches NK killing off. KIR ligands include **HLA-C1/C2 epitopes, the Bw4 motif, and HLA-E**.
- ▶ **Reproductive tolerance** — non-classical **HLA-G** on trophoblast protects the semi-allogeneic fetus from maternal NK/T-cell attack.
- ▶ **Transplantation & transfusion biology** — HLA molecules are the dominant **transplantation antigens**; HLA disparity drives allograft rejection and graft-versus-host disease, and anti-HLA antibodies cause transfusion complications (see below).

HLA and Disease Associations

Disease linkage arises through altered peptide presentation, molecular mimicry, defective tolerance, or linkage disequilibrium with true susceptibility genes.

Disease	HLA association	Notes / mechanism
Axial spondyloarthritis / ankylosing spondylitis	HLA-B27 (class I)	Present in 85–90% of radiographic axSpA vs ~5% of healthy Caucasians; strongest known genetic risk factor
Reactive arthritis, psoriatic, IBD-associated, anterior uveitis	HLA-B27	Part of the B27-linked spondyloarthritis spectrum
Behçet syndrome	HLA-B*51	Positive in 50–60% of patients (also ~20% of normals — not diagnostic)
Type 1 diabetes mellitus	HLA-DR3 / DR4, DQ2/DQ8	Class II-driven islet autoimmunity
Celiac disease	HLA-DQ2 / DQ8	Near-obligate; gluten-derived peptides presented by DQ2/DQ8
Graves' disease	DR3	Iodine as initiating factor
Addison's disease / APS-2	DR3 / DR4; MIC-A 5.1	MIC-A5.1 association independent of DR3/DR4

Disease	HLA association	Notes / mechanism
Myasthenia gravis	DR3, DR7	Thymoma / penicillamine triggers

- ▶ **Arthritogenic peptide / molecular-mimicry theory (AS):** HLA-B27 presents pathogenic microbial peptides to CD8+ cytotoxic T cells that cross-react with self-peptides. Subtype specificity matters — **HLA-B*2704 and B*2705 confer risk**, whereas **B*2706 and B*2709 do not**, differing by single amino-acid residues. ERAP1 (a peptide-trimming enzyme) shows genetic epistasis with B27. Risk of axSpA is ~5% in B27-positive individuals, rising to ~20% in B27-positive first-degree relatives.
- ▶ **Non-HLA susceptibility genes** that interact with HLA: PTPN22, CTLA4, IL-2Rα (autoimmune endocrinopathies).
- ▶ **HLA in infection / host defence:** in HIV, class I alleles **HLA-B*27 and HLA-B*57** are associated with **slower progression** ("elite controllers"), whereas HLA class I **homozygosity** (a narrower epitope repertoire) and the **AH 8.1** haplotype accelerate progression; **KIR3DL1 + HLA-B*57:01** interaction modifies protection.

HLA in Pharmacogenomics — Drug Hypersensitivity

HLA risk alleles are **necessary but not sufficient** for severe cutaneous and hepatic drug reactions; pre-prescription typing can prevent them.

Drug	HLA allele	Reaction
Abacavir	HLA-B*57:01	Abacavir hypersensitivity / SJS-TEN (~55% of carriers react); RCT shows testing eliminates the reaction
Flucloxacillin	HLA-B*57:01	Drug-induced hepatotoxicity (low penetrance)
Carbamazepine	HLA-B*15:02	Stevens-Johnson syndrome / toxic epidermal necrolysis (testing mandated in parts of SE Asia)

- ▶ Severe reactions linked to specific HLA alleles span **SJS/TEN, DRESS, and drug-induced liver injury**; risk-allele frequency varies by ancestry, which guides population-specific screening.

Transplantation and Transfusion Medicine

- ▶ HLA molecules are the **major histocompatibility (transplantation) antigens**; donor–recipient HLA matching reduces rejection in solid-organ and **haematopoietic stem-cell transplantation**, and HLA disparity is the substrate for **graft-versus-host disease (GVHD)**.
- ▶ **Pre-formed anti-HLA antibodies** (from pregnancy, transfusion, prior grafts) cause **hyperacute/antibody-mediated rejection**; **plasma-based removal of anti-HLA antibody** may be performed before kidney transplantation.
- ▶ In transfusion: **leukoreduction** lowers HLA alloimmunisation and febrile non-haemolytic reactions; **irradiation** of cellular products prevents **transfusion-associated GVHD**; donor anti-HLA antibodies are a cause of **TRALI**; HLA alloimmunisation underlies **platelet refractoriness** (requiring HLA-matched platelets).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Structure of MHC class I vs class II.** Class I: single α (heavy) chain with domains $\alpha 1$, $\alpha 2$, $\alpha 3$ + $\beta 2$ -microglobulin, closed peptide-binding groove (short peptide), label "binds CD8 / all nucleated cells". Class II: α and β chains ($\alpha 1/\alpha 2$, $\beta 1/\beta 2$ domains), open-ended groove (longer peptide), label "binds CD4 / professional APCs".
- ▶ **Diagram 2 — Antigen-processing pathways.** Show endogenous pathway (cytosolic protein $\rightarrow$ proteasome $\rightarrow$ TAP $\rightarrow$ ER $\rightarrow$ class I $\rightarrow$ cell surface $\rightarrow$ CD8+ T cell) and exogenous pathway (endocytosis $\rightarrow$ endosome/lysosome $\rightarrow$ fusion with class II vesicle $\rightarrow$ cell surface $\rightarrow$ CD4+ T cell). Label proteasome, TAP, ER, MHC I, MHC II, CD8, CD4.

Clinical / Diagnostic significance

- ▶ HLA-B27 testing supports (does not confirm) a diagnosis of axial spondyloarthritis in a patient with inflammatory back pain and equivocal imaging.
- ▶ HLA-DQ2/DQ8 negativity has a very high negative predictive value to exclude celiac disease.
- ▶ Pharmacogenomic HLA screening before abacavir (B*57:01) and carbamazepine (B*15:02 in at-risk ancestries) prevents life-threatening cutaneous reactions.
- ▶ HLA typing and crossmatching are mandatory for solid-organ and stem-cell transplantation; panel-reactive/anti-HLA antibody assessment stratifies sensitisation and rejection risk.
- ▶ Disease-association data also illuminate pathogenesis (e.g. class I associations implicate CD8 T cells; class II associations implicate CD4-helper-driven autoimmunity).

High-yield exam pointers

- ▶ HLA = human MHC on chromosome 6 (6p21); co-dominant, most polymorphic genes; inherited as haplotypes in linkage disequilibrium.
- ▶ Class I (A, B, C) + $\beta 2$ -microglobulin $\rightarrow$ CD8 (endogenous/proteasome-TAP); Class II (DR, DQ, DP) $\rightarrow$ CD4 (exogenous/endosomal); class III = complement C4/C2/Bf, TNF.
- ▶ MHC restriction + thymic positive/negative selection = central tolerance.
- ▶ NK "missing-self": low self class I $\rightarrow$ NK killing; inhibitory KIRs sense self-MHC; HLA-G mediates fetal tolerance.
- ▶ Strongest single association: HLA-B27 with ankylosing spondylitis (85–90%); B*2704/2705 risk, B*2706/2709 protective; ERAP1 epistasis.
- ▶ Class II autoimmunity: T1DM DR3/DR4, Celiac DQ2/DQ8, Graves/Addison DR3/DR4; Behçet B*51.
- ▶ Pharmacogenetics: B*57:01–abacavir, B*15:02–carbamazepine, B*57:01–flucloxacillin (necessary-not-sufficient).
- ▶ Transplant/transfusion: HLA matching, anti-HLA antibodies $\rightarrow$ rejection, GVHD, TRALI, platelet refractoriness.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Introduction to the Immune System" (MHC class I/II structure, antigen processing/TAP/proteasome, CD1, NK/KIR missing-self); "Spondyloarthritis" (HLA-B27, subtypes, ERAP1, arthritogenic-peptide theory, axSpA risk figures); "Behçet Syndrome" (HLA-B*51); "Autoimmune Polyendocrine Syndromes" (HLA-disease association table — Graves, MG, celiac, T1DM, Addison, MIC-A 5.1; PTPN22/CTLA4); "Pharmacogenomics" (HLA-B*57:01 abacavir/flucloxacillin, HLA-B*15:02 carbamazepine, SJS-TEN/DRESS); "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (protective HLA-B*27/B*57, AH 8.1 haplotype, KIR3DL1–B*57:01); "Transfusion Biology and Therapy" (leukoreduction, irradiation/GVHD, anti-HLA antibodies, TRALI).
- ▶ **Coverage note:** This Harrison 22e corpus has **no dedicated standalone HLA/MHC chapter** — content was synthesised across the immunology, rheumatology, pharmacogenomics, HIV and transfusion chapters. The corpus gives allele-level associations but **not a single consolidated relative-risk table** (e.g. the classic AS relative risk of ~90 is not quoted); the **class III region composition** (C4/C2/Bf, TNF) and **β2-microglobulin** as the class I light chain are stated here as universally accepted standard immunology, as the corpus describes them only in passing.



Drug pharmacokinetics and prescribing in pregnancy

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

Definition / Introduction — *Drug disposition* is the sum of **absorption, distribution, metabolism and excretion (ADME)**, which together determine the concentration of drug delivered to its target. Pregnancy imposes profound, dynamic and progressive physiological changes (in plasma volume, body composition, plasma proteins, hepatic enzyme activity and renal function) that alter every one of these processes, usually lowering plasma concentrations of many drugs and necessitating dose individualisation. Simultaneously, the **placenta is permeable to most drugs**, so the prescriber must balance maternal therapeutic benefit against fetal risk (teratogenicity, fetotoxicity). Rational prescribing therefore requires understanding of *both* altered maternal pharmacokinetics *and* the safety hierarchy of drugs across gestation.

Physiological changes of pregnancy that drive altered pharmacokinetics

System	Change in pregnancy	Pharmacokinetic consequence
Blood / fluid	Plasma volume ↑ ~40–50%; total body water ↑ (~8 L); body fat ↑	↑ volume of distribution (Vd) → lower peak concentration for a given dose
Plasma proteins	Dilutional ↓ albumin (and α1-acid glycoprotein)	↑ free (unbound) fraction of highly protein-bound drugs

System	Change in pregnancy	Pharmacokinetic consequence
Cardiovascular	Cardiac output ↑ ~30–50%; skin, renal & uteroplacental flow ↑	Faster absorption from IM/SC/transdermal/inhaled routes; ↑ hepatic & renal delivery
Gastrointestinal	↓ Gut motility & delayed gastric emptying (progesterone); ↑ gastric pH; nausea/vomiting	Delayed/erratic oral absorption (delayed T _{max} *); altered ionisation of weak acids/bases
Hepatic	Induction of CYP3A4, CYP2D6, CYP2C9, UGT (oestrogen/progesterone); ↓ CYP1A2, CYP2C19	↑ Clearance of many substrates; ↓ clearance of a few
Renal	Renal plasma flow ↑ ~50–80%; GFR ↑ ~50%	↑ Renal clearance of renally-eliminated drugs

Effect of pregnancy on each pharmacokinetic phase (ADME)

- **Absorption** — Delayed gastric emptying and reduced bowel motility delay the *rate* (later, lower peak) but usually not the *extent* of oral absorption; nausea/vomiting and hyperemesis make oral dosing unreliable. Raised gastric pH alters ionisation. Increased cardiac output and cutaneous/pulmonary blood flow enhance absorption from **intramuscular, subcutaneous, transdermal and inhalational** routes.
- **Distribution** — Expanded plasma volume, total body water and fat **increase V_d**, particularly for hydrophilic drugs, lowering peak plasma levels and sometimes requiring a larger loading dose (recall: the loading dose is governed by V_d, the maintenance dose by clearance). The fall in albumin **increases the free fraction** of acidic, highly bound drugs (e.g., phenytoin, valproate); since *only unbound drug is pharmacologically active*, total (bound + free) levels under-read true exposure — **free drug monitoring is preferred** (as Harrison notes for phenytoin).
- **Metabolism** — Sex-steroid-mediated **induction of CYP3A4, CYP2D6, CYP2C9 and UDP-glucuronosyltransferase (UGT)** accelerates clearance and lowers levels of their substrates (the classic example is **lamotrigine**, a UGT substrate whose clearance rises sharply, demanding dose escalation and monthly level monitoring). By contrast **CYP1A2 and CYP2C19 activity fall**, raising concentrations of substrates such as caffeine and theophylline.
- **Excretion** — The ~50% rise in GFR **increases renal clearance** of drugs eliminated unchanged by the kidney (e.g., **lithium, digoxin, low-molecular-weight heparin, atenolol, penicillins, cephalosporins, aminoglycosides**), so standard doses may be sub-therapeutic. Harrison explicitly notes that **antiepileptic drug doses often must be escalated because of increased clearance in pregnancy**, with monthly level checks.
- **Net result** — For *most* affected drugs, clearance rises and free/total levels fall as pregnancy advances, with a return towards baseline postpartum — hence **therapeutic drug monitoring (TDM)** and proactive dose adjustment (up in pregnancy, back down after delivery) are central.

Placental drug transfer and the timing of fetal vulnerability

- **Placental transfer** is mainly by passive diffusion; transfer is favoured by **low molecular weight (<500 Da)**, **high lipid solubility**, **low ionisation** and **low protein binding**. Large/polar/highly-

bound molecules (e.g., heparin, LMWH, insulin) cross poorly — a property exploited therapeutically.

► **Gestational timing determines the type of harm:**

- **Pre-implantation (0–2 weeks post-conception)** — *all-or-none* phenomenon: insult either causes loss or has no residual effect.
- **Embryonic period / organogenesis (~3–8 weeks)** — **maximum risk of major structural malformation**; this is the *critical period* for classical teratogens.
- **Fetal period (9 weeks–term)** — growth restriction and *functional/organ-specific* toxicity rather than gross malformation (e.g., ACE-inhibitor fetopathy, third-trimester NSAID-induced ductus closure, tetracycline tooth staining).

Drugs that are teratogenic / fetotoxic (avoid) and safer alternatives

Teratogen / fetotoxic drug	Characteristic fetal effect
ACE inhibitors, ARBs, MRAs	2nd/3rd-trimester fetopathy: oligohydramnios, renal failure, skull/lung hypoplasia
Warfarin / coumarins	Fetal warfarin syndrome (nasal hypoplasia, stippled epiphyses), CNS injury
Valproate, phenytoin, carbamazepine	Neural-tube & other major malformations; neurodevelopmental harm
Isotretinoin / retinoids	Retinoid embryopathy (craniofacial, cardiac, CNS)
Thalidomide	Limb-reduction defects (phocomelia)
Methotrexate, cyclophosphamide	Aminopterin-type syndrome / cytotoxic malformation
Lithium	Cardiac (Ebstein anomaly)
Tetracyclines (3rd trimester)	Tooth discolouration, impaired bone growth
Aminoglycosides	Fetal ototoxicity
NSAIDs (3rd trimester)	Premature ductus arteriosus closure, oligohydramnios
Diethylstilbestrol	Vaginal clear-cell adenocarcinoma in offspring
Others	Androgens, oestrogens, danazol, misoprostol, ergotamine, radioiodine, ribavirin, sulfonamides (late), griseofulvin, alcohol, tobacco

- **Preferred (relatively safer) agents by indication:** Hypertension — **methyldopa, labetalol, nifedipine** (ACEi/ARB/MRA contraindicated). Epilepsy — **lamotrigine, levetiracetam** (with 4 mg/day folic acid). Anticoagulation — **LMWH / unfractionated heparin** (do not cross placenta). Hypothyroidism — **levothyroxine**, with the dose increased ~30% (≈two extra tablets/week) once pregnancy is confirmed. UTI suppression — **nitrofurantoin or cephalexin**. Nausea/vomiting — **pyridoxine ± doxylamine**. Asthma — managed as in the non-pregnant state. Diabetes — **insulin**. Infections — penicillins, cephalosporins, erythromycin/azithromycin generally acceptable.

Principles to consider when prescribing to a pregnant patient

- ▶ **Prescribe only when clearly indicated** — try non-pharmacological measures first; avoid over-the-counter and "social" drugs (alcohol, tobacco, recreational drugs).
- ▶ **Weigh risk versus benefit both ways** — *untreated* maternal disease (epilepsy, asthma, hypertension, diabetes, infection, thyroid disease, venous thrombosis) is itself harmful to mother and fetus; do **not** withhold essential therapy.
- ▶ **Use the lowest effective dose for the shortest duration**, but adjust *upwards* to compensate for increased Vd and clearance, guided by TDM (AEDs, lithium, digoxin, free phenytoin) and clinical response.
- ▶ **Prefer older, well-characterised drugs** with the longest safety record over newer agents with sparse data; choose **monotherapy over combinations**.
- ▶ **Respect gestational timing** — be most restrictive during organogenesis; remember late-pregnancy fetotoxicities (NSAIDs, ACEi, tetracyclines).
- ▶ **Plan before conception** — substitute known teratogens (e.g., warfarin, valproate, ACE inhibitors, isotretinoin) for safer alternatives *before* pregnancy; give **periconceptional folic acid** (high-dose 4 mg/day with AEDs).
- ▶ **Consult authoritative, current resources** — the FDA's old A/B/C/D/X letter categories have been replaced by the **Pregnancy and Lactation Labeling Rule (PLLR, narrative risk summaries)**; teratogen information services and registries should be used.
- ▶ **Consider lactation** — many drugs enter breast milk; check resources such as **LactMed** before prescribing to a nursing mother.
- ▶ **Anticipate the postpartum reversal** — pregnancy-related PK changes resolve over days to weeks after delivery; doses escalated during pregnancy (e.g., lamotrigine) must be **reduced postpartum** to avoid toxicity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **"PK changes in pregnancy" schematic (pregnant figure with four ADME boxes):** label — *Absorption*: ↓ gastric motility, delayed emptying, ↑ gastric pH, nausea/vomiting; *Distribution*: ↑ plasma volume (+40–50%), ↑ total body water & fat, ↓ albumin → ↑ free drug, ↑ Vd; *Metabolism*: ↑ CYP3A4/2D6/2C9/UGT, ↓ CYP1A2/2C19; *Excretion*: ↑ GFR (~+50%), ↑ renal clearance. Net arrow: "↓ plasma levels of many drugs → dose ↑ / monitor."
- ▶ **Gestational-timing teratogenicity timeline (0 → 40 weeks):** label the three zones — 0–2 wk "all-or-none" | 3–8 wk organogenesis = major malformations (critical period) | 9 wk–term = growth restriction & functional/organ-specific toxicity.

Clinical / Diagnostic significance

- ▶ **Interpret drug levels carefully:** falling *total* phenytoin/valproate levels may reflect lower albumin, not under-treatment — measure **free drug**; conversely rising lamotrigine clearance genuinely lowers exposure and risks breakthrough seizures.
- ▶ **Dose adjustment is bidirectional:** uptitrate during pregnancy and **downtitrate postpartum** for AEDs, lithium and others.

- ▶ **Renally-cleared narrow-therapeutic-index drugs** (lithium, digoxin, LMWH, aminoglycosides) need closer monitoring because of the GFR rise.
- ▶ **Anticoagulation choice:** LMWH/heparin in pregnancy because warfarin is teratogenic and crosses the placenta.
- ▶ **Antihypertensive choice:** methyldopa, labetalol, nifedipine; **never** ACE inhibitors/ARBs/MRAs.
- ▶ **Preconception medication review** is one of the highest-yield interventions to prevent malformation.

High-yield exam pointers

- ▶ ADME framework: pregnancy ↑ Vd, ↓ albumin (↑ free fraction), induces CYP3A4/2D6/2C9/UGT, ↑ GFR ~50% → net ↑ clearance / ↓ plasma levels of many drugs.
- ▶ **Lamotrigine** is the classic drug whose clearance rises markedly (UGT induction) — escalate dose, monitor monthly, **reduce postpartum**.
- ▶ Harrison: AED doses must often be increased due to increased clearance in pregnancy (monthly monitoring).
- ▶ **Organogenesis = 3–8 weeks** is the critical teratogenic window; *all-or-none* before, functional toxicity after.
- ▶ Memorise teratogens: ACEi/ARB, warfarin, valproate/phenytoin/carbamazepine, isotretinoin, thalidomide, lithium (Ebstein), methotrexate, tetracycline, NSAIDs (3rd-trimester ductus), aminoglycosides, DES.
- ▶ Safer choices: HTN → methyldopa/labetalol/nifedipine; anticoagulation → LMWH/heparin; epilepsy → lamotrigine/levetiracetam + 4 mg folate; hypothyroidism → levothyroxine ↑ ~30%.
- ▶ **Free drug**, not total, governs effect — monitor free phenytoin.
- ▶ FDA letter categories replaced by the PLLR narrative labelling; use registries and LactMed for lactation.
- ▶ Treat essential maternal disease — **untreated illness is often more dangerous than the drug**.

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — "Principles of Clinical Pharmacology" (ADME, bioavailability/first-pass, volume of distribution, clearance, half-life and steady state, protein binding and free-drug monitoring, CYP phase I/II metabolism, altered clearance in special populations).
- ▶ Harrison's *Principles of Internal Medicine*, 22e — "Medical Disorders During Pregnancy" (increased AED clearance and dose escalation, antiepileptic choice and folic acid, levothyroxine dose increase, infections and prescribing in pregnancy).
- ▶ CMDT 2026 — "Obstetrics & Obstetric Disorders" (Table 22–1 teratogenic/fetotoxic drugs; antihypertensives in pregnancy; ACEi/ARB/MRA contraindication; nausea/vomiting therapy; lactation/LactMed; vaccination in pregnancy).

Coverage note: The corpus does **not** provide a single consolidated account of pregnancy pharmacokinetics — Harrison details the general ADME/clinical-pharmacology principles and gives pregnancy-specific clearance data only for antiepileptics, while CMDT supplies the teratogen list and disease-specific drug choices. The quantitative physiological changes of pregnancy (plasma-volume +40–50%, GFR +50%, specific CYP induction/inhibition, +8 L body water) and the gestational-timing/all-or-none framework are stated here as **universally accepted standard internal-medicine pharmacology**, applied to the general PK principles that Harrison does cover. The FDA A/B/C/D/X categories and their replacement by the PLLR are standard regulatory knowledge not found verbatim in the corpus.



Preoperative cardiac risk assessment

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

Definition / Introduction — Perioperative cardiac risk assessment is the individualized, stepwise evaluation of a patient scheduled for **noncardiac surgery** to estimate the probability of **major adverse cardiovascular events (MACE)** — myocardial infarction (MI), pulmonary edema, ventricular fibrillation/cardiac arrest, complete heart block and cardiac death — and to guide risk-reduction strategies. Cardiovascular complications remain a leading cause of perioperative morbidity and mortality. The contemporary approach (ACC/AHA 2024 and ESC 2022 guidelines) integrates **surgical urgency, active cardiac conditions, validated risk indices, functional capacity, cardiac biomarkers and selective noninvasive testing**, with the primary aim of detecting clinical cardiovascular instability rather than indiscriminate testing.

Initial Clinical Evaluation and Surgical Urgency

- ▶ **History and physical examination** with a **12-lead resting ECG** form the foundation; standardized preoperative questionnaires (age, anticoagulant use, prior MI/angina/heart failure/arrhythmia, renal disease, diabetes, orthopnea) identify intermediate- and high-risk patients needing detailed evaluation.

- ▶ History should focus on **occult cardiac or pulmonary disease**; examination should look for signs of failure (*raised JVP, S3 gallop, bilateral rales*) and significant murmurs (especially **aortic stenosis**).
- ▶ **Determine surgical urgency first**: a true **emergency** procedure proceeds without further risk stratification (risk is unavoidably higher); medical optimization and surveillance continue postoperatively.
- ▶ Screen for **active/unstable cardiac conditions** that mandate evaluation and treatment *before* elective surgery: **acute coronary syndrome (ACS)**, decompensated heart failure, severe symptomatic valvular disease (especially aortic stenosis), and uncontrolled symptomatic arrhythmias. Patients with ACS are managed with goal-directed therapy before any preoperative assessment proceeds.
- ▶ Routine preoperative laboratory testing is **not** required in healthy patients undergoing elective low-risk procedures; tests are ordered only for specific clinical indications.

Estimating Risk: Surgery-Specific Risk and Validated Risk Indices

- ▶ Perioperative risk is a **combination of surgical (procedure-specific) and clinical (patient-specific) risk**, dichotomized into **low (<1%)** versus **elevated (≥1%)** risk of MACE.

Surgical risk gradient	Procedures
Higher	Emergent major operations (especially elderly); aortic and other non-carotid major vascular surgery; prolonged surgery with large fluid shifts/blood loss
Intermediate	Major thoracic or abdominal surgery; carotid endarterectomy; head/neck; orthopedic; prostate surgery
Lower	Eye (e.g., cataract), skin and superficial surgery; endoscopic procedures

- ▶ The **Revised Cardiac Risk Index (RCRI, Lee et al., 1999)** is the favored index for its accuracy and simplicity — six predictors, one point each:

RCRI predictor (1 point each)	Defining features
High-risk surgery	Intraperitoneal, intrathoracic, or suprainguinal vascular surgery (except carotid endarterectomy)
Ischemic heart disease	Prior MI, current ischemic angina, sublingual nitrate use, positive exercise test, pathological Q waves, prior PCI/CABG with current angina
Congestive heart failure	History of pulmonary edema or paroxysmal nocturnal dyspnea, S3 gallop, bilateral rales, pulmonary edema on chest x-ray
Cerebrovascular disease	History of TIA or stroke
Diabetes mellitus	Preoperative treatment with insulin
Chronic renal insufficiency	Serum creatinine >2 mg/dL (>176.8 μmol/L)

- ▶ **Estimated rates of major cardiac events**: 0 points ≈ **0.4%**, 1 point ≈ **0.9–1.3%**, 2 points ≈ **6–7%**, ≥3 points ≈ **11%** (derivation cohort); pooled external validation gives 0.4%, 1%, 2.4% and 5.4%

respectively. Patients with ≥ 3 predictors are very high risk ($\geq 11\%$) and benefit most from further stratification or avoidance of surgery.

- ▶ "Elevated risk" (ACC/AHA) = ≥ 2 RCRI predictors or calculated risk of perioperative MI/cardiac arrest $> 1\%$.
- ▶ Other validated tools:

Tool	Key inputs / remarks
Goldman multifactorial index (1977)	Original 9-variable index (age > 70 , recent MI, S3/JVD, arrhythmia, aortic stenosis, emergency/major surgery) — historical
NSQIP MICA calculator (Gupta, 2011)	Age, ASA class, functional dependence, creatinine, procedure type — predicts 30-day MI/cardiac arrest
ACS-NSQIP universal surgical risk calculator (Bilimoria, 2013)	21 preoperative variables; best overall discrimination
SORT (Surgical Outcome Risk Tool)	ASA-PS grade, urgency, severity of surgery, malignancy, age > 65
AUB-HAS2 index	Heart disease, Angina/dyspnea Symptoms, Age ≥ 75 , Hemoglobin < 12 , vascular Surgery, emergency Surgery — predicts 30-day death/MI/stroke; outperformed RCRI in validation
ASA-PS classification	P1 (normal healthy) $\rightarrow$ P6 (brain-dead organ donor); component of several calculators

Functional Capacity Assessment

- ▶ Functional capacity is expressed in **metabolic equivalents (METs)**. **Poor exercise tolerance** = inability to walk **four blocks** or climb **two flights of stairs** at normal pace, or failure to achieve 4 METs (e.g., carrying 15–20 lb, golf, doubles tennis) because of dyspnea, angina or fatigue.
- ▶ Patients with **moderate or better** (≥ 4 METs) capacity (climbing a flight of stairs, walking up a hill, walking on level ground at 4 mph) generally need **no further cardiac testing** before elective surgery.
- ▶ *Subjective clinician estimates of capacity are unreliable* (METS study); the structured **Duke Activity Status Index (DASI)** is the advocated instrument — a 12-item questionnaire (estimated METs = $[DASI \times 0.43 + 9.6]/3.5$); a **DASI score ≥ 34** $\rightarrow$ **proceed to surgery**.
- ▶ **Cardiopulmonary exercise testing (CPET)**: an anaerobic threshold of approximately **10 mL O₂/kg/min** (range 9.9–11) discriminates patients at higher perioperative risk; used for "prehabilitation" planning and shared decision-making.

Cardiac Biomarkers

- ▶ BNP/NT-proBNP measurement is recommended (ACC/AHA 2024) in patients with **both elevated calculated risk and poor/unknown functional capacity**.
- ▶ Normal values — BNP < 92 ng/L or NT-proBNP < 300 ng/L — **imply acceptable cardiac risk**; no further risk-stratification testing is needed. Levels above these thresholds carry a **fourfold increase in 30-day death/MI** (meta-analysis); in the VISION cohort, preoperative NT-proBNP correlated directly with vascular death and myocardial injury.

- ▶ Preoperative **troponin** elevation predicts 30-day mortality; Canadian/European guidelines also advocate **routine postoperative troponin surveillance in high-risk patients**.

Noninvasive Testing and Coronary Angiography

- ▶ There is **no role for routine preoperative stress testing**; testing is reserved for patients with **poor** (<4 METs) or **unknown functional capacity** in whom results would **change management**.
- ▶ Options: **dobutamine stress echocardiography** or **myocardial perfusion imaging** with vasodilator stress (dipyridamole, adenosine or regadenoson) using thallium-201/technetium-99m; **coronary CT angiography (CCTA)** improves prognostication over RCRI but without proven outcome benefit.
- ▶ The 2024 guideline emphasis: ischemia testing is performed primarily to **exclude high-risk coronary anatomy** (left main or multivessel CAD with reduced EF), not to detect any CAD.
- ▶ **Prophylactic coronary revascularization** (CABG/PCI) purely to "get the patient through surgery" is **not recommended** — the CARP trial showed no perioperative or long-term benefit (left main disease excluded). Revascularize only for guideline-concordant indications independent of surgery.

Stepwise Algorithm for Perioperative Cardiac Risk Assessment (ACC/AHA-based)

- ▶ **Step 1 — Urgency:** Emergency surgery → **proceed to surgery** with medical optimization, intra-/postoperative surveillance; no further preoperative testing.
- ▶ **Step 2 — Active cardiac conditions:** Evidence of ACS, decompensated HF, severe symptomatic valvular disease, unstable arrhythmia → **treat per guideline-directed therapy first**; multidisciplinary (cardiology–anesthesia–surgery) discussion. Severe valve disease, severe pulmonary hypertension, CIEDs, congenital heart disease, recent stroke and severe frailty warrant condition-specific evaluation regardless of calculated score.
- ▶ **Step 3 — Estimate combined risk with RCRI or NSQIP MICA:** if <1% MACE risk / <2 RCRI predictors (or low-risk surgery such as cataract or endoscopy) → **proceed to surgery**.
- ▶ **Step 4 — Functional capacity:** elevated risk but ≥4 METs (DASI ≥34) → **proceed to surgery**.
- ▶ **Step 5 — Biomarkers:** poor/unknown capacity → measure BNP/NT-proBNP; if BNP <92 ng/L / NT-proBNP <300 ng/L → **proceed**.
- ▶ **Step 6 — Abnormal biomarker → multidisciplinary discussion:** pharmacologic stress imaging or CCTA *only if results will alter management*; if **high-risk findings** (left main / multivessel CAD with reduced EF) → optimize guideline-directed therapy, revascularize only for independent indications, consider **alternative invasive/noninvasive or palliative management, deferral**, or proceed with informed knowledge of elevated risk.
- ▶ At every exit point, apply **perioperative medical risk reduction**:

Therapy	Perioperative recommendation
Beta-blockers	Continue if chronic; never start on the day of surgery ; consider initiation ≥1 week before surgery only in select high-risk patients (≥3 RCRI factors or intermediate/high-risk ischemia) — <i>POISE</i> : fixed high-dose metoprolol reduced MI but increased death and stroke

Therapy	Perioperative recommendation
Statins	Continue if chronic; initiate in vascular surgery patients and those with clinical indications (e.g., atorvastatin 20 mg daily)
ACE inhibitors/ARBs	Continue, or restart as soon as clinically feasible postoperatively
Aspirin	Continue only when cardiac risk outweighs bleeding risk; do not initiate de novo (POISE-2)
DAPT / coronary stents	Delay elective surgery ≥ 30 days after bare-metal stent, 6 months after DES (stable CAD)/elective PCI, 12 months after ACS (3 months acceptable if delay is risky, e.g., cancer surgery). Hold clopidogrel 5 days, prasugrel 7 days, ticagrelor 3–5 days; continue aspirin and restart P2Y ₁₂ inhibitor early
Alpha-2 agonists	Not recommended — clonidine increased hypotension and nonfatal cardiac arrest (POISE-2)
Calcium channel blockers	No evidence as prophylaxis
SGLT2 inhibitors	Stop 3–4 days before surgery (euglycemic ketoacidosis risk)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flowchart: stepwise perioperative cardiac risk algorithm.** Boxes top-to-bottom with exact labels: "Patient scheduled for noncardiac surgery" → branch 1 "Emergency surgery? — Yes → Proceed to surgery + postoperative surveillance"; branch "No" → "Acute coronary syndrome / unstable cardiac condition? — Yes → Guideline-directed evaluation and treatment first"; "No" → "Step 1: Estimate MACE risk (RCRI / NSQIP MICA)" → "<1% or <2 RCRI predictors → Proceed to surgery"; "Elevated risk" → "Step 2: Functional capacity ≥ 4 METs (DASI ≥ 34)? — Yes → Proceed"; "No/unknown" → "Step 3: BNP <92 ng/L or NT-proBNP <300 ng/L? — Yes → Proceed"; "Abnormal" → "Step 4: Multidisciplinary discussion $\pm$ stress imaging/CCTA (only if it changes management)" → "Step 5: High-risk CAD → optimize GDMT / revascularize for independent indication / alternative or palliative approach / proceed with known risk". Add a side box: "Perioperative medical therapy: continue beta-blocker and statin, continue/restart ACEi, aspirin individualized, stop SGLT2i 3–4 days".
- **Bar diagram of RCRI risk stratification:** x-axis "RCRI 0, 1, 2, ≥ 3 "; y-axis "cardiac event rate (%)" with bars labelled "0.4–0.5%, 0.9–1.3%, 6–7%, $\geq 11\%$ " and zones "Low / Intermediate / High risk".

Clinical / Diagnostic significance

- **Postoperative MI** typically occurs **within 3 days** of surgery and is usually **silent** — suspect it with unexplained hypotension, hypoxemia or delirium; even isolated troponin elevation predicts higher mortality.

- ▶ **Severe aortic stenosis:** symptomatic patients should undergo **valve intervention (SAVR/TAVI) first** if surgery can be deferred; asymptomatic severe AS with preserved EF can usually undergo low/intermediate-risk surgery safely; balloon valvotomy is only a bridge.
- ▶ **Heart failure** confers risk equal to or greater than CAD — postpone elective surgery until decompensation (raised JVP, S3, pulmonary edema) is controlled; echocardiography for unexplained dyspnea or clinical deterioration, not routinely.
- ▶ **Hypertension:** only severe BP (**>180/110 mmHg**) justifies considering deferral of elective surgery.
- ▶ **Recent MI:** highest risk within **30 days**; risk declines progressively thereafter — time-stratify surgery accordingly.
- ▶ Mechanism pearl: perioperative stress (tachycardia, hypercoagulability) causes both **type 1 MI (plaque rupture)** and the now-predominant **type 2 MI (supply-demand mismatch)** — explaining why fixed-stenosis testing misses many events.

High-yield exam pointers

- ▶ **RCRI six predictors:** high-risk surgery, ischemic heart disease, CHF, cerebrovascular disease, insulin-treated diabetes, creatinine >2 mg/dL — one point each; event rates $\approx 0.4 / 1 / 6-7 / \geq 11\%$ for 0/1/2/ ≥ 3 points.
- ▶ **Elevated risk** = ≥ 2 RCRI predictors or >1% calculated MACE; ≥ 3 **RCRI factors** = candidate for noninvasive testing/beta-blocker initiation.
- ▶ **4 METs rule:** able to climb a flight of stairs/walk up a hill → proceed without testing; **DASI ≥ 34** is the structured equivalent.
- ▶ **Biomarker gate:** BNP <92 ng/L or NT-proBNP <300 ng/L → acceptable risk, proceed.
- ▶ Stress testing only if **poor/unknown capacity AND results would change management**; goal is to exclude **left main/multivessel CAD**.
- ▶ **No prophylactic revascularization** (CARP trial); stent-to-surgery delays: BMS 30 days, DES 6 months (stable), 12 months after ACS.
- ▶ **Never start a beta-blocker on the day of surgery** (POISE); continue chronic beta-blockers and statins; stop **SGLT2 inhibitors 3–4 days** before.
- ▶ Emergency surgery bypasses the algorithm; ACS always trumps the operation.
- ▶ Postoperative MI is usually **painless, within 72 h** — screen high-risk patients with troponin.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — "Medical Evaluation of the Patient Undergoing Noncardiac Surgery" (stepwise algorithm, RCRI, functional status, surgical risk gradation, perioperative therapies) and "Approach to Medical Consultation"; Braunwald's Heart Disease — "Anesthesia and Noncardiac Surgery in Patients With Heart Disease" (2024 ACC/AHA and 2022 ESC algorithms, risk-calculator comparison, DASI, CPET, biomarker data); CMDT 2026 — "Preoperative Evaluation & Perioperative Management" (2024 ACC/AHA five-step approach, biomarker thresholds, perioperative drug management). ASA-PS classification per Harrison 22e table.



Hypersensitivity reactions

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

Definition / Introduction — *Hypersensitivity* denotes an exaggerated or inappropriate adaptive immune response to an antigen (allergen, autoantigen, drug, or microbial product) that results in host tissue injury rather than protective immunity. Harrison describes four immunopathologic mechanisms of immune injury — immediate (IgE-mediated) hypersensitivity, antibody-mediated cytotoxic reactions, immune-complex formation, and delayed-type hypersensitivity — which correspond to the classic **Gell and Coombs Types I–IV**. Types I–III are antibody-mediated and Type IV is T cell (cell)-mediated. A single disease may involve more than one mechanism, and the same effector pathway that normally clears antigen becomes pathogenic when antigen persists or tolerance fails.

Gell and Coombs classification — overview

Type	Synonym	Key immune reactant	Effector mechanism	Onset	Prototype disorders
I	Immediate / anaphylactic	IgE on mast cells/basophils	Allergen cross-links IgE → mediator release	Seconds–minutes (within ~12 h)	Anaphylaxis, allergic rhinitis, atopic asthma, urticaria
II	Cytotoxic	IgG/IgM vs cell-surface or matrix antigen	Complement (classic pathway) + Fc-mediated lysis/ADCC	Minutes–hours	Transfusion reaction, Goodpasture's, pemphigus vulgaris, AIHA
III	Immune-complex	Soluble Ag–Ab complexes (IgG/IgM)	Complex deposition → complement → neutrophil injury	Hours (3–10 h)	SLE, post-streptococcal glomerulonephritis, vasculitis, serum sickness
IV	Delayed / cell-mediated	TH1/TH17/CD8 T cells, macrophages	Cytokine-driven inflammation, no antibody	48–72 h	Tuberculin reaction, contact dermatitis, granulomatous disease

Type I — Immediate (IgE-mediated) hypersensitivity

- ▶ **Sensitisation:** *TH2*-type helper cells (and the *TFH13* subset) secreting IL-4, IL-5, IL-6, IL-10 (and IL-13) drive B-cell class-switching to IgE on first allergen exposure.
- ▶ **Effector cells:** Mast cells and basophils bear **high-affinity Fc receptors for IgE (FcεRI)**; cell-bound antiallergen IgE effectively "arms" these cells.
- ▶ **Trigger:** Re-exposure → allergen cross-links surface IgE → degranulation and mediator release.
- ▶ **Mediators** released fall into three functional groups (Harrison):
 - *Increase vascular permeability and contract smooth muscle:* **histamine, platelet-activating factor (PAF), SRS-A** (slow-reacting substance of anaphylaxis = leukotrienes), bradykinin.
 - *Chemotactic/activating for other inflammatory cells:* ECF-A (eosinophil chemotactic factor of anaphylaxis), NCF (neutrophil chemotactic factor), **leukotriene B4**.
 - *Modulate release of other mediators:* PAF, BK-A.
- ▶ **Clinical spectrum:** systemic **anaphylaxis** (hypotension, bronchospasm, angioedema), allergic rhinitis/conjunctivitis, atopic (extrinsic) asthma, urticaria–angioedema, food and drug allergy.
- ▶ A *late-phase* reaction (4–12 h) driven by recruited eosinophils and TH2 cells follows the immediate wheal-and-flare in many patients.

Type II — Antibody-mediated cytotoxic hypersensitivity

- ▶ **Mechanism:** Complement-fixing (C1-binding) antibodies — IgM, IgG1, IgG2, IgG3 — directed against antigens on *normal or foreign cells/tissues* bind complement via the **classic pathway**, initiating a cascade (analogous to immune-complex injury) that culminates in **cell lysis or tissue injury** (membrane-attack complex) and Fc-mediated opsonophagocytosis/ADCC.
- ▶ **Three sub-patterns** (standard immunology): (a) *complement/cell lysis*, (b) *opsonisation–phagocytosis*, (c) *antibody alters cell function* without destruction (receptor stimulation or blockade).
- ▶ **Examples cited in Harrison:**
 - **Red-cell lysis in transfusion reactions** (and autoimmune haemolytic anaemia, haemolytic disease of the newborn).
 - **Goodpasture's syndrome** — anti-glomerular basement membrane antibody against the **type IV collagen α3 chain**.
 - **Pemphigus vulgaris** — anti-epidermal (desmoglein) antibody inducing blistering skin disease.
- ▶ *Receptor-directed (functional) variants* — Graves' disease (stimulating anti-TSH-receptor Ab) and myasthenia gravis (blocking anti-AChR Ab) — are the classic "Type V/Type II functional" examples.

Type III — Immune-complex-mediated hypersensitivity

- ▶ **Mechanism:** After antigen exposure, soluble **antigen–antibody (immune) complexes** circulate; if **not cleared by the reticuloendothelial system**, they deposit in **blood-vessel walls** and in tissues such as **renal glomeruli**, activate complement, and recruit neutrophils → **vasculitis or glomerulonephritis**.

- ▶ **Determinants of injury:** the quantity and physicochemical properties (size, charge, antigen:antibody ratio) of complexes determine whether they are pathogenic; complexes formed in slight antigen excess deposit most readily.
- ▶ **Complement link:** deficiencies of early classic-pathway components (C1q, C1r/s, C4, C2) cause *inefficient clearance of immune complexes*, predisposing to immune-complex-mediated autoimmune syndromes — **SLE and SLE-like syndromes, glomerulonephritis, and vasculitis** (Harrison Table 360-12).
- ▶ **Clinical examples:** systemic lupus erythematosus, post-streptococcal/membranoproliferative glomerulonephritis, cryoglobulinaemic and other small-vessel vasculitides, serum sickness, and the local *Arthus reaction*.

Type IV — Delayed-type (cell-mediated) hypersensitivity

- ▶ **Definition (Harrison):** inflammatory reactions **initiated by mononuclear leukocytes, not by antibody alone**; "delayed" because the secondary cellular response appears 48–72 h after antigen exposure, versus the <12 h immediate response.
- ▶ **Effector axis:** antigen processed by DCs → presented to CD4⁺ T cells; IL-12 from APCs induces IFN-γ (TH1 response). Classic DTH is centred on IFN-γ-, IL-2-, and TNF-α-secreting TH1 cells and macrophages; NK cells contribute to contact hypersensitivity.
- ▶ **Granuloma formation:** under sustained IFN-γ, macrophages undergo **epithelioid transformation and fuse into multinucleated giant cells** → **granulomatous inflammation**.
- ▶ **Prototype test:** intradermal **tuberculin purified protein derivative (PPD)** in a previously *M. tuberculosis*-exposed host produces an **indurated area at 48–72 h**.
- ▶ **DTH-driven diseases (Harrison):** fungal (histoplasmosis), mycobacterial (**tuberculosis, leprosy**), chlamydial (lymphogranuloma venereum), helminthic (schistosomiasis), toxin (berylliosis), and **hypersensitivity pneumonitis** (organic dusts); DTH also drives tissue damage in **rheumatoid arthritis, temporal arteritis, and granulomatosis with polyangiitis**, and underlies **allergic contact dermatitis**.

Type IV subtype	Dominant T cell / effector	Example
IVa	TH1 + macrophage (IFN-γ)	Tuberculin reaction, granuloma, contact dermatitis
IVb	TH2 + eosinophil	Chronic asthma, DRESS
IVc	Cytotoxic CD8 ⁺ T cell	Stevens-Johnson syndrome / TEN, contact dermatitis
IVd	T cell + neutrophil	Acute generalised exanthematous pustulosis (AGEP), Behçet

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Four-panel Gell-Coombs schematic** (one box per type). Labels: *Type I* — allergen, IgE, FcεRI, mast cell, granules (histamine/leukotrienes/PAF); *Type II* — target cell-surface antigen, IgG/IgM, complement (C1→MAC), phagocyte (Fc receptor); *Type III* — soluble antigen + antibody → immune complex, deposition in vessel wall/glomerulus, complement, neutrophil; *Type IV* — antigen-presenting cell, CD4⁺ TH1 cell, IFN-γ/IL-2/TNF-α, macrophage → epithelioid/giant cell granuloma.
- ▶ **Time-course line graph** of skin reaction: x-axis = hours after challenge; label *immediate wheal-and-flare (minutes, Type I)*, *late-phase (4–12 h)*, and *delayed induration (48–72 h, Type IV / tuberculin)*.

Clinical / Diagnostic significance

- ▶ **Mechanism guides diagnosis:** serum tryptase and skin-prick/specific-IgE testing for Type I; direct/indirect Coombs (antiglobulin) test and tissue immunofluorescence for Type II; complement (low C3/C4), ANA/anti-dsDNA, cryoglobulins and immune-complex glomerular deposits for Type III; **patch testing** and the **tuberculin/IGRA** read at 48–72 h for Type IV.
- ▶ **Mechanism guides therapy:** Type I — adrenaline (first-line for anaphylaxis), H1-antihistamines, glucocorticoids, allergen avoidance/immunotherapy, anti-IgE (omalizumab); Types II/III — glucocorticoids, plasma exchange, rituximab/cytotoxic agents, IVIg for selected immune-complex disease; Type IV — topical/systemic glucocorticoids, calcineurin inhibitors, and avoidance of the contact/drug allergen.
- ▶ **Tolerance failure is the upstream lesion:** breakdown of **central (AIRE-dependent thymic)** and **peripheral (Treg/anergy) tolerance** converts physiologic responses into autoimmune Type II/III/IV disease (Harrison Ch 361). Environmental triggers — drugs (**procainamide, phenytoin** → **drug-induced lupus**), infections (EBV), and loss of Treg cells — precipitate disease in genetically susceptible hosts (e.g., **HLA-B27**).
- ▶ **Severe cutaneous adverse reactions** (SJS/TEN, DRESS, AGEP) are T cell-mediated (Type IV) drug hypersensitivities and demand immediate drug withdrawal.

High-yield exam pointers

- ▶ **Types I–III are antibody-mediated; Type IV is T cell-mediated** — the single most testable contrast.
- ▶ **Type I onset within ~12 h vs Type IV induration at 48–72 h** — memorise the tuberculin timing.
- ▶ Type I effector = **mast cell + FcεRI + IgE**; key mediators histamine, **SRS-A (leukotrienes)**, PAF, ECF-A.
- ▶ Type II antibodies that fix complement = **IgM, IgG1, IgG2, IgG3**; triad of examples — **transfusion reaction, Goodpasture's (anti-type IV collagen α3), pemphigus vulgaris**.
- ▶ Type III injury site = **vessel walls and renal glomeruli**; **early complement deficiency (C1q, C4, C2) → poor clearance → SLE/immune-complex disease**.
- ▶ Type IV hallmark = **granulomatous inflammation** (epithelioid + multinucleated giant cells, IFN-γ-driven); seen in TB, leprosy, sarcoid-type reactions, contact dermatitis.

- ▶ **Adrenaline is the first-line drug for Type I anaphylaxis** — not antihistamines.
- ▶ **Procainamide and phenytoin** are classic causes of drug-induced lupus (immune-complex/Type III autoimmunity).

SOURCE & COVERAGE

Harrison 22e — Ch 360 "Introduction to the Immune System" (Immediate-Type Hypersensitivity, Cytotoxic Reactions of Antibody, Immune-Complex Formation, Delayed-Type Hypersensitivity Reactions; Table 360-12) + Ch 361 "Mechanisms of Regulation and Dysregulation of the Immune System" (tolerance, Treg, autoimmunity). **Coverage note (spec gap = true):** Harrison describes the four immune-injury mechanisms but does **not** use the eponym "*Gell and Coombs*" nor the explicit numbered labels *Type I–IV*; this universally accepted immunology framework has been mapped onto Harrison's named mechanisms. The **Type IV sub-classification (IVa–d)**, the **Type II sub-patterns / functional "Type V"** (Graves', myasthenia gravis), the **Arthus/serum-sickness** examples, and specific **diagnostic test and drug-dose** details are standard textbook internal medicine added for completeness and are not verbatim in the provided chapters.



Inherited mitochondrial disorders in adults

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

Definition / Introduction — Mitochondrial disorders are a clinically and genetically heterogeneous group of multisystem diseases caused by defective **oxidative phosphorylation (OXPHOS)**, arising from mutations in either the **mitochondrial genome (mtDNA)** or the **nuclear genome (nDNA)**. Because mitochondria generate ATP in virtually every nucleated cell, any organ can be affected, but high-energy tissues — brain, eye, skeletal and cardiac muscle, endocrine glands, kidney and liver — dominate the picture. The term *inherited mitochondrial disorders* in adults principally denotes the **maternally transmitted mtDNA diseases** (e.g., LHON, MELAS, MERRF) plus nuclear-encoded disorders that secondarily destabilise mtDNA (e.g., POLG-related PEO, MNGIE). Many present for the first time in adolescence/adulthood, or are childhood diseases surviving into adult life.

Mitochondrial genome and unique genetic principles

- ▶ **mtDNA structure:** a circular, double-stranded molecule of **16,569 nucleotides** containing **37 genes** — **13** encode protein subunits of the ETC, **22** encode tRNAs and **2** encode rRNAs (12S, 16S). The non-coding **control region (D-loop)** governs replication/transcription.
- ▶ **Division of labour:** mtDNA encodes only 13 of the ~89 respiratory-chain subunits — **Complex I** (7: ND1, 2, 3, 4, 4L, 5, 6), **Complex III** (1: cytochrome *b*), **Complex IV/COX** (3: COX1, 2, 3) and **Complex V** (2: ATPase 6, 8). **Complex II (SDH), CoQ10 and cytochrome c are entirely nuclear-encoded** — hence SDH staining serves as an internal control. ~1500 nuclear genes support mitochondrial biogenesis; mtDNA is replicated by nuclear-encoded **polymerase-γ (POLG)**.
- ▶ **Maternal inheritance:** mtDNA is transmitted exclusively through the **ovum**; sperm mitochondria are degraded. Affected **mothers transmit to all offspring of both sexes, but only**

daughters transmit onward; an affected father never transmits — paternal transmission virtually excludes an mtDNA disorder.

- ▶ **Heteroplasmy & homoplasmy**: each cell carries hundreds–thousands of mtDNA copies. Coexistence of mutant and wild-type mtDNA = **heteroplasmy**; uniformity = **homoplasmy**. Pathogenic mutations are usually heteroplasmic (LHON and m.1555A>G deafness are homoplasmic exceptions).
- ▶ **Threshold effect**: disease appears only when mutant load exceeds a critical level (typically 70–90%), and the threshold is lower in oxidative-dependent tissues (brain, eye, heart, muscle).
- ▶ **Mitotic segregation & the bottleneck**: random partition of mtDNA at cell division shifts heteroplasmy across tissues and with age (clonal expansion), explaining variable, age-dependent penetrance and intrafamilial variability. A **germline bottleneck** during oogenesis produces large, unpredictable shifts in mutant load between mother and child.
- ▶ **Nuclear (Mendelian) mtDNA disorders**: mutations in nuclear maintenance genes (POLG, Twinkle/PEO1, ANT1, TYMP) cause **multiple mtDNA deletions or depletion**, inherited autosomal dominant/recessive.

Classic mtDNA syndromes affecting adults

Syndrome	Cardinal features	Commonest mutation (gene)	Genetics
LHON (Leber hereditary optic neuropathy)	Subacute, painless, sequential central visual loss in young men	m.11778G>A (<i>ND4</i> , ~69%), m.14484T>C (<i>ND6</i>), m.3460G>A (<i>ND1</i>) — Complex I	Homoplasmic , maternal; M:F ≈ 8:1
MELAS	Stroke-like episodes <40 y, encephalopathy (seizures/dementia), lactic acidosis, migraine, short stature, deafness, diabetes	m.3243A>G (<i>MT-TL1</i> , tRNA-Leu, ~80%); m.3271T>C (~10%)	Heteroplasmic, maternal
MERRF	Myoclonus , epilepsy, cerebellar ataxia, myopathy with ragged-red fibres , deafness, lipomas	m.8344A>G (<i>MT-TK1</i> , tRNA-Lys, ~80–90%)	Heteroplasmic, maternal
NARP / MILS	Neuropathy, ataxia, retinitis pigmentosa ; >90% load → maternally inherited Leigh syndrome	m.8993T>G (<i>MT-ATP6</i> , Complex V)	Heteroplasmic, maternal
CPEO	Late bilateral ptosis + ophthalmoplegia , proximal myopathy, exercise intolerance	Single large-scale deletion/duplication	Mostly sporadic (somatic)
Kearns-Sayre syndrome	Triad: PEO + onset <20 y + pigmentary retinopathy ; plus cardiac conduction block , ataxia, CSF protein >100 mg/dL, short stature, diabetes	Single large deletion (4977-bp "common deletion")	Sporadic
Pearson syndrome	Infantile sideroblastic anaemia + pancytopenia + exocrine pancreatic insufficiency + lactic acidosis ; survivors evolve to KSS	Large single deletion	Sporadic

Syndrome	Cardinal features	Commonest mutation (gene)	Genetics
MIDD	Maternally inherited diabetes + sensorineural deafness	m.3243A>G	Maternal
Aminoglycoside / non-syndromic deafness	Sensorineural hearing loss, precipitated by aminoglycosides (<i>ecogenetic</i>)	m.1555A>G (12S rRNA)	Homoplasmic, maternal (1:500)

- ▶ **MNGIE** (mitochondrial neurogastrointestinal encephalomyopathy): an **autosomal-recessive** (nuclear) disorder of the **thymidine phosphorylase gene** (TYMP/ECGF1) causing secondary multiple mtDNA deletions/depletion — ptosis, PEO, severe **GI dysmotility with pseudo-obstruction**, cachexia, peripheral neuropathy and **leukoencephalopathy**; onset in late teens, death usually before 40. Diagnosed by low leukocyte thymidine phosphorylase and raised **plasma thymidine and deoxyuridine**.
- ▶ **POLG-related disease**: adPEO/arPEO, **SANDO** (sensory ataxic neuropathy, dysarthria, ophthalmoplegia), parkinsonism and Alpers syndrome — **valproate is contraindicated** (risk of fatal hepatic failure).
- ▶ **Other nuclear "dynamics" genes**: *MFN2* → Charcot-Marie-Tooth type 2; *OPA1* → dominant optic atrophy with deafness/neuropathy.

Clinical features by organ system

- ▶ **CNS**: stroke-like episodes, seizures, myoclonus, migraine, cerebellar ataxia, dystonia, parkinsonism, cognitive decline/dementia, sensorineural deafness, optic atrophy.
- ▶ **Peripheral nerve**: length-dependent sensorimotor or autonomic polyneuropathy.
- ▶ **Skeletal muscle (mitochondrial myopathy)**: ptosis, external ophthalmoplegia, exercise intolerance, myalgia, proximal weakness, rhabdomyolysis/myoglobinuria.
- ▶ **Cardiac: conduction block** (especially KSS — may need pacemaker), hypertrophic then dilated cardiomyopathy, Wolff-Parkinson-White pre-excitation (with m.3243A>G).
- ▶ **Endocrine**: diabetes mellitus, short stature, hypothyroidism, hypoparathyroidism, hypogonadism, premature ovarian failure.
- ▶ **Ophthalmic**: pigmentary ("salt-and-pepper") retinopathy, cataract, optic atrophy, ophthalmoplegia.
- ▶ **GI / hepatic / renal**: dysphagia, gastroparesis, pseudo-obstruction, pancreatitis; hepatopathy; renal tubular acidosis / **Fanconi syndrome**.

Investigation of suspected mtDNA disease

- ▶ **Biochemistry**: blood and CSF **lactate** (CSF lactate more specific with CNS disease), **lactate-to-pyruvate ratio** (>20 suggests an OXPHOS defect; <20 suggests pyruvate dehydrogenase defect), CK (often normal/mildly raised), plasma/urine amino acids, urinary organic acids (TCA intermediates), plasma acylcarnitines, and **GDF-15** (sensitive/specific serum marker of mitochondrial myopathy).
- ▶ **Neuroimaging**: MRI — MELAS shows cortical stroke-like lesions in **posterior cerebrum that do not respect vascular territories**, sparing white matter; Leigh syndrome shows symmetrical

T2/FLAIR signal in **basal ganglia (putamen), globus pallidus and brainstem**; basal-ganglia calcification on CT; **MR spectroscopy** detects a lactate peak.

- ▶ **Cardiac/other:** ECG and echocardiography (conduction defects, cardiomyopathy); EMG/NCS; audiometry; ophthalmology/ERG.
- ▶ **Muscle biopsy:** **ragged-red fibres** on modified Gomori trichrome (subsarcolemmal mitochondrial accumulation), intensely "**ragged-blue**" fibres on SDH stain, scattered **COX-negative fibres**, and **paracrystalline "parking-lot" inclusions** on electron microscopy. RRFs are absent in NARP/MILS and LHON.
- ▶ **Molecular genetics (now first-line):** targeted PCR/RFLP for common point mutations (3243, 8344, 8993, 11778/14484/3460); whole **mtDNA next-generation sequencing**; **long-range PCR / Southern blot** for deletions; nuclear gene panels and **WES/WGS**. Because heteroplasmy varies between tissues, a **negative blood test (e.g., m.3243A>G load falls in blood with age)** should **prompt urine sediment or skeletal-muscle testing**; deletions are best detected in muscle.

Management

- ▶ **General:** no curative therapy — multidisciplinary, largely **supportive and surveillance-based**. Aggressively treat seizures (recognise subtle/subclinical seizures in MELAS), cardiac conduction disease (**pacemaker/ICD in KSS**), diabetes, endocrinopathy, dysphagia/PEG feeding, ptosis (props/surgery), cataract, and hearing loss (aids, **cochlear implant**).
- ▶ **Cofactors/vitamins (limited evidence):** **CoQ10** (up to ~200 mg three times daily; clearly beneficial in primary CoQ10 deficiency), riboflavin, **L-carnitine**, creatine, α -lipoic acid, vitamins C/E; **idebenone** (a CoQ analogue) is approved (EMA) for LHON.
- ▶ **Disease-specific:** **L-arginine / L-citrulline** (NO precursors) for MELAS stroke-like episodes (acute and prophylactic); **folinic acid** for CSF folate deficiency; **dichloroacetate (DCA)** lowers lactate but causes peripheral neuropathy; **allogeneic haematopoietic stem-cell / bone-marrow transplantation** to restore thymidine phosphorylase in MNGIE.
- ▶ **Drugs to avoid:** **valproate** (especially with *POLG* mutations), **aminoglycosides** in m.1555A>G carriers, propofol/barbiturates, and **metformin/statins** caution (lactic acidosis); strongly advise **LHON carriers to avoid tobacco and alcohol** (penetrance reaches ~93% in male smokers).
- ▶ **Reproductive options:** genetic counselling is difficult because the bottleneck makes transmitted load unpredictable; **prenatal/preimplantation diagnosis is reliable only for NARP m.8993T>G**. Options include **oocyte donation**, PGD, and **mitochondrial replacement therapy (MRT)** — *maternal spindle transfer* or *pronuclear transfer* into a donor egg (licensed in the UK).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Circular mtDNA map (16,569 bp):** draw the circle showing the **D-loop / control region**, the two rRNAs (12S, 16S), and the disease-linked loci — *ND1/ND4/ND6* (LHON), *MT-TL1/tRNA-Leu* position 3243 (MELAS), *MT-TK1/tRNA-Lys* position 8344 (MERRF), *MT-ATP6* position 8993 (NARP/MILS), 12S rRNA 1555 (aminoglycoside deafness) and the "**common deletion**" (4977 bp) region. Label: heavy/light strands, OXPHOS complexes I, III, IV, V encoded.
- ▶ **Diagram 2 — Respiratory chain & heteroplasmy threshold:** Complexes I→II→CoQ10→III→cytochrome c→IV→V across the inner membrane with H⁺ pumping and ATP synthesis; alongside, a bar showing **wild-type vs mutant mtDNA** with a marked "**threshold (70–90%)**" above which disease is expressed.

Clinical / Diagnostic significance

- ▶ Consider mitochondrial disease in any **unexplained progressive multisystem disorder**, particularly combinations that "don't fit" a single nuclear gene — e.g., diabetes + deafness, stroke + lactic acidosis, ptosis + cardiac block + retinopathy.
- ▶ A **stroke not conforming to a vascular territory** in a young adult with lactic acidosis is MELAS until proven otherwise.
- ▶ **Ragged-red fibres are neither universal nor specific** (also seen in inclusion-body myositis, ageing, zidovudine myopathy) — interpret with COX/SDH histochemistry and genetics.
- ▶ Genetic diagnosis directs **counselling, cascade testing and reproductive planning**, and flags **drug avoidances** (valproate, aminoglycosides).

High-yield exam pointers

- ▶ mtDNA = 16,569 bp, 37 genes (13 protein, 22 tRNA, 2 rRNA); **strict maternal inheritance, no recombination, heteroplasmy, threshold effect.**
- ▶ LHON = homoplasmic Complex I point mutations (11778/14484/3460), young men, painless central vision loss; idebenone; avoid tobacco/alcohol.
- ▶ MELAS = m.3243A>G (tRNA-Leu); diagnostic triad: stroke-like episode <40 y + encephalopathy + lactic acidosis/RRF; treat with **L-arginine**.
- ▶ MERRF = m.8344A>G (tRNA-Lys); myoclonus + epilepsy + ataxia + RRF + lipomas.
- ▶ NARP/MILS = m.8993T>G (ATPase 6); >90% load → Leigh syndrome; the **one mutation with reliable prenatal diagnosis**.
- ▶ KSS = single large mtDNA deletion (**4977-bp common deletion**); PEO + onset <20 + retinopathy + heart block (**pacemaker**); CSF protein >100.
- ▶ MNGIE = autosomal-recessive TYMP defect; PEO + GI pseudo-obstruction + neuropathy + leukoencephalopathy; ↑ plasma thymidine; allogeneic SCT.
- ▶ m.1555A>G 12S-rRNA = aminoglycoside-induced ototoxic deafness (**ecogenetic** — avoid aminoglycosides).
- ▶ **Lactate:pyruvate >20** = OXPHOS defect; muscle = **ragged-red** (Gomori), **ragged-blue** (SDH), **COX-negative fibres, paracrystalline inclusions**.

- ▶ **Avoid valproate in POLG disease;** therapy is supportive; MRT (**spindle/pronuclear transfer**) prevents transmission.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Mitochondrial DNA and Heritable Traits and Diseases" (Skorecki & Cohen).
- ▶ **Bradley and Daroff's Neurology in Clinical Practice, 8e** — Chapter "Mitochondrial Disorders" (Turner, Pitceathly & Schapira), used for the adult syndrome spectrum (CPEO/KSS, MNGIE, POLG/SANDO), muscle-biopsy histochemistry, the diagnostic algorithm and management.
- ▶ *Coverage note:* CMDT has no dedicated chapter on inherited mitochondrial disease; current-management details (CoQ10/idebenone doses, L-arginine, MRT, allogeneic SCT for MNGIE) are drawn from the two texts above and reflect universally accepted internal-medicine practice.



Limbic system

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

Definition / Introduction — The **limbic system** is a phylogenetically ancient, ring-like ("limbus" = border) network of cortical and subcortical structures encircling the corpus callosum and upper brainstem, formed of **limbic cortex** (hippocampus, amygdala, entorhinal cortex), **paralimbic cortex** (cingulate gyrus, insula, temporopolar and orbitofrontal cortex), the **anterior and medial thalamic nuclei**, the **medial/basal striatum and basal forebrain**, and the **hypothalamus**. It integrates **emotion, motivation, autonomic and endocrine tone, olfaction, and declarative (explicit) memory**, and is the substrate of amnesia, temporal-lobe epilepsy and limbic encephalitis.

Components and gross anatomy

- ▶ **Limbic cortex (core)** — *hippocampal formation* (archicortex: hippocampus proper/cornu ammonis, dentate gyrus, subiculum), *amygdala* (housed in the **uncus** of the medial temporal lobe), and *entorhinal cortex* — the gateway for cortical input into the hippocampus.
- ▶ **Paralimbic (mesocortical) belt** — *cingulate gyrus, parahippocampal gyrus, insula, temporopolar and orbitofrontal cortex*. The cingulate gyrus sweeps around the splenium of the corpus callosum and **blends into the parahippocampal gyrus**, forming a continuous limbic lobe (pericallosal + mesial-temporal + insular + orbital cortex of *Broca*).
- ▶ **Olfactory structures** — olfactory bulb/tract, anterior perforated substance and primary olfactory (paleo)cortex; olfaction is the only sensory modality reaching cortex without an obligatory thalamic relay.
- ▶ **Subcortical relays** — *fornix* (efferent hippocampal tract), *mammillary bodies* (hypothalamus), *anterior and mediodorsal thalamic nuclei, septal nuclei and nucleus basalis of Meynert* (basal forebrain, cholinergic), *retrosplenial cortex* and the *cingulum bundle*.

- ▶ **Diencephalic hub** — the *hypothalamus* links the system to homeostasis, the autonomic nervous system and the pituitary (neuroendocrine output).

The Papez circuit (memory loop)

- ▶ Originally proposed by **James Papez (1937)** as the anatomical substrate of *emotion*; in modern usage it is the **posterior limbic circuit for explicit (declarative) memory**.
- ▶ Closed reverberating loop:

Hippocampus → fornix → mammillary body → mammillothalamic tract (of Vicq d'Azyr) → anterior thalamic nucleus → cingulate gyrus (via internal capsule) → cingulum → parahippocampal/entorhinal cortex → back to hippocampus.

- ▶ The *mediodorsal thalamic nucleus*, *retrosplenial cortex* (an alternative hippocampo-thalamic route) and *basal forebrain* are functionally integral; bilateral damage to **any node** of this circuit produces amnesia.

Functional organisation

Functional division	Key structures	Behaviour subserved	Disease correlate
Anterior (emotional-affiliative)	Amygdala, anterior paralimbic/orbitofrontal cortex (overlaps <i>salience network</i>)	Emotion, motivation, fear, autonomic tone, endocrine drive	Temporal-lobe epilepsy; behavioural-variant FTD
Posterior (mnemonic) = Papez circuit	Hippocampus, entorhinal cortex, posterior paralimbic cortex, limbic thalamic nuclei	Declarative memory for recent episodes/experiences	Amnesic state; Alzheimer's disease
Olfactory	Olfactory bulb/tract, piriform cortex, amygdala, entorhinal cortex	Smell perception and its emotional/memory linkage	Uncinate fits (olfactory hallucinations)
Homeostatic	Hypothalamus, mammillary bodies, septal nuclei	Autonomic, neuroendocrine, feeding, sexual, rage/defence	Wernicke-Korsakoff; septal rage

- ▶ **Amygdala** — assigns emotional (especially *fearful*) salience to stimuli and tags emotionally charged events for stronger memory; bilateral lesions impair recognition of fear in faces.
- ▶ **Anterior cingulate cortex** — modulates autonomic activity, emotional response selection and the affective component of pain; part of the *rostral limbic system* (with periaqueductal grey, ventral striatum, orbitofrontal and anterior insular cortex). Bilateral lesions cause **akinetism**; cingulotomy is used for intractable pain/OCD.
- ▶ **Hippocampus** — encodes new declarative memories and spatial maps (*place cells*); damage spares previously consolidated remote memories and **implicit/procedural learning**.

Major connections and neurochemistry

- ▶ **Afferents** — all sensory association cortices funnel into limbic cortex via the entorhinal cortex; the *perirhinal cortex* relays visual/object information and the *parahippocampal cortex* relays spatial (dorsal-stream) information to the hippocampus.

- ▶ **Principal efferent tracts** — the **fornix** (hippocampus → mammillary body/septum), the **mammillothalamic tract** (mammillary body → anterior thalamus), the **stria terminalis** and **ventral amygdalofugal pathway** (amygdala → hypothalamus/septum/brainstem), and the **medial forebrain bundle** (septum/hypothalamus ↔ brainstem).
- ▶ **Cholinergic supply** — the **basal forebrain** (*nucleus basalis of Meynert, medial septal nucleus*) provides the major cholinergic input to hippocampus and neocortex; its degeneration underlies the memory deficit of AD and the rationale for **cholinesterase inhibitors**.
- ▶ **Other modulators** — *mesolimbic dopamine* (ventral tegmental area → nucleus accumbens/amygdala) underlies reward and motivation; serotonergic and noradrenergic projections modulate limbic affective tone; the hippocampus is densely glutamatergic and **selectively vulnerable to hypoxia, hypoglycaemia and seizure-induced excitotoxicity** (hippocampal sclerosis).

The amnestic syndrome (clinical hallmark of limbic damage)

- ▶ Defined as a disturbance of **explicit memory** in the absence of deficits of attention, language or visuospatial function; *always implies bilateral limbic injury* (hippocampo-entorhinal complex or thalamus). Unilateral left hippocampal lesions cause only transient amnesia.
- ▶ Components: prominent **anterograde amnesia** (cannot store new information) > **retrograde amnesia** (recent memories more vulnerable than remote — *Ribot's gradient*).
- ▶ **Confabulation** (filling gaps with implausible information) occurs when the lesion also disrupts the frontothalamic network, as in **Wernicke-Korsakoff syndrome** and head trauma.
- ▶ **Implicit/procedural memory is preserved** — patients acquire new motor/perceptual skills without conscious recollection.
- ▶ Bedside test: 4–5 word list registration, then delayed recall at 5–10 min; amnestics fail recall and may forget that a list was given. Recognition better than recall suggests a milder, retrieval-stage defect.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Medial sagittal view of the limbic system** — label: *cingulate gyrus, parahippocampal gyrus, uncus (amygdala), hippocampus, fornix, mammillary body, anterior thalamic nucleus, septal nuclei, olfactory bulb/tract, hypothalamus, corpus callosum*.
- ▶ **Papez circuit loop** — draw the closed loop with labelled arrows: *Hippocampus → Fornix → Mammillary body → Mammillothalamic tract → Anterior thalamic nucleus → Cingulate gyrus → Cingulum → Entorhinal/parahippocampal cortex → Hippocampus*.

Clinical / Diagnostic significance

- ▶ **Alzheimer's disease (AD)** — neurofibrillary degeneration begins in the **entorhinal cortex and hippocampus**, explaining the early selective episodic-memory loss; spreads to limbic then neocortical areas. Prodrome = **amnestic mild cognitive impairment (aMCI)**; MRI shows hippocampal/medial-temporal atrophy; FDG-PET shows posterior-cingulate/precuneus hypometabolism.

- ▶ **Wernicke-Korsakoff syndrome** — thiamine deficiency damages the **mammillary bodies** and medial thalamus; Korsakoff psychosis = persistent recent-memory loss with confabulation.
- ▶ **Herpes simplex encephalitis** — necrotising involvement of medial temporal/limbic cortex causes amnesia and a **Klüver-Bucy-type picture** (hyperorality, hypermetamorphosis, inappropriate sexual displays, emotional blunting, visual agnosia/"psychic blindness") — classically from bilateral anterior-temporal/amygdala damage.
- ▶ **Autoimmune & paraneoplastic limbic encephalitis** — subacute confusion, depression/agitation, severe short-term-memory deficit and temporal-lobe seizures with **bilateral mesial-temporal T2/FLAIR hyperintensity**. Antibodies: **anti-LGI1** (faciobrachial dystonic seizures + hyponatremia), **anti-NMDAR** (young women, psychosis, dyskinesias, ovarian teratoma), **anti-AMPA**, **anti-GABA-B** (seizures, SCLC), **anti-Ma2** (testicular tumour), **anti-Hu** (SCLC).
- ▶ **Temporal-lobe (limbic) epilepsy** — aura of fear, déjà vu, **uncinate fits** (olfactory/gustatory hallucinations); interictal *Geschwind syndrome* (hyposexuality, hypergraphia, hyperreligiosity).
- ▶ **Transient global amnesia** — acute, self-limited (24–48 h) isolated anterograde amnesia with repetitive questioning; ~20% recur.
- ▶ **Other amnesic causes** — PCA/ACA territory infarcts, fornix/septal lesions (colloid cyst, anterior communicating artery aneurysm rupture), thalamic and medial-temporal tumours, head trauma, anoxia, Pick's disease/FTLD, LATE (limbic-predominant age-related TDP-43 encephalopathy).

High-yield exam pointers

- ▶ Limbic system = **emotion + memory + olfaction + autonomic/endocrine homeostasis**; "limbus" = border ring around the corpus callosum.
- ▶ **Papez circuit mnemonic**: *Hippocampus–Fornix–Mammillary body–Mammillothalamic tract–Anterior thalamus–Cingulate–back to Hippocampus*.
- ▶ **Bilateral limbic lesions** are required to produce a *persistent* amnesic state.
- ▶ **Anterograde amnesia > retrograde**; **confabulation** = added frontothalamic involvement (Wernicke-Korsakoff).
- ▶ **Implicit/procedural memory is spared** in pure amnesia.
- ▶ **Mammillary bodies** = Wernicke-Korsakoff; **hippocampus/entorhinal cortex** = early Alzheimer's disease.
- ▶ **Klüver-Bucy syndrome** = bilateral anterior temporal/amygdala damage → placidity, hyperorality, hypersexuality, hypermetamorphosis, visual agnosia.
- ▶ **Limbic encephalitis** = subacute amnesia + seizures + psychiatric change + bilateral mesial-temporal FLAIR signal → screen for **LGI1, NMDAR, AMPAR, GABA-B, Ma2, Hu** antibodies and occult malignancy.
- ▶ **Anterior cingulate lesion** → akinetic mutism; **septal lesion** → rage/irritability.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Aphasia, Memory Loss, and Other Cognitive Disorders" (limbic network for explicit memory, Papez circuit, amnestic state, causes); "Dementia / Alzheimer's Disease" (entorhinal-hippocampal onset, amnestic MCI, LATE); "Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis" (limbic encephalitis, antibody panel); "Nutrition / Wernicke-Korsakoff" (mammillary bodies, thiamine, Korsakoff psychosis).
- ▶ **Brazis – Localization in Clinical Neurology** — "The Localization of Lesions Affecting the Cerebral Hemispheres" (limbic lobe anatomy, full Papez-circuit node list, amygdala in fear/emotional memory, cingulate emotion processing, temporal-lobe behavioural syndromes, basal forebrain/retrosplenial cortex).
- ▶ Coverage note: The corpus covers *limbic function, circuitry and clinical correlates* in depth; the **Klüver-Bucy** eponym and its component features are universally accepted standard neurology (the feature-set is described in Brazis under herpes-encephalitis/temporal-lobe damage) and are included as such.



Monoclonal antibodies — clinical pharmacology

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

Definition / Introduction — **Monoclonal antibodies (mAbs)** are laboratory-engineered immunoglobulins of a single specificity, directed against one defined epitope (antigen) and produced in large, high-affinity quantities. In therapeutics, animal-derived antigen-combining sequences are grafted into human immunoglobulin genes (**chimerized** or **humanized** products) or generated *de novo* from mice carrying human immunoglobulin gene loci (**fully human** antibodies). They form the backbone of modern targeted and immunologic cancer therapy and of immunomodulation in inflammatory disease, acting with precision but carrying a distinctive class toxicity profile (infusion reactions, immune-related adverse events, cytokine release). The generic suffix **-mab** denotes a monoclonal antibody.

Structure, Nomenclature and Production

- ▶ **Basic unit** is an IgG immunoglobulin: two **Fab** arms carry the antigen-binding *variable regions* (the complementarity-determining regions, CDRs, confer specificity); the **Fc** stem recruits effector functions (complement, Fc-receptor-bearing immune cells).
- ▶ **Production**: very large quantities of high-affinity mAbs against specific tumor/cell antigens are produced, then the rodent antigen-combining sequences are grafted into human Ig genes, or the antibody is derived from mice bearing human Ig gene loci — progressively reducing immunogenicity.
- ▶ **Nomenclature by source** (WHO stem system — standard, see Coverage note):

Type	Suffix	Sequence origin	Examples
Murine	-omab	100% mouse (highly immunogenic)	(largely obsolete)

Type	Suffix	Sequence origin	Examples
Chimeric	-ximab	mouse variable + human constant	Rituximab, Cetuximab, Infliximab
Humanized	-zumab	only CDRs murine	Trastuzumab, Pertuzumab, Bevacizumab, Alemtuzumab, Obinutuzumab
Fully human	-umab	entirely human	Panitumumab, Ofatumumab, Ipilimumab, Nivolumab, Durvalumab

- ▶ Less immunogenic constructs allow repeated dosing with lower risk of anti-drug antibodies and hypersensitivity.

Mechanisms of Action

- ▶ **Direct signal blockade / antiproliferative effect** — binding a growth-driving surface receptor interrupts intracellular signalling (e.g., *trastuzumab* interrupts HER2/neu signals; *pertuzumab* blocks HER2 dimerization; anti-CD20 agents interrupt signals driving lymphomagenesis).
- ▶ **Antibody-dependent cell-mediated cytotoxicity (ADCC)** — Fc engages NK/effector cells; *obinutuzumab* has altered glycosylation that enhances killer-cell activation.
- ▶ **Complement-dependent cytotoxicity (CDC)** — *alemtuzumab* (anti-CD52) activates complement against the target cell.
- ▶ **Immune-response activation** — anti-tumor mAbs both kill tumor cells and stimulate host anti-tumor immune mechanisms.
- ▶ **Checkpoint release** — immunoregulatory mAbs bind antigens on *host* immune cells (not tumor) to reactivate suppressed cytotoxic T cells (anti-PD-1/PD-L1, anti-CTLA4, anti-LAG3).
- ▶ **Bridging (bispecific)** — *BiTe* antibodies physically tether a T cell to a tumor cell, forcing immune killing.
- ▶ **Targeted delivery** — *antibody-drug conjugates (ADCs)* and radio-/toxin-conjugates ferry a cytotoxic "warhead" selectively to the antigen-bearing tumor cell.

Pharmacokinetics and Administration

- ▶ **Large proteins** — not orally bioavailable (digested in the gut); given **intravenously** or **subcutaneously**.
- ▶ **Slow elimination** — therapeutic antibodies are eliminated *very slowly*, probably by **lysosomal uptake and degradation**, giving a long half-life that permits **infrequent dosing** (e.g., **monthly injections**).
- ▶ **Not metabolized by cytochrome P450** and not renally excreted as intact protein — hence few classical pharmacokinetic drug interactions, though pharmacodynamic immune interactions occur.
- ▶ Distribution is largely confined to plasma and interstitial fluid; placental transfer (IgG) is relevant in pregnancy, and all conjugated cytotoxic mAbs carry embryofetal toxicity warranting contraception.

Therapeutic Strategies and Target Classification

Four general antibody strategies are recognised, plus a stroma-directed group:

Strategy	Mechanism	Representative targets and agents
Anti-tumor cell antibodies	Bind tumor surface antigen → block signalling, recruit immune/complement attack	CD20 — Rituximab, Ofatumumab, Obinutuzumab; CD52 — Alemtuzumab; EGFR — Cetuximab, Panitumumab; HER2/neu — Trastuzumab, Pertuzumab; CD38 — Daratumumab, Isatuximab
Bispecific T-cell engagers (BiTe)	One arm binds tumor antigen, other binds CD3 → drags T cell onto tumor	CD19×CD3 — Blinatumomab
Immunoregulatory (checkpoint) antibodies	Target host immune-cell receptors to release the brakes on T cells	CTLA4 — Ipilimumab; PD-1 — Nivolumab, Pembrolizumab, Cemiplimab; PD-L1 — Atezolizumab, Avelumab, Durvalumab; LAG3 — Relatlimab
Antibody conjugates (ADC / radio / toxin)	Antibody delivers a cytotoxic "warhead" to the tumor	See ADC table below
Stroma-directed antibodies	Target tumor-supporting vasculature	VEGF — Bevacizumab; VEGFR2 — Ramucirumab

Major Classes and Antibody-Drug Conjugates

- ▶ **Anti-CD20 (rituximab, ofatumumab):** B-cell lymphomas — used alone and with chemotherapy/radiation; *obinutuzumab* (enhanced ADCC) is valuable in **chronic lymphocytic leukemia**.
- ▶ **Anti-CD52 (alemtuzumab):** complement-activating; chronic lymphoid leukemia and T-cell malignancies; **tumor lysis syndrome prophylaxis** may be needed.
- ▶ **Anti-EGFR (cetuximab, panitumumab):** chemorefractory colorectal cancer and head-and-neck cancer with radiation; cause an **acneiform rash** (topical antibiotic + steroid cream) and photosensitivity.
- ▶ **Anti-HER2 (trastuzumab, pertuzumab):** HER2-overexpressing breast and certain GI cancers; pertuzumab blocks HER2 dimerization and augments trastuzumab; both are **cardiotoxic**, especially after anthracyclines — check and monitor LV function.
- ▶ **BiTe (blinatumomab):** anti-CD19 × anti-CD3; active in B-cell acute lymphocytic leukemia; toxicities are **cytokine release syndrome** (fever, hypotension, tachycardia) and neurologic deterioration (early sign: deteriorating handwriting → cortical dysfunction) needing dose-pausing ± glucocorticoids.
- ▶ **Checkpoint inhibitors:** *ipilimumab* (anti-CTLA4) was the first proof that purely immunoregulatory antibodies are safe and effective; *nivolumab/pembrolizumab* (anti-PD-1) and *atezolizumab* (anti-PD-L1) benefit many cancers; *pembrolizumab* first-line in PD-L1-expressing metastatic NSCLC (a milestone replacing chemotherapy); *relatlimab* (anti-LAG3) augments nivolumab in melanoma. **Tissue-agnostic** approval applies to MSI-high / mismatch-repair-deficient tumors and high **tumor mutational burden** (≥10 mutations/megabase).

Antibody-drug conjugates (humanized mAb + linker + cytotoxic payload; linker controls intracellular vs extracellular "bystander" release):

Payload class	ADC	Target	Indication / key toxicity
DNA disruptor (calicheamicin)	Gemtuzumab ozogamicin	CD33	AML; hepatic veno-occlusive disease
	Inotuzumab ozogamicin	CD22	ALL; VOD, myelosuppression
	Loncastuximab tesirine	CD19	Refractory DLBCL; vascular leak
Microtubule (maytansine/auristatin)	Ado-trastuzumab emtansine	HER2	Breast (trastuzumab-resistant); cardiac/pulmonary
	Brentuximab vedotin	CD30	Hodgkin lymphoma; neuropathy
	Enfortumab vedotin	Nectin-4	Urothelial cancer
	Belantamab mafodotin	BCMA	Myeloma; ocular keratopathy
Topoisomerase I	Fam-trastuzumab deruxtecan	HER2	Breast/gastric/NSCLC; interstitial lung disease
	Sacituzumab govitecan	Trop2	Triple-negative breast; diarrhea (UGT1A1*28)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **IgG monoclonal antibody structure:** label *Fab region*, *Fc region*, *antigen-binding site* (*variable region V_H / V_L*), *complementarity-determining regions (CDRs)*, *heavy chain*, *light chain*, *hinge region*, *disulfide bonds*; shade murine vs human portions to contrast *chimeric vs humanized vs fully human*.
- **Four therapeutic strategies schematic (after Fig. 78-4):** central *tumor cell* bearing surface *tumor antigen (T-Ag)*; label (1) *anti-tumor-cell antibody* → ADCC/CDC/signal block; (2) *BiTe* bridging a *T cell (CD3)* to *tumor (CD19)*; (3) *checkpoint axis* — *PD-1 / PD-L1* and *CTLA4* with *immunoregulatory antibody*; (4) *antibody-drug conjugate* (*antibody-linker-warhead*); and *anti-VEGF antibody* on a *tumor blood vessel*.

Clinical / Diagnostic significance

- **Biomarker-guided use:** HER2 overexpression, EGFR/RAS status, CD-antigen expression, MSI/mismatch-repair status and tumor mutational burden select responders — molecular/liquid biopsy is integral to prescribing.
- **Pre-treatment screening:** assess **hepatitis B and C status** before anti-B-cell antibodies (risk of reactivation and opportunistic infection); baseline **echocardiography/LVEF** before anti-HER2 agents; ophthalmologic exam before ocular-toxic ADCs.
- **Beyond oncology:** the same biology underlies *infliximab* (anti-TNF, chimeric), *rituximab* and *abatacept* used to treat severe immune-mediated disease — including, per Harrison, severe immunologically-mediated **adverse drug reactions** refractory to steroids.

- ▶ **Immune-related adverse events (irAEs)** from checkpoint inhibitors are unpredictable, can appear **late** even during sustained tumor control, and demand a low threshold for high-dose glucocorticoids; **myocarditis**, though rare, can be rapidly fatal.

High-yield exam pointers

- ▶ Suffix **-mab** = monoclonal antibody; **-ximab** chimeric, **-zumab** humanized, **-umab** fully human (decreasing immunogenicity).
- ▶ Effector mechanisms: **signal blockade**, **ADCC**, **CDC**, **immune activation**; conjugates add targeted cytotoxic delivery.
- ▶ PK: **not oral**, IV/SC, **no CYP metabolism**, slow lysosomal degradation → long half-life → **monthly dosing**.
- ▶ Trastuzumab/pertuzumab → **cardiotoxicity** (worse post-anthracycline); cetuximab → **acneiform rash**; bevacizumab → **hypertension**, **proteinuria**, **thrombosis**, **bleeding**, **GI perforation**.
- ▶ Blinatumomab (BiTe) → **cytokine release syndrome** + **neurotoxicity**; checkpoint inhibitors → **immune-related AEs** (colitis, thyroiditis, hepatitis, myocarditis).
- ▶ Gemtuzumab/inotuzumab ozogamicin → **veno-occlusive disease**; belantamab → **keratopathy**; trastuzumab deruxtecan → **interstitial lung disease**.
- ▶ Checkpoint biomarkers: **MSI-high** / **mismatch-repair deficient** / **TMB ≥10 mut/megabase** = tissue-agnostic indication.
- ▶ First-line: **infusion-reaction prophylaxis** (glucocorticoid ± antihistamine, slow infusion); severe irAEs → **high-dose steroids**, then rituximab/infliximab/abatacept/mycophenolate/plasmapheresis.

SOURCE & COVERAGE

Harrison 22e — Ch 78 "Principles of Cancer Treatment" (antibody-mediated therapeutic approaches, BiTe, immunoregulatory/checkpoint antibodies, stroma-directed antibodies, antibody-drug conjugates; Fig. 78-4; Tables 78-4 and 78-6) and Ch 71 "Principles of Clinical Pharmacology" (antibody pharmacokinetics — slow lysosomal elimination/monthly dosing; immune-checkpoint-related ADRs and their management with steroids/rituximab/infliximab/abatacept/mycophenolate/plasmapheresis).

Coverage note: Harrison does not provide a dedicated mAb-pharmacology chapter (spec gap = true). Antibody **structure detail** (Fab/Fc/CDR domains) and the **WHO -omab/-ximab/-zumab/-umab stem nomenclature** are universally accepted standard immunology/pharmacology added for completeness — they are not stated verbatim in the provided chapters (Harrison uses the broader terms "chimerized," "humanized," and "fully human," and loosely labels some agents "humanized"). The statements that mAbs are non-oral, lack CYP metabolism, and undergo placental transfer are standard pharmacology; only "slow lysosomal elimination with monthly dosing" is given explicitly in Ch 71. Non-oncology examples (infliximab, abatacept use) and individual ADC/checkpoint indications are grounded in the cited tables/figure.



Neurotransmitters

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

Definition / Introduction — Neurotransmitters are endogenous chemical messengers synthesised by neurons, stored in synaptic vesicles, released into the synaptic cleft in a calcium-dependent manner on depolarisation, and acting on specific pre- or post-synaptic receptors to alter the excitability of the target cell. They are the molecular currency of **chemical synaptic transmission** and the principal targets of nearly every centrally acting drug — antidepressants, antipsychotics, anxiolytics, anti-parkinsonian agents, analgesics and drugs of abuse all act by modulating neurotransmitter synthesis, release, receptor signalling, reuptake or degradation. Harrison frames their clinical relevance through the **monoamine hypothesis of mood disorders**, the **dopaminergic reward circuit** of addiction, and the **GABA/glutamate excitatory-inhibitory balance**.

Defining criteria and classification

A substance qualifies as a neurotransmitter if it is **synthesised in the neuron**, **stored and released on stimulation**, **mimics the effect of nerve stimulation when applied exogenously**, **binds specific receptors**, and has a defined **mechanism of inactivation** (reuptake or enzymatic degradation).

Class	Members	Key biosynthetic point
Amino acids	Glutamate (principal excitatory); GABA (principal inhibitory); glycine (inhibitory)	GABA synthesised from glutamate by glutamic acid decarboxylase (GAD1)
Biogenic amines (monoamines) — catecholamines	Dopamine, norepinephrine, epinephrine	Derived from tyrosine; tyrosine hydroxylase = rate-limiting enzyme of catecholamine biosynthesis
Biogenic amines — indoleamine / imidazole	Serotonin (5-HT, from tryptophan); histamine	Monoamine reuptake/oxidation governs synaptic levels
Acetylcholine	ACh	Synthesised from choline + acetyl-CoA; terminated by acetylcholinesterase
Neuropeptides	Endorphins, enkephalins; orexin (hypocretin); β -endorphin, melanocortin; CRF	Co-released with classical transmitters
Endocannabinoids	Anandamide, 2-arachidonoylglycerol	Retrograde messengers acting on CB1
Gaseous / unconventional	Nitric oxide, carbon monoxide; purines (ATP, adenosine)	Not vesicular; freely diffusible (NO/CO)

Major neurotransmitter systems and their CNS pathways

Harrison's circuit diagram of mood and reward (Fig. 462-3) maps each monoamine to a discrete brainstem/midbrain source nucleus projecting diffusely to the limbic system.

Transmitter	Source / projection	Main receptors	Principal action	Disease correlation
Dopamine	Ventral tegmental area (VTA), substantia nigra → nucleus accumbens, cortex	D1–D5 (metabotropic)	Reward "rheostat", motor control, cognition	Parkinson disease, schizophrenia, addiction
Norepinephrine	Locus coeruleus (LC) → widespread	α- and β-adrenergic	Arousal, vigilance, mood, stress	Depression, anxiety
Serotonin (5-HT)	Dorsal raphe / raphe nuclei → widespread	5-HT ₁ –7 (5-HT ₃ is ionotropic)	Mood, sleep, appetite, impulse control	Depression, OCD, anxiety
Glutamate	Cortical/limbic glutamatergic neurons	NMDA, AMPA, kainate, mGluR	Principal excitatory; long-term potentiation/synaptic plasticity	Excitotoxicity, schizophrenia
GABA	Interneurons (GAD1)	GABA-A (ionotropic Cl ⁻), GABA-B (metabotropic)	Principal inhibitory transmitter	Epilepsy, anxiety, spasticity
Acetylcholine	Basal forebrain, brainstem	Nicotinic (ionotropic), muscarinic	Arousal, memory, autonomic control	Alzheimer disease, myasthenia
Endogenous opioids	Arcuate/hypothalamic peptidergic neurons	μ, δ, κ opioid (Gi/o)	Analgesia, reward, mood	Addiction, pain
Endocannabinoids	Post-synaptic, retrograde	CB1	Retrograde dampening of release	Addiction

Life cycle of chemical synaptic transmission

- **Synthesis** — precursor amino acids/choline converted by rate-limiting enzymes (e.g., tyrosine hydroxylase for catecholamines, GAD for GABA).
- **Storage** — packaging into synaptic vesicles by vesicular transporters.
- **Release** — action potential opens voltage-gated Ca^{2+} channels at the terminal; Ca^{2+} influx triggers exocytotic, quantal release into the cleft.
- **Receptor activation** — binding to **ionotropic** (ligand-gated ion channel, fast) or **metabotropic** (G-protein-coupled, slow/modulatory) receptors on the post-synaptic membrane.
- **Termination** — (1) **reuptake** by membrane transporters (e.g., the **dopamine transporter, DAT**; serotonin and norepinephrine transporters); (2) **enzymatic degradation** (monoamine oxidase, catechol-O-methyltransferase, acetylcholinesterase).
- **Plasticity** — repeated activity alters **synaptic strength** (long-term potentiation/depression) and **gene expression** via second messengers and transcription factors (**cAMP–CREB, ΔFosB**), the molecular basis of learning and of addiction.

Receptor types and signal transduction

- ▶ **Ionotropic receptors** — ligand-gated channels giving rapid responses: NMDA / AMPA / kainate (glutamate), GABA-A (Cl^-), nicotinic ACh, 5-HT₃.
- ▶ **Metabotropic receptors** — G-protein-coupled, modulatory: dopaminergic, adrenergic, most serotonergic, GABA-B, muscarinic, opioid and cannabinoid receptors.
- ▶ **Example (opioid signalling, Fig. 462-2)** — μ -opioid agonists couple to **Gi/o**, **inhibit adenylyl cyclase** $\rightarrow$ $\downarrow$ cAMP $\rightarrow$ $\downarrow$ PKA, activate K^+ channels and inhibit Ca^{2+} channels, hyperpolarising the neuron; chronic exposure **upregulates the cAMP–CREB pathway**, underlying tolerance, dependence and withdrawal.
- ▶ **Second-messenger relevance** — lithium (mood stabiliser) competes with magnesium to inhibit **GSK3 β** and phosphoinositide-signalling enzymes, illustrating how transmitter-downstream cascades are themselves drug targets.

Neurotransmitters and drugs of abuse / reward circuitry

All addictive drugs converge on promoting **dopamine neurotransmission in the nucleus accumbens** (VTA target), though their initial molecular targets differ (Harrison Table 462-1):

Drug	Transmitter affected	Target (action)
Opioids	Endorphins, enkephalins	μ - and δ -opioid receptors (agonist)
Psychostimulants (cocaine, amphetamine, methamphetamine)	Dopamine	DAT (cocaine = antagonist; amphetamine/methamphetamine = reverse transport)
Nicotine	Acetylcholine	Nicotinic cholinergic receptors (agonist)
Ethanol	GABA / glutamate / 5-HT / ACh	GABA-A (positive allosteric modulator); NMDA glutamate (antagonist); 5-HT ₃ (positive allosteric modulator)
Marijuana	Endocannabinoids (anandamide, 2-AG)	CB1 receptor (agonist)
Phencyclidine, ketamine	Glutamate	NMDA receptor (antagonist)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Chemical synapse / transmitter life cycle** — label: pre-synaptic terminal, mitochondrion, synaptic vesicles, voltage-gated Ca^{2+} channel, synaptic cleft, **transmitter molecules**, post-synaptic **ionotropic** and **metabotropic receptors**, **reuptake transporter** (e.g., DAT), degrading enzyme (MAO/acetylcholinesterase), post-synaptic density.
- ▶ **Monoamine source-nuclei map** (after Fig. 462-3) — label: VTA (dopaminergic), locus coeruleus (noradrenergic), dorsal raphe (serotonergic), nucleus accumbens, amygdala, hippocampus, prefrontal cortex, hypothalamus; arrows for glutamatergic, GABAergic, dopaminergic and peptidergic projections.

Clinical / Diagnostic significance

- ▶ **Mood disorders** — tricyclics (imipramine) block serotonin/norepinephrine reuptake and MAO inhibitors (tranylcypromine) raise monoamines, giving rise to the **monoamine deficiency hypothesis** of depression; the delayed (weeks) clinical response shows efficacy depends on downstream **neuroplastic/BDNF-mediated adaptation**, not the acute rise in transmitter.
- ▶ **Rapid-acting antidepressants** — **ketamine**, a non-competitive NMDA **glutamate-receptor antagonist**, produces antidepressant effects within hours in treatment-resistant depression, redirecting focus to **glutamatergic transmission and synaptic plasticity**.
- ▶ **Psychedelics / MDMA** — 5-HT_{2A} partial agonism (psychedelics) and serotonin-releasing action (MDMA) are under study for depression and PTSD.
- ▶ **Parkinson disease** — degeneration of **midbrain dopaminergic neurons**; basis for dopamine-replacement therapy and experimental fetal/stem-cell-derived dopamine-neuron grafts.
- ▶ **Addiction** — convergence on the **VTA–nucleus accumbens dopamine reward pathway**; cAMP–CREB and ΔFosB adaptations drive tolerance, dependence and relapse.
- ▶ **Gut–brain axis** — gut bacteria synthesise **GABA and serotonin** and signal to the CNS via the vagus nerve, modulating anxiety- and depression-like behaviour (Ch. 435).

High-yield exam pointers

- ▶ **Glutamate** = principal excitatory; **GABA** = principal inhibitory transmitter of the CNS.
- ▶ **Tyrosine hydroxylase** = rate-limiting enzyme of catecholamine synthesis; **GAD (GAD1)** synthesises GABA from glutamate.
- ▶ Source nuclei: **dopamine** — VTA/substantia nigra; **norepinephrine** — locus coeruleus; **serotonin** — raphe nuclei.
- ▶ **Ionotropic** (NMDA, AMPA, GABA-A, nicotinic, 5-HT₃) = fast; **metabotropic** (GPCR: dopaminergic, adrenergic, GABA-B, opioid, muscarinic) = slow/modulatory.
- ▶ Transmitter action terminated by **reuptake** (DAT, SERT, NET) or **enzymatic degradation** (MAO, COMT, acetylcholinesterase).
- ▶ **Ketamine** = NMDA antagonist, a rapid-acting antidepressant; **lithium** acts on GSK3 β / phosphoinositide signalling.
- ▶ Drugs of abuse converge on **dopamine release in the nucleus accumbens** (Table 462-1).

- Opioids → Gi/o → ↓cAMP/PKA, with chronic cAMP–CREB **upregulation** underlying dependence.

SOURCE & COVERAGE

Harrison 22e — Ch 462 "Biology of Psychiatric Disorders" (monoamine hypothesis, signal transduction, Fig. 462-2 opioid/LC signalling, Fig. 462-3 mood–reward circuitry, Table 462-1 drugs of abuse) and Ch 435 "Pathobiology of Neurologic Diseases" (GABA/serotonin and the gut–brain axis; dopaminergic-neuron degeneration).

Coverage note (spec gap = true): Harrison covers neurotransmitters *through disease biology*, not as a basic-physiology topic — the defining criteria, the systematic chemical classification (amino-acid / monoamine / cholinergic / peptide / endocannabinoid / gaseous-purinergeric), the stepwise synaptic-transmission cycle, the ionotropic-vs-metabotropic receptor framework, and individual receptor subtype lists (D1–D5, α/β-adrenergic, 5-HT1–7, κ-opioid, glycine, histamine, muscarinic) are supplied here as **universally-accepted standard internal-medicine/neuroscience scaffolding**, not verbatim from the two provided chapters. All transmitter-source nuclei, enzymes, receptor mechanisms, drug-of-abuse targets and clinical correlations stated are grounded in Ch 462/435.



Pharmacogenomics

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

Definition / Introduction — **Pharmacogenetics** is the study of how *single* inherited genetic variants determine unusual (beneficial or adverse) responses to a drug in an individual or family; **pharmacogenomics** extends this to *multiple* variants across whole genomes and populations to explain variability in drug efficacy and toxicity. The genes involved — those governing drug metabolism, transport, targets, and immune recognition — are collectively termed **pharmacogenes**. The discipline aims to choose effective drugs and doses, avoid adverse drug reactions (ADRs) in high-risk individuals, guide drug development, and serves as a cornerstone of **precision (personalised) medicine**.

Core concepts and metabolizer phenotypes

- The commonest variant is a **single nucleotide polymorphism (SNP)**; *non-synonymous* (amino-acid-changing) SNPs are a frequent cause of altered pharmacogene function. Other variants: small insertions/deletions, splice and promoter variants, **copy-number variation** (gene deletion or duplication). SNP assays may miss large duplications, and the highly polymorphic **HLA locus** on chromosome 6 is best characterised by sequencing.
- The frequency of pharmacogene variants **varies strikingly by ancestry**, so specific ethnic groups can be at unusually high risk of aberrant drug response.
- A **multimodal (non-unimodal)** distribution of plasma drug concentration signals that one gene predominates in that drug's metabolism, classically yielding four phenotypes (illustrated by CYP2D6):

Phenotype	Genotype	Enzyme activity	Consequence for a substrate
Poor metabolizer (PM)	2 loss-of-function alleles	Absent/very low	↑ steady-state level, longer time to steady state; toxicity (or no effect if prodrug)
Intermediate metabolizer (IM)	1 functional / 2 reduced-function alleles	Reduced	Modestly altered handling
Normal / extensive metabolizer (EM)	1–2 functional alleles	Normal	Expected response
Ultrarapid metabolizer (UM)	Gene duplication (2–12 copies)	Very high	↓ parent-drug level (drug failure), or toxicity if active metabolite formed

- The combination of alleles on the two chromosomes (the **diplotype**) determines the phenotype. **Phenocopying** occurs when a co-prescribed inhibitor converts a genetic EM into a functional PM.

Genetic variants affecting pharmacokinetics (PK)

- Discovery uses **candidate-gene** approaches (knowing the metabolic pathway) and unbiased **genome-wide association (GWA)** studies; results require replication.

Gene / product	Drug(s)	Clinical effect of variant
CYP3A4 / CYP3A5	Tacrolimus, vincristine	CYP3A5 splice variant in Europeans/Asians → low activity; African "expressers" eliminate tacrolimus faster (↓ efficacy), lower vincristine-neuropathy risk
CYP2D6	Codeine, metoprolol/carvedilol, propafenone, nortriptyline, tamoxifen	PM 5–10% of Europeans/Africans (few Asians); codeine→morphine fails in PMs and is dangerous in UMs
CYP2C19	Clopidogrel, omeprazole	PM ~20% Asians, 2–3% others, >50% Oceania; LOF → clopidogrel failure (stent thrombosis/stroke); 2C1917 UM → ↑ bleeding
CYP2C9 (+ VKORC1)	Warfarin, phenytoin, glipizide, losartan	↑ phenytoin neurotoxicity, glipizide hypoglycaemia; ↓ warfarin dose; losartan (prodrug) fails
DPYD (dihydropyrimidine dehydrogenase)	5-fluorouracil, capecitabine, tegafur	LOF (2A, 13, rs67376798) → severe/fatal toxicity; dose-reduce IMs
TPMT	Azathioprine, 6-mercaptopurine	Inactive homozygote (~1/300) → fatal pancytopenia (2, 3A, 3B, 3C)
NUDT15	Thiopurines	LOF → excess myelosuppression (esp. East Asians)
NAT2	Isoniazid, procainamide, hydralazine	"Slow acetylators" (~50% Europeans/Africans) → INH hepatitis, drug-induced lupus

Gene / product	Drug(s)	Clinical effect of variant
UGT1A1	Irinotecan, atazanavir	Gilbert's promoter variant → irinotecan diarrhoea/marrow suppression, unconjugated hyperbilirubinaemia
SLCO1B1 (OATP1B1)	Simvastatin	Noncoding SNP → ↑ myopathy (accounts for ~60% of risk)
MDR1 (P-glycoprotein) / MATE1, MATE2	Digoxin / metformin	Altered efflux (digoxin toxicity) / uptake (metformin glucose-lowering)

- For **warfarin**, polymorphisms in **CYP2C9** (PK) plus the **VKORC1** promoter (PD target) account for up to ~50% of dose variability, with a smaller contribution from **CYP4F2** (vitamin K metabolism).

Genetic variants affecting pharmacodynamics (PD) and disease-pathway interactions

- **VKORC1 promoter** (–1639G>A) variant (common in Asians) lowers transcription and warfarin dose requirement (~30% of variability alone).
- **β₂- and β₁-adrenergic receptor** polymorphisms modulate response to β-agonists in asthma and β-blocker heart-rate/BP lowering in heart failure/hypertension.
- **Drug–disease gene interactions**: CYP inducers precipitate attacks in the **porphyrias**; **G6PD** deficiency (African, Mediterranean, South-Asian descent) → haemolysis with **primaquine** and **rasburicase**; **RYR1** (ryanodine receptor) variants → **malignant hyperthermia** with volatile anaesthetics/succinylcholine; subclinical **congenital long-QT** unmasked by QT-prolonging drugs (torsades); **ACKR1** variant → benign ethnic neutropenia.

Immunogenetics — HLA and severe cutaneous/hepatic ADRs

HLA risk alleles are **necessary but not sufficient** (a third, unidentified factor is needed); frequencies vary by ancestry, underpinning population-specific screening.

HLA allele	Drug	Reaction
HLA-B*57:01	Abacavir	Hypersensitivity (55% of carriers react); also flucloxacillin hepatotoxicity
HLA-B*15:02	Carbamazepine	SJS/TEN (Han Chinese, SE Asians)
HLA-A*31:01	Carbamazepine	SJS/TEN, DRESS (Europeans)
HLA-B*58:01	Allopurinol	SJS/TEN (Korean, Han Chinese, Japanese, Thai)

- These manifest as **Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN)**, **DRESS**, and drug-induced liver injury.

Pharmacogenomics of tumour and pathogen genomes (somatic / targeted therapy)

- Tumour genotyping selects targeted agents and spares non-responders: **Trastuzumab** for **HER2 (Herceptin-receptor)**–positive breast cancer (and potentiates anthracycline cardiotoxicity);

Imatinib targets **BCR-ABL1** (Philadelphia chromosome, CML) and **c-KIT** (GIST); **Vemurafenib** inhibits **BRAF V600E** ($\approx 40\%$ of melanomas, not wild-type BRAF); **Crizotinib** for ALK-rearranged NSCLC. Rapid emergence of resistance often necessitates combinations (e.g., BRAF + MEK inhibitors).

Pharmacogenomics in drug development

- ▶ Human genetics validates and de-risks targets: rare **gain-of-function PCSK9** variants cause familial hypercholesterolaemia, while **loss-of-function PCSK9** SNPs (2.5% of African-Americans) lower LDL and coronary risk without harm — directly spawning **PCSK9 monoclonal antibodies**. Other genetics-driven targets: **HSD17B13** (chronic liver disease), **ANGPTL3** (hyperlipidaemia). Large biobanks (**UK Biobank**, **All of Us**) and **polygenic risk scores** extend this approach to drug "repurposing".

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Population distribution of CYP2D6 activity** (Fig 72-1A): x-axis "Enzymatic activity (lesser $\rightarrow$ greater)", y-axis "Population frequency"; three labelled humps — **Poor metabolizers (PM, 2 mutant alleles)**, **Extensive metabolizers (EM, 1–2 wild-type alleles)**, **Ultrarapid metabolizers (UM, gene duplication >2 copies)**; mark the **antimode** separating PMs from EMs.
- ▶ **Gene-dose effect on drug concentration** (Fig 72-1B): plot Concentration vs Time for a single dose then chronic therapy; curves labelled **PM (highest AUC, longest $t_{1/2}$)**, **EM**, **UM (lowest AUC, fastest clearance)** — show higher and later steady state in PMs.

Clinical / Diagnostic significance

- ▶ **Implementation models:** *Point-of-care* (variant assay ordered at prescription, result in 1–2 h) vs *preemptive* genotyping (panel tested in advance, stored in the **EHR** with real-time **clinical decision support [CDS]**).
- ▶ **Guidelines:** the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** and the **Dutch Pharmacogenetics Working Group** publish drug–gene dosing recommendations; the **FDA** embeds pharmacogenetic data in package inserts (e.g., codeine black-box warning forbidding use in children <12 y).
- ▶ **Evidence base:** an RCT showed **HLA-B*57:01** testing *eliminates* abacavir SJS/TEN — the strongest case for mandatory testing. **HLA-B*15:02** screening was mandated before carbamazepine in parts of SE Asia (though some prescribers simply switched to phenytoin, also an SJS/TEN risk). Warfarin pharmacogenetic dosing trials showed no/modest benefit. A **2023 European trial (Swen et al., 6944 patients, 7 countries)** of a **12-gene/50-variant** preemptive panel reduced clinically relevant ADRs (across 42 drugs) by **30%**, supporting preemptive screening.
- ▶ **Decision to test** depends on the magnitude/clinical importance of the genetic effect, strength of evidence (anecdote $\rightarrow$ post-hoc $\rightarrow$ RCT), availability of alternative therapy or therapeutic drug monitoring, and cost-benefit.

High-yield exam pointers

- ▶ Define and distinguish pharmacogenetics (single variant/individual) from pharmacogenomics (genome-wide/population).
- ▶ Memorise the PM/IM/EM/UM scheme with CYP2D6 and the codeine story (PM = no analgesia; UM = fatal respiratory depression, FDA ban <12 y after tonsillectomy).
- ▶ TPMT/NUDT15 → thiopurine myelosuppression; DPYD → 5-FU/capecitabine toxicity; UGT1A1 → irinotecan; CYP2C19 → clopidogrel failure; SLCO1B1 → simvastatin myopathy.
- ▶ Warfarin = CYP2C9 + VKORC1 (up to 50% of dose variability).
- ▶ HLA-B*57:01–*abacavir*, HLA-B*15:02–*carbamazepine*, HLA-B*58:01–*allopurinol* (necessary-but-not-sufficient).
- ▶ G6PD–*primaquine*/rasburicase haemolysis; RYR1–malignant hyperthermia; NAT2 slow acetylators–INH hepatitis/drug-induced lupus.
- ▶ Oncology targets: HER2–trastuzumab, BCR-ABL1/c-KIT–imatinib, BRAF V600E–vemurafenib, ALK–crizotinib.
- ▶ Implementation: CPIC guidelines, FDA labels, preemptive EHR + CDS; Swen 2023 panel cut ADRs by 30%.
- ▶ PCSK9 loss-of-function → PCSK9 inhibitors: genetics validating drug targets.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Pharmacogenomics" (Dan Roden) and "Principles of Clinical Pharmacology" (PK/PD variability framework: metabolizer phenotypes, steady state, loading doses).
- ▶ **CMDT 2026** — Appendix "Therapeutic Drug Monitoring, Pharmacogenetic Tests..." (TPMT 2/3A/3B/3C, DPYD 2A/13/rs67376798, CYP2C19*17, VKORC1 –1639G>A, HLA-B*57:01 *abacavir*, HLA-B*15:02 *carbamazepine*, HLA-B*58:01 *allopurinol* screening).
- ▶ HLA-B*58:01–*allopurinol* and HLA-A*31:01–*carbamazepine* associations cross-checked in CMDT 2026 and *Bologna, Dermatology* (severe cutaneous adverse reactions).
- ▶ Coverage note: The corpus covers this topic richly via a dedicated Harrison chapter; the online Harrison tables (e72-1/e72-2) listing exhaustive allele frequencies are referenced but not reproduced in the text — allele-level detail above is drawn from the CMDT pharmacogenetic appendix.



Plasma enzymes in clinical medicine

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

Definition / Introduction — Plasma (serum) enzymes are protein catalysts measurable in circulating blood. A small group are *functional* enzymes that act within plasma (e.g., coagulation factors), but most have no physiological role in serum and, in Harrison's words, "have no known function in the serum and behave like other serum proteins." Because individual enzymes are concentrated in specific tissues, the **pattern, magnitude and isoenzyme composition** of an enzyme elevation localise the organ injured, gauge its severity, and track response to treatment — the basis of "enzyme diagnosis." No single enzyme measures total organ function, so enzymes are interpreted together as a *battery*.

Classification of plasma enzymes

Category	Behaviour in disease	Representative enzymes
Functional (plasma-specific)	Synthesised mainly by hepatocytes, act <i>in</i> plasma; levels fall when synthesis fails	Coagulation factors (II, VII, IX, X), pseudocholinesterase, lipoprotein lipase, ceruloplasmin, renin
Non-functional — secretory	Normally secreted by exocrine glands; spill into blood when gland/duct injured	Amylase, lipase (pancreas), prostatic acid phosphatase
Non-functional — cellular (cytosolic / organelle)	Leak from damaged cells; levels rise with tissue injury	AST, ALT, LDH, CK, GGT, 5'-nucleotidase, aldolase

- ▶ Harrison frames hepatic enzymes pragmatically into those whose serum rise reflects (1) **damage to hepatocytes** and (2) **cholestasis** — a clinically useful subdivision of the "cellular" group.

Mechanisms of altered plasma enzyme activity

- ▶ **Increased entry from damaged cells** — the dominant mechanism. Enzymes are "released into the blood in greater amounts when there is damage to the liver cell membrane, resulting in increased permeability." *Cell necrosis is not required* — increased membrane permeability suffices, and there is a **poor correlation** between enzyme level and degree of damage. Hence the absolute aminotransferase value has **no prognostic significance** in acute hepatocellular injury.
- ▶ **Increased synthesis / enzyme induction** — alkaline phosphatase synthesis is induced in cholestasis and rapid bone turnover; GGT is induced by alcohol and enzyme-inducing drugs.
- ▶ **Decreased clearance** — serum enzymes are probably cleared by the reticuloendothelial system; each has a characteristic **half-life (measured in days)** that determines how long it stays elevated.
- ▶ **Reduced production** — *functional* enzymes (clotting factors) fall when hepatic synthetic capacity fails.

Hepatic plasma enzymes (grounded in Harrison Ch 348)

Hepatocellular ("leakage") enzymes — the aminotransferases

- ▶ AST is present (decreasing order of concentration) in liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes and erythrocytes — so it is **non-specific**. ALT is found primarily in liver and is therefore the **more liver-specific** indicator.

- ▶ Normal range $\approx 10\text{--}40$ IU/L. Levels up to 300 IU/L are non-specific and seen in any liver disorder (commonest cause of minimal elevation = fatty liver disease).
- ▶ **Striking elevation** >1000 IU/L occurs almost exclusively with extensive hepatocellular injury: (1) **viral hepatitis**, (2) **ischemic liver injury** (prolonged hypotension / acute heart failure), (3) **toxin- or drug-induced injury**. A gallstone passing into the common bile duct can transiently push them to 1000–2000 IU/L, after which they fall quickly into a cholestatic pattern.
- ▶ **AST:ALT ratio** — ALT $\geq$ AST in most acute hepatocellular disease; ratio <1 in chronic viral hepatitis and NAFLD, rising >1 as cirrhosis develops. A ratio $>2:1$ is **suggestive** and $>3:1$ **highly suggestive** of alcohol-related liver disease (AST rarely >300 IU/L, ALT often normal because of alcohol-induced **pyridoxal-phosphate [vitamin B6] deficiency**).

Cholestatic enzymes — alkaline phosphatase, 5'-nucleotidase, GGT

- ▶ ALP and 5'-nucleotidase lie *in or near the bile canalicular membrane*; GGT is in the endoplasmic reticulum and bile-duct epithelium — its more diffuse location makes it **less specific** for cholestasis.
- ▶ **ALP isoenzymes** arise from liver, bone, placenta and (less often) small intestine. Physiological rises: age >60 ($1\text{--}1.5\times$), blood groups **O and B** after a fatty meal (intestinal ALP), childhood/adolescent bone growth, and late pregnancy (placental ALP).
- ▶ A **<3 -fold** rise is non-specific (almost any liver disease); **>4 -fold** points to cholestasis, infiltrative disease (cancer, amyloidosis) or high-turnover bone disease (**Paget's**).
- ▶ To confirm a raised ALP is hepatic: **fractionate by electrophoresis**, or measure **GGT / 5'-nucleotidase** (both rise with hepatic ALP but are normal in bone disease). GGT is also a marker of occult alcohol use.

Feature	Hepatocellular pattern	Cholestatic pattern
Dominant enzymes	AST, ALT	ALP, GGT, 5'-NT
Typical magnitude	AST/ALT often very high (may be >1000)	ALP $>4\times$ normal
Classic causes	Viral / ischemic / toxic hepatitis	Biliary obstruction, PBC, infiltration, drugs
Confirmatory step	AST:ALT ratio; viral & autoimmune serology	GGT/5'-NT to confirm hepatic ALP; ultrasound for ducts

Extra-hepatic organ-specific enzymes (standard internal medicine)

Organ / system	Enzyme(s)	Principal clinical use
Heart	CK-MB, AST, LDH (LDH-1)	Myocardial infarction — but troponin (a regulatory protein, <i>not</i> an enzyme) is now the preferred marker
Skeletal muscle	Total CK (CK-MM), aldolase	Rhabdomyolysis, inflammatory myopathy, very high CK in Duchenne dystrophy

Organ / system	Enzyme(s)	Principal clinical use
Pancreas	Amylase, lipase	Acute pancreatitis ($\geq 3 \times$ ULN); lipase more specific and longer-lasting
Bone	ALP (bone isoenzyme)	Paget's disease, osteomalacia, rickets, bone metastases
Prostate	Acid phosphatase	Carcinoma prostate (historical; replaced by PSA)
Blood / marrow	LDH	Intravascular hemolysis, megaloblastic anaemia, tumour lysis, lymphoma
Lung / granuloma	Angiotensin-converting enzyme (ACE)	Sarcoidosis disease activity
Serous cavities	Adenosine deaminase (ADA)	Tuberculous pleural / pericardial / peritoneal effusion, TB meningitis
Toxicology	Pseudocholinesterase, RBC acetylcholinesterase	Fall in organophosphate poisoning; deficiency $\rightarrow$ scoline (suxamethonium) apnoea
RBC	Glucose-6-phosphate dehydrogenase	Deficiency $\rightarrow$ drug/infection-triggered hemolysis

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hepatocyte enzyme-leak schematic** — draw a hepatocyte abutting a sinusoid and a bile canaliculus. Label: *cytosol* $\rightarrow$ AST / ALT (leakage enzymes); *bile canaliculus membrane* $\rightarrow$ ALP and 5'-nucleotidase; *endoplasmic reticulum & bile-duct epithelium* $\rightarrow$ GGT; add an arrow "cell-membrane damage $\rightarrow$ $\uparrow$ permeability $\rightarrow$ enzyme leak into sinusoid $\rightarrow$ $\uparrow$ serum level."
- ▶ **Serum cardiac-enzyme time-activity curve after acute MI** — x-axis "Days after onset of chest pain," y-axis "Serum activity ($\times$ upper normal)," plotting CK-MB (peak ~ 24 h), AST (peak ~ 48 h) and LDH (peak 3–6 days), with Troponin overlaid and labelled "not an enzyme." (*standard medicine*)

Clinical / Diagnostic significance

- ▶ **Use as a battery** — aminotransferases + ALP + bilirubin + albumin + prothrombin time. Multiple or persistently abnormal tests make liver disease likely; all-normal results make occult disease unlikely.
- ▶ **Pattern recognition** directs the work-up: hepatocellular (AST/ALT dominant) vs cholestatic (ALP/GGT dominant) steers imaging and the chronically-abnormal-liver-tests algorithm (Fig. 348-1).
- ▶ **Isoenzymes / second enzymes localise the source** — GGT or 5'-NT confirm that a raised ALP is hepatic; CK-MB confirms myocardial origin of a raised total CK.
- ▶ **Synthetic-function tests gauge severity** — albumin (synthesised exclusively by hepatocytes, half-life 18–20 days, $\sim 4\%$ /day turnover) reflects *chronic* disease, whereas the PT/INR reflects clotting factors with short half-lives (6 h for factor VII to 5 days for fibrinogen) and is the single best

acute index of hepatic synthesis. PT prolonged **>5 s above control and uncorrected by parenteral vitamin K** is a poor prognostic sign; INR + bilirubin feed the MELD score.

- ▶ **Caveats** — enzymes lack sensitivity and specificity: they can be normal in serious liver disease and abnormal in disease that does not affect the liver, and their magnitude does not equal prognosis in acute hepatocellular injury.

High-yield exam pointers

- ▶ **Functional** enzymes (clotting factors, pseudocholinesterase) **fall** in disease; **cellular leakage** enzymes (AST, ALT, CK, LDH) **rise**.
- ▶ **ALT is more liver-specific than AST**; aminotransferases **>1000 IU/L** = viral, ischemic or toxic hepatitis.
- ▶ **AST:ALT >2:1** → **alcoholic**; **<1** → **viral/NAFLD**; flips to **>1** as **cirrhosis** develops.
- ▶ **ALP >4× normal** = cholestasis / infiltration / Paget's; confirm hepatic origin with **GGT** or **5'-nucleotidase**.
- ▶ **Factor VIII** is the only clotting factor *not* made solely by hepatocytes (vascular endothelium) — so it stays normal in liver failure.
- ▶ **Vitamin-K-dependent factors** = **II, VII, IX, X**; the PT measures factors **II, V, VII, X**.
- ▶ **Lipase > amylase** for specificity in acute pancreatitis; **troponin > CK-MB** for MI (troponin is *not* an enzyme).
- ▶ **Pseudocholinesterase** ↓ in organophosphate poisoning and underlies scoline apnoea; **ADA** ↑ in tuberculous effusions; **ACE** ↑ in sarcoidosis; **LDH** ↑ in hemolysis and tumour lysis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 348 "Evaluation of Liver Function" (hepatocellular leakage vs cholestatic enzymes; AST/ALT tissue distribution, normal ranges, >1000 IU/L causes and AST:ALT ratio; ALP isoenzymes, GGT and 5'-nucleotidase; albumin and coagulation-factor synthetic function). **Coverage note:** Harrison 22e has no dedicated "plasma enzymes" chapter. Ch 348 fully grounds the hepatic and synthetic-function enzymes and *all numerical values, ratios and tissue distributions* stated above. The general functional-vs-non-functional classification and the extra-hepatic enzymes (CK/CK-MB, LDH isoenzymes, amylase/lipase, aldolase, acid phosphatase/PSA, ACE, pseudocholinesterase, ADA, G6PD) and the cardiac-enzyme time-activity curve are *universally accepted standard internal-medicine/biochemistry* that Harrison covers within the respective disease chapters (acute MI, acute pancreatitis, the myopathies) — not the supplied chapter — and are flagged as such.



Polymerase chain reaction — technique and applications

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

Definition / Introduction — The **polymerase chain reaction (PCR)** is a type of **nucleic acid amplification test (NAAT)** that uses specific **oligonucleotide primers** and a **DNA polymerase** to amplify a defined target region of DNA *in vitro*, generating millions of copies from a minute starting template. Because each cycle theoretically doubles the target, amplification is **exponential**, conferring extraordinary analytical sensitivity. PCR underpins modern molecular diagnostics in internal medicine — from genetic mutation analysis to pathogen detection and antimicrobial-resistance genotyping — and permits testing on vanishingly small amounts of DNA (leukocytes, buccal cells, single cells, or even a hair root).

Reaction components ("ingredients")

Component	Role
Template DNA	The double-stranded DNA containing the target sequence to be amplified
Primer pair (forward + reverse)	Short specific oligonucleotides flanking the target; define the region amplified and provide the free 3'-OH for polymerase extension
Thermostable DNA polymerase (<i>Taq</i> , from <i>Thermus aquaticus</i>)	Heat-stable enzyme that synthesizes the new strand and survives repeated denaturation temperatures
dNTPs (dATP, dGTP, dCTP, dTTP)	Building blocks incorporated into the nascent strand
Mg ²⁺ + buffer	Cofactor essential for polymerase activity; buffer maintains optimal pH/ionic conditions
Thermal cycler	Programmable instrument that rapidly raises and lowers temperature through each cycle

- ▶ **Primer specificity is critical:** highly sensitive amplification methods require a high degree of sequence identity between primer pairs and their short target; even a **single base-pair mismatch** — particularly near the 3' end of the primer — may interfere with detection (Harrison Ch 126). This is the basis of "diagnostic escape" when a pathogen acquires a deletion/mutation at the primer site.

Steps of one PCR cycle (thermal cycling)

- ▶ **1. Denaturation (~94–95 °C):** heat separates the double-stranded template into two single strands by breaking hydrogen bonds.
- ▶ **2. Annealing (~50–65 °C):** temperature is lowered so the forward and reverse primers hybridize to their complementary single-stranded targets.
- ▶ **3. Extension / elongation (~72 °C):** *Taq* polymerase adds dNTPs to the 3' end of each primer, synthesizing a new complementary strand in the 5'→3' direction.
- ▶ These three steps constitute **one cycle**; the cycle is repeated typically **25–40 times**, and because product of one cycle is template for the next, copy number rises **exponentially** ($\approx 2^n$), yielding millions–billions of copies.

- The amplified product ("**amplicon**") is then detected — classically by **agarose gel electrophoresis**, or read in real time (see below). **DNA sequencing can be performed directly on PCR products** (Harrison Ch 479).

Major variants / modifications of PCR

Variant	Key principle	Representative use
Reverse-transcriptase PCR (RT-PCR)	RNA first converted to cDNA by reverse transcriptase, then amplified	Detection of RNA viruses — SARS-CoV-2 (core acute-phase assay), HIV, HCV, influenza, RSV (Harrison Ch 126)
Real-time / quantitative PCR (qPCR)	Amplicon accumulation measured cycle-by-cycle via fluorescence, allowing quantification of starting copies	Viral load quantification (HIV PCR can detect as few as 20 copies/mL of blood) and treatment monitoring
Multiplex PCR	Several primer sets in one reaction detect multiple targets simultaneously	Syndromic panels — e.g., respiratory viral panel (influenza, parainfluenza, RSV, adenovirus, rhinovirus, enterovirus, metapneumovirus, coronaviruses)
Nested PCR	Two sequential amplifications with inner primers boost specificity/sensitivity	Detection of low-copy targets (<i>standard molecular biology</i> — see Coverage note)
Isothermal amplification	Amplifies at a single constant temperature, avoiding thermal-cycling hardware	Point-of-care / field testing in resource-limited settings; pairs with CRISPR Cas12a/Cas13a nucleic-acid sensors (Harrison Ch 126)
Digital / droplet PCR	Partitioning enables absolute quantification	Low-abundance targets, minimal residual disease (<i>standard</i> — see Coverage note)

- A related NAAT chemistry, the **ligase chain reaction**, is also used to amplify/detect nucleic acids (Harrison Ch 126).

Applications in internal medicine

- **Infectious disease — pathogen detection** (Harrison Ch 126):
 - **Viral diagnosis and monitoring:** HIV, HBV, HCV, SARS-CoV-2, influenza, RSV — for initial diagnosis, response to therapy, and (in some cases) genotypic prediction of drug resistance. RT-PCR for SARS-CoV-2 was the largest molecular-diagnostic deployment to date.
 - **Tuberculosis:** amplification of the **rpoB** gene for species-specific identification of *M. tuberculosis*.
 - **Fastidious/unculturable bacteria:** *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, *Clostridioides difficile*.
 - **16S ribosomal RNA gene PCR:** broad-range amplification/sequencing of the conserved 16S rRNA gene to identify bacteria in culture-negative infections.
 - **Toxin-gene detection:** *C. difficile* toxins A and B, Shiga toxin — distinguishes pathogens from colonizers.

► **Antimicrobial-resistance genotyping (Harrison Ch 126):**

Target gene(s)	Resistance detected
<i>mecA</i>	Methicillin resistance in <i>S. aureus</i> (MRSA)
<i>vanA</i> / <i>vanB</i>	Vancomycin resistance in enterococci (VRE)
<i>rpoB</i> polymorphisms	Rifampin resistance in <i>M. tuberculosis</i> ($\approx 95\%$ of rifampin resistance); probes for <i>inhA</i> and <i>katG</i> detect up to 85% of isoniazid resistance
KPC, NDM, OXA-48, IMP, VIM	Carbapenemase production in Enterobacteriaceae

► **Human genetics (Harrison Ch 479):**

- **Mutational analysis** of discrete sequence alterations from small DNA amounts (leukocytes, single cells, buccal cells, hair roots).
- **Direct sequencing of PCR products** to characterize specific mutations and predict disease spectrum.
- **Genotyping of short tandem repeats (STRs / polymorphic microsatellite markers)** — di-, tri-, tetranucleotide repeats characterized readily by PCR — for **linkage and association studies**.
- **Preimplantation/prenatal genetic diagnosis:** with IVF, PCR-based diagnosis on a **single cell** from the four- to eight-cell embryo or the first polar body.

► **Oncology (Harrison Ch 479):** somatic (tumor-biopsy) versus germline (peripheral-cell) mutational analysis to guide therapy integrating genetic/genomic information.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "One PCR cycle":** a double-stranded template, with three labelled arrows/boxes: (1) **Denaturation** 94–95 °C → **single strands**; (2) **Annealing** 50–65 °C → **forward & reverse primers bind**; (3) **Extension** 72 °C → **Taq polymerase + dNTPs synthesize new strands**. Add a side note "**repeat $\times 25\text{--}40$ cycles $\rightarrow$ exponential 2^n amplification.**" Label: *template DNA, forward primer, reverse primer, Taq polymerase, dNTPs, new strand, amplicon*.
- **Diagram 2 — "Exponential amplification curve":** copy number (y-axis, log scale) versus cycle number (x-axis), showing geometric doubling. Labels: *1 $\rightarrow$ 2 $\rightarrow$ 4 $\rightarrow$ 8 ... copies, exponential phase, plateau*.

Clinical / Diagnostic significance

- **Sensitivity:** detects minute pathogen loads (e.g., HIV down to ~ 20 copies/mL), enabling earlier diagnosis and treatment than antigen detection or serology — the progression from antigen detection to PCR transformed understanding of HIV natural history.
- **Speed and real-time management:** NAATs supply etiologic diagnosis far faster than culture/serology, informing triage, antibiotic stewardship, and infection control (pivotal in the COVID-19 response).

- ▶ **Resistance prediction:** genotypic detection (e.g., *rpoB* for MDR-TB, carbapenemase genes) guides directed therapy when phenotypic susceptibility is slow or impossible.
- ▶ **Limitations / pitfalls:** technical complexity and reagent/instrument needs; risk of **false negatives** from primer-site mutation/deletion ("diagnostic escape"); risk of **false positives** from contamination — necessitating careful sample processing and standardized pipelines; targets only **known, prespecified** sequences (unlike unbiased metagenomic sequencing).
- ▶ **Emerging deployability:** isothermal amplification, lyophilized reagents (no cold chain), and CRISPR-Cas12a/Cas13a readouts are extending NAATs to point-of-care and field settings.

High-yield exam pointers

- ▶ PCR = a NAAT: amplifies a specific DNA region using **specific oligonucleotide primers + DNA polymerase** (Harrison's exact definition).
- ▶ **Three steps per cycle:** denaturation → annealing → extension; **25–40 cycles** → **exponential 2ⁿ amplification**.
- ▶ **Taq polymerase** (thermostable, from *Thermus aquaticus*) is the workhorse enzyme; **thermal cycler** drives the temperature changes.
- ▶ RT-PCR converts RNA→cDNA — used for SARS-CoV-2, HIV, HCV; qPCR/real-time PCR quantifies viral load.
- ▶ **Multiplex PCR = syndromic panels** (respiratory, GI, meningoencephalitis).
- ▶ Resistance genes to remember: **mecA** (MRSA), **vanA/vanB** (VRE), **rpoB** (rifampin/MDR-TB, ~95%), **inhA/katG** (isoniazid, up to 85%), carbapenemases KPC/NDM/OXA-48/IMP/VIM.
- ▶ **16S rRNA gene PCR** identifies culture-negative bacteria; **STR/microsatellite PCR** is used in genetic linkage studies.
- ▶ A **single base-pair primer mismatch near the 3' end** can abolish detection — basis of "diagnostic escape."
- ▶ PCR enables testing from a **single cell** (preimplantation diagnosis) and **direct sequencing of PCR products**.

SOURCE & COVERAGE

Harrison 22e — Ch 126 "Microbial Genomics and Infectious Disease" (PCR/NAAT definition, RT-PCR, multiplex syndromic panels, 16S rRNA, resistance-gene targets and numbers, primer-mismatch specificity, isothermal/CRISPR methods); Ch 479 "Principles of Human Genetics" (PCR for mutational analysis from small DNA amounts, direct sequencing of PCR products, STR genotyping, single-cell preimplantation diagnosis). **Coverage note (spec gap = true):** Harrison covers PCR only thinly within these chapters — it gives the formal definition and applications but does **not** spell out the stepwise thermal-cycling temperatures, the *Taq/Thermus aquaticus* enzyme detail, the dNTP/Mg²⁺ reaction mix, the 2ⁿ kinetics, or Kary Mullis's invention (1983; Nobel Prize 1993). These, together with **nested PCR** and **digital/droplet PCR**, are included here as universally-accepted standard molecular biology to satisfy the "technique" portion of the ask and are flagged as outside the verbatim Harrison text. All organism names, gene targets, percentage figures (95% rpoB, 85% inhA/katG), the 20-copies/mL HIV figure, and the primer 3'-mismatch point are taken directly from Harrison Ch 126.



Pregnancy-induced hypertension

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

Definition / Introduction — Pregnancy-induced hypertension (PIH) is the development of a blood pressure (BP) ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic, recorded on two occasions ≥ 4 h apart, *after 20 weeks' gestation* in a previously normotensive woman. It is the clinical anchor of the broader **hypertensive disorders of pregnancy (HDP)** — a spectrum spanning **gestational hypertension, preeclampsia, eclampsia and the HELLP syndrome** — and is a leading cause of maternal and perinatal morbidity and mortality worldwide. The CDC estimated that 16% of US deliveries in 2019 were complicated by an HDP, and the prevalence is rising. The only definitive cure is **delivery of the fetus and placenta**.

Classification of hypertensive disorders of pregnancy

- ▶ **Gestational hypertension** — new-onset BP $\geq 140/90$ after 20 weeks, *without* proteinuria or other end-organ features; BP normalises postpartum. With severe features it is reclassified as preeclampsia.
- ▶ **Preeclampsia** — new-onset hypertension ($\geq 140/90$) *plus* proteinuria, or end-organ dysfunction, after 20 weeks (may occur up to 6 weeks postpartum).
- ▶ **Eclampsia** — new-onset generalised tonic-clonic seizures in a woman with preeclampsia.
- ▶ **Chronic hypertension** — hypertension predating pregnancy or evident before 20 weeks.
- ▶ **Chronic hypertension with superimposed preeclampsia** — new proteinuria/end-organ features arising on a background of chronic hypertension.

Disorder	Onset	Proteinuria / end-organ features
Chronic hypertension	Pre-pregnancy or <20 weeks	Variable
Gestational hypertension	>20 weeks	Absent
Preeclampsia	>20 weeks (up to 6 wks postpartum)	Present (proteinuria <i>or</i> end-organ damage)
Eclampsia	Preeclampsia + seizures	Present

Diagnostic criteria (preeclampsia)

- ▶ **Hypertension:** BP $\geq 140/90$ mmHg on two occasions ≥ 4 h apart after 20 weeks.
- ▶ **Proteinuria:** ≥ 300 mg/24 h, or urine protein/creatinine ratio ≥ 0.3 . *Edema is no longer a diagnostic criterion.*
- ▶ **Preeclampsia without proteinuria** may still be diagnosed when hypertension is accompanied by end-organ involvement (thrombocytopenia, renal/hepatic impairment, pulmonary edema, or cerebral/visual symptoms).
- ▶ **Severe features** (any one qualifies as "preeclampsia with severe features"):
 - Severe hypertension: BP $\geq 160/110$ mmHg.
 - CNS: new headache unresponsive to medication, visual disturbance (scotomas, blurring), clonus, hyperreflexia.
 - Unrelenting severe **epigastric / right-upper-quadrant pain** (hepatic capsule stretch).
 - **Pulmonary edema.**
 - **Thrombocytopenia** platelets $< 100 \times 10^9/L$.
 - **Renal insufficiency** creatinine > 1.1 mg/dL.
 - **Hepatic impairment** transaminases $\geq 2 \times$ normal.
- ▶ **HELLP syndrome** — *Hemolysis, Elevated Liver enzymes, Low Platelets* — a severe subtype of preeclampsia and a major cause of maternal morbidity/mortality; additional complications include coagulopathy/DIC, cerebrovascular accident, hepatic capsular rupture and placental abruption.

Pathophysiology

- ▶ Precise cause unknown; central mechanism is **abnormal placentation** with failed remodelling of spiral arteries $\rightarrow$ **chronic uteroplacental ischaemia**.
- ▶ **Angiogenic imbalance:** excess of the anti-angiogenic factor **soluble fms-like tyrosine kinase-1 (sFlt-1)** and reduced **placental growth factor (PlGF)**. A circulating **sFlt-1/PlGF ratio ≥ 40** predicts development of preeclampsia with severe features within the next 2 weeks.
- ▶ **Exaggerated maternal systemic inflammatory response** and generalised endothelial dysfunction $\rightarrow$ vasoconstriction, raised peripheral resistance, capillary leak and a procoagulant state.
- ▶ **Impaired cerebral autoregulation** explains neurological features and the risk of stroke / seizures even at modestly elevated BP; headache may reflect **posterior reversible encephalopathy syndrome (PRES)** within the reversible cerebral vasoconstriction syndrome spectrum.

- ▶ New-onset hypertension of pregnancy arises from reduced placental perfusion and elevated peripheral resistance, which typically resolves after delivery.

Risk factors

- ▶ Nulliparity (primigravida), previous preeclampsia, multifetal gestation.
- ▶ Chronic hypertension, chronic kidney disease, pregestational and gestational diabetes.
- ▶ SLE, antiphospholipid antibody syndrome, thrombophilia.
- ▶ Maternal age ≥ 35 years, pre-pregnancy BMI >30 (obesity), obstructive sleep apnoea.
- ▶ Assisted reproductive technology / in-vitro fertilisation; low socioeconomic status; family history.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Angiogenic-imbalance pathway of preeclampsia (flow diagram).** Labels: *Abnormal placentation* $\rightarrow$ *failed spiral-artery remodelling* $\rightarrow$ *uteroplacental ischaemia* $\rightarrow$ $\uparrow$ sFlt-1 and $\downarrow$ PlGF (sFlt-1/PlGF ratio ≥ 40) $\rightarrow$ *maternal endothelial dysfunction* $\rightarrow$ *vasoconstriction + capillary leak + procoagulant state* $\rightarrow$ *Hypertension, Proteinuria, end-organ injury (CNS/PRES, Liver/HELLP, Kidney, Haematological).*
- ▶ **Target-organ involvement of preeclampsia-eclampsia (labelled body map).** Labels: *Brain (seizures/eclampsia, PRES, stroke), Eye (retinal haemorrhage, scotomas), Lungs (pulmonary edema), Liver (epigastric pain, HELLP, capsular rupture), Kidney (proteinuria, oliguria, $\uparrow$ creatinine), Blood (thrombocytopenia, haemolysis, DIC), Placenta (abruption, fetal growth restriction, oligohydramnios).*

Clinical / Diagnostic significance

- ▶ **Investigations:** serial BP; urine dipstick + protein/creatinine ratio or 24-h urinary protein; CBC with platelets; peripheral smear/LDH/haptoglobin/bilirubin (haemolysis); AST/ALT; serum creatinine and uric acid; coagulation profile if HELLP/DIC suspected; fetal surveillance (ultrasound for growth restriction, oligohydramnios, umbilical Doppler, non-stress test). sFlt-1/PlGF ratio aids risk prediction where available.
- ▶ **Differential diagnosis:** chronic hypertension, CKD, primary seizure disorder, immune thrombocytopenia, TTP, haemolytic-uraemic syndrome, acute fatty liver of pregnancy, gallbladder/pancreatic disease.
- ▶ **Prevention:** low-dose aspirin (81 mg/day orally) for women at increased risk, started between 12–28 weeks (optimally before 16 weeks) and continued until delivery (Harrison: initiated 12–14 weeks in high-risk women). Calcium, antioxidants (vitamins C/E), salt restriction and diuretics are *not* proven effective.

Management

- ▶ **Definitive treatment = delivery** of fetus and placenta; timing balances maternal risk against fetal prematurity.
 - Preeclampsia *without* severe features: expectant management with close maternal–fetal monitoring; **deliver at 37 weeks.**

- Preeclampsia *with* severe features: **deliver**, unless <34 weeks and eligible for expectant management in a tertiary unit; deliver before 34 weeks for unremitting symptoms, worsening labs, refractory severe hypertension, or fetal compromise.
- ▶ **Acute severe hypertension (BP $\geq 160/110$):** treat promptly (within 60 min) to reduce stroke risk; target BP 140–150/90–100 mmHg (avoid over-correction → placental hypoperfusion). First-line IV agents:
 - **Labetalol** 10–20 mg IV every 20 min as needed.
 - **Hydralazine** 5–10 mg IV every 20 min.
 - **Immediate-release nifedipine** 10–20 mg orally, repeat at 20 min, then 10–20 mg every 4–6 h (max 180 mg/day) — useful when no IV access.
- ▶ **Seizure prophylaxis & treatment — magnesium sulfate (drug of choice):**
 - Loading 4–6 g IV (over 15–20 min for prophylaxis; over ~4 min to abort an eclamptic seizure), then maintenance 2–3 g/hour; continue 24 h postpartum.
 - Therapeutic level 4–7 mEq/L; reduce dose/withhold if serum creatinine >1.0 mg/dL or oliguria.
 - **Monitor for toxicity** — loss of deep tendon reflexes, respiratory depression, oliguria; **antidote = calcium gluconate 1 g IV over 2 min**. Phenytoin/benzodiazepines only if magnesium unavailable.
- ▶ **Fetal lung maturity:** if <34 weeks, give antenatal corticosteroids — **betamethasone 12 mg IM every 24 h $\times$ 2 doses**, or **dexamethasone 6 mg IM every 12 h $\times$ 4 doses** (do not delay delivery in unstable severe disease).
- ▶ **Eclampsia:** turn patient to the side (prevent aspiration), secure airway/oxygenation, control seizures with magnesium sulfate, control BP, stabilise the mother, then deliver (vaginal delivery preferred; caesarean for obstetric indications).
- ▶ **Chronic hypertension in pregnancy:** preferred agents **labetalol** and **extended-release nifedipine**; **methyldopa** has a good safety record. Target BP <140/90 mmHg (CHAP trial — treating mild chronic hypertension to <140/90 reduces preeclampsia and preterm birth). **ACE inhibitors, ARBs and mineralocorticoid-receptor antagonists are contraindicated** (stillbirth, fetal renal/congenital anomalies).
- ▶ **Postpartum:** continue magnesium 24 h; remain vigilant for late-onset (postpartum) preeclampsia/eclampsia — treat as antepartum with hydralazine and magnesium.

Long-term significance

- ▶ Women with gestational hypertension or preeclampsia carry an increased lifelong risk of **chronic hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus**; preeclampsia is a recognised female-specific cardiovascular risk marker warranting risk-factor modification at postnatal visits.

High-yield exam pointers

- ▶ **PIH/HDP = BP $\geq 140/90$ after 20 weeks**; classified into gestational HTN, preeclampsia, eclampsia, chronic HTN, and superimposed preeclampsia.

- ▶ **Preeclampsia** = hypertension + proteinuria (or end-organ damage) after 20 weeks; edema is no longer required.
- ▶ **Severe features:** BP $\geq 160/110$, platelets $< 100 \times 10^9/L$, creatinine > 1.1 mg/dL, transaminases $\geq 2 \times$ normal, pulmonary edema, cerebral/visual symptoms, epigastric pain.
- ▶ **HELLP** = Hemolysis, Elevated Liver enzymes, Low Platelets — severe-subtype preeclampsia.
- ▶ Pathophysiology: $\uparrow$ sFlt-1, $\downarrow$ PlGF; sFlt-1/PlGF ratio ≥ 40 predicts severe disease.
- ▶ **Magnesium sulfate** is the drug of choice for seizure prophylaxis/treatment; **calcium gluconate** is the antidote.
- ▶ Acute severe BP: **IV labetalol or hydralazine** (target 140–150/90–100); **ACEI/ARB contraindicated** throughout pregnancy.
- ▶ **Low-dose aspirin 81 mg** from 12–16 weeks for prevention in high-risk women.
- ▶ **Delivery is the only cure** — at 37 weeks (no severe features) or earlier for severe disease; corticosteroids if < 34 weeks.

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — "Medical Disorders During Pregnancy" (preeclampsia, gestational hypertension, eclampsia/HELLP, pathophysiology, treatment) and "Hypertension" (hypertensive disorders of pregnancy, antihypertensive choice).
- ▶ CMDT 2026 — "Obstetrics & Obstetric Disorders" (diagnostic criteria, severity table, magnesium sulfate protocol, antihypertensive doses, corticosteroids, aspirin prophylaxis, eclampsia management) and "Systemic Hypertension" (chronic hypertension agents, methyldopa safety; CHAP trial).

Coverage note: No dedicated subspecialty obstetrics text was provided in the spec (specialty_books empty); grounding therefore rests on Harrison 22e plus CMDT 2026, which together cover the topic at exam depth.



Pyrogenic cytokines in pathogenesis of fever

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

Definition / Introduction — A **pyrogen** (Greek *pyro*, "fire") is any substance that causes fever. Fever is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with a raised hypothalamic set point* (e.g., from 37°C to 39°C) — fundamentally distinct from hyperthermia, in which the set point is unchanged and no pyrogenic molecules are involved. **Pyrogenic cytokines** are small host-derived proteins (formerly called *endogenous pyrogens*) — chiefly **IL-1, IL-6 and TNF** — that act as the central molecular link translating an infectious or inflammatory stimulus into a rise in the hypothalamic thermostat. They are the obligatory intermediaries between exogenous pyrogens and the prostaglandin E₂ (PGE₂)-driven elevation of the set point that produces fever.

Classification of pyrogens

- ▶ **Exogenous pyrogens** — derived from *outside* the host; mostly microbial products, microbial toxins, or whole microorganisms (including viruses).
 - Classic example: **lipopolysaccharide (endotoxin)** of all gram-negative bacteria — a highly pyrogenic molecule. An IV dose of just **2–3 ng/kg** in human volunteers produces fever, leukocytosis, acute-phase proteins, and malaise.
 - Cell-wall components of **gram-positive** organisms are less pyrogenic, but these organisms elaborate **superantigen toxins** that induce fever — *Staphylococcus aureus* toxic shock syndrome toxin-1 (TSST-1), staphylococcal enterotoxins, and streptococcal pyrogenic exotoxins — pyrogenic in animals at **1–10 µg/kg**.
- ▶ **Endogenous pyrogens = pyrogenic cytokines** — host proteins produced in response to exogenous pyrogens *or* to sterile inflammation. Fever can therefore arise **without microbial infection** (e.g., pericarditis, trauma, stroke, routine immunizations all induce IL-1, TNF and/or IL-6).

Feature	Exogenous pyrogens	Pyrogenic (endogenous) cytokines
Origin	Outside host (microbes/toxins)	Host myeloid & endothelial cells
Prototype	Endotoxin (LPS)	IL-1, IL-6, TNF
Pyrogenic IV dose	LPS 2–3 ng/kg; superantigens 1–10 µg/kg	IL-1, TNF 10–100 ng/kg; IL-6 1–10 µg/kg
Acts via	Inducing cytokine synthesis (and TLRs)	Inducing PGE ₂ → raises set point
Needs microbe?	Yes	No (also sterile inflammation)

The pyrogenic cytokines

- ▶ Cytokines are small proteins (**molecular mass 10,000–20,000 Da**) that regulate immune, inflammatory and hematopoietic processes; IL-1 and IL-6 also drive the **neutrophilic leukocytosis** of infection.
- ▶ **Each pyrogenic cytokine is encoded by a separate gene**, and each independently causes fever in laboratory animals and in humans.

- ▶ A wide spectrum of bacterial and fungal products induces their synthesis and release.

Cytokine	Key features in fever
IL-1	Prototype pyrogen; fever at low IV dose 10–100 ng/kg ; shares signalling pathway with Toll-like receptors
TNF	Pyrogenic at 10–100 ng/kg ; central to sterile and septic fever
IL-6	Induced by IL-1/TNF; less potent — fever needs 1–10 µg/kg ; induces hepatic C-reactive protein (CRP)
IFN (esp. interferon-α)	Fever is a <i>prominent side effect of interferon-α therapy</i>
Ciliary neurotropic factor (CNTF)	A member of the IL-6 family ; also pyrogenic

Pathogenesis: how pyrogenic cytokines raise the hypothalamic set point

- ▶ **Source cells:** *Myeloid cells (monocytes/macrophages) and endothelial cells* are the primary producers. On encountering an exogenous pyrogen they release **IL-1, IL-6 and TNF** into the systemic circulation.
- ▶ **Site of action — the circumventricular organs:** During fever, **PGE2 is elevated** in hypothalamic tissue and the third cerebral ventricle, with the highest concentrations near the **organum vasculosum of the lamina terminalis (OVLT)** — networks of enlarged ("leaky") capillaries surrounding the hypothalamic regulatory centres. Destruction of these organs abolishes the febrile response to pyrogens.
- ▶ **Cytokines do NOT enter the brain parenchyma:** Most animal studies show pyrogenic cytokines do *not* cross from the circulation into the brain itself. Instead, circulating exogenous pyrogens and pyrogenic cytokines **interact with the endothelium of these capillaries** — this interaction is the *first step* in raising the set point.
- ▶ **PGE2 is the final common mediator:** Cytokine–endothelium interaction induces **PGE2** synthesis. The enzyme **cyclooxygenase** acts on **arachidonic acid** (released from membrane phospholipid — the *rate-limiting step*) to form PGE2. Of the **four PGE2 receptors**, the **EP-3 receptor is essential for fever**: deleting the EP-3 gene in mice abolishes fever after IL-1 or endotoxin, whereas deleting the other receptor genes leaves fever intact.
- ▶ **PGE2 → cAMP → set point:** PGE2 is *not itself a neurotransmitter*. PGE2 released from the brain side of the hypothalamic endothelium triggers **PGE2 receptors on glial cells**, causing rapid release of **cyclic AMP (cAMP)** — the actual neurotransmitter. cAMP activates neuronal endings of the thermoregulatory centre, and this elevation of cAMP **raises the hypothalamic set point** (directly or by inducing other neurotransmitters).
- ▶ **Toll-like receptors (TLRs):** Distinct receptors for microbial products on the hypothalamic endothelium — **Toll-like receptors** — closely resemble **IL-1 receptors** and *share the same signal-transducing mechanism*; direct activation of either TLRs or IL-1 receptors yields **PGE2 production and fever**.
- ▶ **Peripheral PGE2 and constitutional symptoms:** Circulating cytokines also induce PGE2 in peripheral tissues, accounting for the **myalgias and arthralgias** of fever. Some systemic PGE2

escapes pulmonary destruction and reaches the hypothalamus via the **internal carotid**, but it is the rise in *brain* PGE₂ that initiates the set-point change.

- ▶ **Effector limb:** Once the set point is raised, the vasomotor centre triggers **vasoconstriction** (heat conservation — cold hands/feet, the patient "feels cold"), **shivering** and **non-shivering thermogenesis** (heat production), plus behavioural adjustments, until blood temperature matches the new febrile setting.

Production of cytokines within the CNS

- ▶ Cytokines made *inside the brain* account for the hyperpyrexia of CNS haemorrhage, trauma or infection.
- ▶ Viral CNS infections induce **microglial (and possibly neuronal) production** of IL-1, TNF and IL-6.
- ▶ The cytokine concentration needed to cause fever is **several orders of magnitude lower** with direct intracerebral/intraventricular injection than with systemic injection; thus CNS-generated cytokines raise the set point while **bypassing the circumventricular organs**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Fig. 20-1 — "Chronology of events required for the induction of fever"** (vertical flow chart). Labels, top to bottom:
 - Infection, microbial toxins, mediators of inflammation, immune reactions
 - → Monocytes/macrophages, endothelial cells, others
 - → Pyrogenic cytokines: IL-1, IL-6, TNF, IFN (entering Circulation)
 - → Hypothalamic endothelium
 - → PGE₂ → Cyclic AMP (cAMP)
 - → Elevated thermoregulatory set point → Heat conservation, heat production → FEVER
 - Include a side arrow labelled "Microbial toxins" acting directly on the hypothalamic endothelium (via Toll-like receptors).
- ▶ **Optional inset — hypothalamic set-point thermostat:** label OVLT (*organum vasculosum lamina terminalis*), EP-3 receptor on glial cell, thermoregulatory neuron, normothermic set point 37°C → febrile set point 39°C.

Clinical / Diagnostic significance

- ▶ **Measuring circulating cytokines is NOT useful** — IL-1 and TNF are often below assay detection limits or do not coincide with fever. For occult/low-grade fever the most valuable markers are CRP and ESR; IL-6 (**which induces CRP**) can be informative, but IL-6 levels fluctuate during a febrile illness whereas CRP stays elevated.
- ▶ **Anticytokine therapy blunts fever and raises infection risk:** Agents blocking IL-1, IL-6, IL-12/23, IL-17 or TNF (used in Crohn disease, rheumatoid arthritis, psoriasis) lower host defences — e.g., latent *M. tuberculosis* can disseminate on anti-TNF therapy, and anti-IL-17

raises systemic candidiasis risk. Low-grade fever in such patients warrants early, rigorous evaluation.

- ▶ **Therapeutic blockade reduces fever in autoinflammatory disease:** Fevers of familial Mediterranean fever, hyper-IgD syndrome, adult/juvenile Still disease (IL-1 β -mediated, often via NLRP3/pyrin inflammasomes) are dramatically reduced by **anakinra** or **canakinumab**.
- ▶ **Antipyretics target the PGE2 limb:** Cyclooxygenase inhibitors are potent antipyretics; antipyretic potency correlates with **inhibition of brain cyclooxygenase**. **Aspirin and acetaminophen are equally effective**; acetaminophen is a poor peripheral COX inhibitor but is oxidised by brain P450 (and inhibits **COX-3**, found only in the CNS). **Glucocorticoids act at two levels** — inhibiting **phospholipase A2** ($\downarrow$ arachidonic acid $\rightarrow$ $\downarrow$ PGE2) *and* blocking **transcription of pyrogenic-cytokine mRNA**.
- ▶ **Blunted febrile response** is expected in newborns, the elderly, chronic hepatic/renal failure, and patients on glucocorticoids/NSAIDs/anticytokines — active disease may exist without fever; septic shock may even cause hypothermia.

High-yield exam pointers

- ▶ Pyrogenic cytokines = the *renamed* endogenous pyrogens: IL-1, IL-6, TNF, IFN, and CNTF (IL-6 family).
- ▶ PGE2 is the final mediator; **EP-3 receptor** is *essential* for fever (knockout abolishes it).
- ▶ **cAMP** — not PGE2 — is the neurotransmitter that resets the hypothalamic thermostat.
- ▶ Pyrogenic doses: LPS 2–3 ng/kg; IL-1/TNF 10–100 ng/kg; IL-6 1–10 μ g/kg; superantigens 1–10 μ g/kg.
- ▶ Cytokines act at the **OVLt/circumventricular organs** and do *not* cross into brain parenchyma.
- ▶ **TLRs and IL-1 receptors share the same signalling pathway** $\rightarrow$ PGE2 $\rightarrow$ fever.
- ▶ Fever (raised set point, cytokine/PGE2-mediated, *responds* to antipyretics) vs **hyperthermia** (set point unchanged, no pyrogens, *does not* respond to antipyretics).
- ▶ IL-6 induces **CRP**; CRP is a more stable marker than IL-6 for monitoring occult fever.
- ▶ CNS-generated IL-1/TNF/IL-6 explain **hyperpyrexia of CNS haemorrhage, trauma, infection**.

SOURCE & COVERAGE

Harrison 22e — Ch 20 "Fever" (Dinarello & Surana). Full coverage of pyrogens, pyrogenic cytokines and the PGE2/EP-3/cAMP pathogenesis of fever; spec.gap = false and no fabrication required. All doses, the four-receptor/EP-3 point, OVLT, TLR–IL-1R sharing, and CNS cytokine production are taken verbatim from this chapter. (Inflammasome detail, e.g., NLRP3/pyrin, is referenced by Ch 20 but elaborated in Chaps 360/381, cited only in passing here.)



Recombinant DNA technology

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

Definition / Introduction — *Recombinant DNA (rDNA) technology* is the set of laboratory techniques by which DNA segments from two or more different sources are joined *in vitro* to create a novel **recombinant (chimeric) DNA molecule**, which is then introduced into a living host cell where it can be propagated (cloned) and/or expressed. It is the foundational enabling technology of modern molecular medicine: as Harrison emphasises, peptide hormones, growth factors, cytokines and vaccines can now be manufactured in large quantities using recombinant DNA and RNA technology, and the same toolkit underpins molecular diagnostics, gene therapy and gene editing. The three essential operations are: **cut** (a specific gene), **paste** (into a vector), and **clone/express** (in a host cell).

Molecular toolkit (key enzymes and reagents)

Tool	Function	Note
Restriction endonucleases	Cleave double-stranded DNA at specific palindromic recognition sequences; the " <i>molecular scissors</i> "	Generate cohesive (<i>sticky</i>) or blunt ends; e.g. EcoRI, BamHI, HindIII
DNA ligase	Forms phosphodiester bonds joining vector and insert; the " <i>molecular glue</i> "	Seals the recombinant molecule
Reverse transcriptase	Synthesises complementary DNA (cDNA) from an mRNA template	Source of intron-free coding sequence for expression
DNA polymerase (thermostable, <i>Taq</i>)	Template-directed synthesis of new DNA strands	Engine of PCR
Modifying enzymes	Alkaline phosphatase, polynucleotide kinase, terminal transferase	Prevent self-ligation, add/label ends
Vector	Self-replicating DNA vehicle that carries the foreign gene into the host	Plasmid, phage, viral, artificial chromosome
Host cell	Site of replication/expression	<i>E. coli</i> , yeast, mammalian or insect cells

Principle — steps of gene cloning

- ▶ **1. Isolation of the gene/DNA of interest.** The target sequence is obtained by (a) restriction digestion of genomic DNA, (b) reverse transcription of mRNA into cDNA (yields the coding sequence without introns — preferred for protein expression in bacteria), or (c) direct amplification by PCR.
- ▶ **2. Insertion into a vector ("recombination").** Vector and insert are cut with the *same* restriction enzyme so that complementary sticky ends anneal; **DNA ligase** then covalently joins them to form the **recombinant (chimeric) DNA molecule**.
- ▶ **3. Introduction into a host cell.** The recombinant vector is taken up by competent bacteria (**transformation**), or by mammalian cells (**transfection**), or delivered by a **viral vector** (**transduction**).

- ▶ **4. Selection and screening of recombinant clones.** Host cells carrying the construct are identified using **selectable markers** (e.g., antibiotic-resistance genes), **blue–white (lacZ / β -galactosidase)** screening with X-gal, and **colony/nucleic-acid hybridisation** with labelled probes.
- ▶ **5. Amplification and expression.** The positive clone is propagated to generate millions of identical copies (a *clone/gene library*); an **expression vector** with a suitable promoter drives synthesis of the encoded protein, which is then harvested and purified.

Vectors — cloning vehicles

Vector	Approx. insert capacity	Host / use
Plasmid	up to ~10 kb	<i>E. coli</i> ; routine cloning, expression
Bacteriophage λ	~15–20 kb	Genomic libraries
Cosmid	~35–45 kb	Larger inserts
BAC (bacterial artificial chromosome)	up to ~300 kb	Large fragments, genome projects
YAC (yeast artificial chromosome)	up to ~1–2 Mb	Very large fragments
Viral vectors — retro-/lentiviral, adenoviral, adeno-associated virus (AAV)	retro/lenti ~8 kb; adeno 8–30 kb; AAV ~5 kb	<i>In vivo/ex vivo</i> gene therapy (see below)

Core analytical & amplification techniques

- ▶ **Polymerase Chain Reaction (PCR):** cyclical *in vitro* amplification — **denaturation** (~94–95 °C) → **primer annealing** (~50–65 °C) → **extension** (~72 °C, *Taq* polymerase); each cycle doubles the target, giving exponential (2^n) amplification. Enables testing from minute amounts of DNA (leukocytes, single cells, buccal cells, hair roots). **RT-PCR** converts RNA → cDNA before amplification (e.g., SARS-CoV-2, HIV viral-load); **quantitative/real-time PCR** measures copy number.
- ▶ **Hybridisation/blotting:** **Southern blot** (DNA), **Northern blot** (RNA), **Western blot** (protein); **FISH** (fluorescence *in situ* hybridisation) and array/bead-based methods detect deletions/duplications and chromosomal rearrangements.
- ▶ **DNA sequencing:** Sanger (dideoxy) sequencing of PCR products, now largely superseded by **next-generation sequencing (NGS)** — whole-exome (WES), whole-genome (WGS) and targeted gene panels — allowing unbiased, cost-effective mutational analysis.
- ▶ **Genome editing:** **CRISPR/Cas9** uses a bacterial Cas9 nuclease complexed with a **guide RNA** (ribonucleoprotein) to introduce a site-specific double-strand break; repair by non-homologous end-joining disrupts a gene, or homology-directed repair with a donor template corrects it.

Applications in clinical medicine

- ▶ **1. Recombinant therapeutic proteins** — produced in microbial/mammalian cells: **human insulin** (the first licensed recombinant drug, 1982) and modified **insulin analogues** with favourable kinetics; **GLP-1 receptor agonists**; growth hormone, erythropoietin, granulocyte colony-stimulating factor, interferons, clotting **factor VIII/IX**, and tissue plasminogen activator.

Targeted modification of the recombinant peptide yields improved therapeutics (Harrison's explicit examples: insulin analogues, GLP-1 agonists for type 2 diabetes and weight management).

- ▶ **2. Vaccines** — recombinant subunit vaccines (e.g., hepatitis B surface antigen, HPV) and, most recently, **mRNA vaccines against SARS-CoV-2**.
- ▶ **3. RNA-based therapeutics** — **small interfering RNA (siRNA)** to treat hypercholesterolaemia; antisense oligonucleotides; guide RNAs/mRNAs delivered by **lipid nanoparticles**.
- ▶ **4. Gene transfer & gene editing therapy** — a nucleic acid is the active agent, delivered by an engineered **vector**; strategies are *gene addition* (supply a missing gene) or *gene editing* (correct the endogenous locus). Approved products include:

Product	Indication	Vector / approach
Strimvelis	ADA-SCID	Retroviral, autologous HSCs (<i>ex vivo</i>)
Luxturna (voretigene neparvovec)	Biallelic <i>RPE65</i> retinal dystrophy (Leber congenital amaurosis)	AAV2, subretinal injection
Zolgensma (onasemnogene abeparvovec)	Spinal muscular atrophy type 1 (<i>SMN1</i>)	AAV9, single IV infusion
Zynteglo (betibeglogene autotemcel)	Transfusion-dependent β -thalassaemia	Lentiviral β^A -T87Q globin gene, autologous HSCs
Kymriah / Yescarta (CAR-T)	R/R B-cell leukaemia/lymphoma	Lenti-/retroviral anti-CD19 CAR, autologous T cells
CRISPR gene-editing therapy	Sickle cell disease, β -thalassaemia	CRISPR/Cas9 (FDA-approved 2023)

- ▶ **5. Molecular diagnosis** — PCR-based detection and identification of pathogens difficult to culture (mycobacteria, viruses, parasites) and tracking of outbreaks; carrier detection and mutational analysis of monogenic disease (e.g., CFTR $\Delta F508$ in cystic fibrosis); **prenatal diagnosis** (amniocentesis, chorionic villus sampling) and **non-invasive prenatal testing/liquid biopsy** using cell-free DNA (cfDNA); tumour genotyping to select **actionable, targeted therapies**.
- ▶ **6. Pharmacogenomics** — genotype-guided drug selection and dosing to optimise efficacy and minimise adverse effects.
- ▶ **7. Research tools** — gene mapping/linkage studies, transgenic and knockout animal models, and functional genomics.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Gene-cloning flowchart (label clearly):** *Gene of interest* (source DNA) and *Plasmid vector* (showing origin of replication, selectable marker / ampR, lacZ) → both cut by the Restriction endonuclease (EcoRI) producing sticky ends → joined by DNA ligase → Recombinant (chimeric) plasmid → Transformation into *E. coli* host → Selection (antibiotic resistance + blue–white screening) → Recombinant colony → Cloning / Protein expression.
- ▶ **PCR cycle:** three boxes — Denaturation (94–95 °C) → Annealing of forward & reverse primers (50–65 °C) → Extension (72 °C, *Taq* polymerase, dNTPs), with an arrow showing exponential amplification (2ⁿ); label *template DNA*, *primers*, *dNTPs*, *thermal cycler*.

Clinical / Diagnostic significance

- ▶ Enables manufacture of pure, abundant, non-immunogenic human proteins (insulin, clotting factors), eliminating the infection risk and supply limits of animal/cadaveric/pooled-plasma sources.
- ▶ Permits diagnosis from minute samples and at the molecular level — carrier testing, prenatal/preimplantation diagnosis, infectious-disease detection and viral-load monitoring.
- ▶ Drives **precision/personalized medicine**: tumour mutational profiling guides targeted therapy; pharmacogenomic genotyping individualises prescribing.
- ▶ Provides definitive (potentially curative) therapy for previously untreatable genetic diseases via gene transfer and CRISPR gene editing.

High-yield exam pointers

- ▶ rDNA = joining DNA from two sources *in vitro*; three steps — cut (restriction enzyme) → paste (ligase) → clone/express (vector + host).
- ▶ Restriction endonucleases = molecular scissors; DNA ligase = molecular glue.
- ▶ Sticky (cohesive) ends allow vector–insert annealing; same enzyme must cut both.
- ▶ Recombinant selection: antibiotic-resistance markers + blue–white (lacZ) screening + colony hybridisation.
- ▶ PCR: denature 94–95 °C → anneal 50–65 °C → extend 72 °C (*Taq*); RT-PCR for RNA targets.
- ▶ Blotting mnemonic: Southern–DNA, Northern–RNA, Western–protein.
- ▶ **Human insulin (1982)** = first licensed recombinant therapeutic protein; mRNA SARS-CoV-2 vaccines and siRNA for hypercholesterolaemia are modern rDNA/RNA products.
- ▶ Gene-therapy vectors: retro/lentiviral (integrating, ex vivo), adenoviral, AAV (non-integrating), lipid nanoparticles; FDA approved the first CRISPR therapy (sickle cell disease/β-thalassaemia) in 2023.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (recombinant DNA/RNA technology for therapeutic proteins, vaccines, siRNA; PCR, FISH, NGS, mutational and prenatal analysis; CFTR/ Δ F508) and "Gene and Cell-Based Therapy in Clinical Medicine" (gene delivery vehicles/vectors, transduction, CRISPR/Cas9, approved gene/cell-therapy products including Strimvelis, Luxturna, Zolgensma, Zynteglo, Kymriah/Yescarta).
- ▶ **Coverage note:** Harrison 22e covers the *applications* of rDNA technology in depth but treats the **wet-lab cloning methodology only thinly** — the chapter explicitly states the detailed mutation-detection/molecular techniques were "discussed in previous versions of this chapter." Accordingly, the enzyme toolkit, the step-wise cloning protocol, the cloning-vector capacity figures (plasmid/phage/cosmid/BAC/YAC), blue-white screening and the blotting/Sanger details are presented as **standard, universally accepted molecular biology** rather than verbatim Harrison content; the spec flags this topic as a known thin-coverage (gap) area. The viral-vector packaging limits and all gene-therapy product details are taken directly from Harrison 22e.



Stem cell therapy

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

Definition / Introduction — A **stem cell** is an undifferentiated cell defined by two cardinal properties: *self-renewal* (the ability to divide while preserving an undifferentiated state) and *differentiation* (the capacity to generate the mature effector cells of a tissue). **Stem cell therapy** is the therapeutic exploitation of these properties to regenerate, replace, or genetically correct a diseased lymphohematopoietic or other tissue. In clinical practice today it spans three overlapping domains: (1) **hematopoietic cell transplantation (HCT)** — the dominant, well-established modality; (2) **gene-modified autologous stem-cell products** (ex vivo gene addition or gene editing); and (3) engineered immune effector cells (**CAR-T therapy**). Tens of thousands of lives are saved annually by stem-cell-based therapies.

Stem cell — properties and classification

- ▶ **Two cardinal functions** (Harrison, *Hematopoietic Stem Cells*): self-renewal sustains the stem-cell pool; differentiation produces mature cells. A dividing stem cell yields one of three outcomes — two stem cells, two differentiating cells (both *symmetric*), or one of each (*asymmetric division*).
- ▶ Self-renewal is regulated by **intrinsic factors** (Bmi-1, Gfi-1, PTEN, STAT5, p21, p18, HoxB4) and **extrinsic niche signals** (Notch, Wnt, Sonic hedgehog, angiogenin, Tie2/Ang-1).
- ▶ **Classification by potency**: *totipotent* (zygote → whole organism + placenta); *pluripotent* (embryonic stem cells, induced pluripotent stem cells [iPSC] → all three germ layers); *multipotent/adult (somatic)* stem cells — e.g., hematopoietic stem cells (HSC), mesenchymal stem cells (MSC).

Stem-cell type	Source	Potency	Principal clinical role
Hematopoietic (HSC)	Marrow, mobilised blood, cord blood	Multipotent	Established — HCT, gene therapy vehicle
Embryonic (ESC)	Inner cell mass	Pluripotent	Investigational
Induced pluripotent (iPSC)	Reprogrammed somatic cells	Pluripotent	Investigational/disease modelling
Mesenchymal (MSC)	Marrow stroma, fat, cord	Multipotent	Investigational (immunomodulation)
Cancer stem-like cells	Tumours	—	Relapse source; therapeutic target

The hematopoietic stem cell — markers, niche and mobilisation

- ▶ The HSC sustains all blood and immune lineages plus tissue-fixed macrophages (Kupffer cells, alveolar macrophages, osteoclasts, microglia, Langerhans cells). The estimated stem-cell pool of **20,000–200,000 cells** produces hundreds of billions of blood cells daily.
- ▶ **Surface phenotype (mainly murine-derived):** CD34, Thy-1 (CD90), c-Kit (CD117), CD133, CD164, and c-Mpl (CD110, the thrombopoietin receptor).
- ▶ **Niche:** for most of life the HSC resides in the **bone-marrow perivascular/endosteal niche**, regulated by mesenchymal and endothelial cells producing **kit ligand and CXCL12 (SDF-1)**, plus sympathetic neurons, Schwann cells, osteoblasts and osteoclasts. The niche both nurtures and constrains stem-cell number.
- ▶ **Homing & mobilisation:** circulating HSCs roll on endothelial **P-/E-selectins** (via CD162/CD44), firmly adhere through **VLA-4/VCAM-1** integrins, and home via **CXCL12–CXCR4** signalling. Clinically, **G-CSF** and **plerixafor** (a CXCR4 antagonist) disrupt this retention to release stem cells into blood, enabling harvest by **leukapheresis** rather than marrow puncture.
- ▶ **Clonal dynamics:** HSCs acquire ~17 somatic mutations per year; expansion of clones bearing *DNMT3A*, *TET2*, or *ASXL1* mutations underlies **clonal hematopoiesis of indeterminate potential (CHIP)**, predisposing to myeloid malignancy and adverse inflammatory outcomes.

SOURCE & COVERAGE

- Sources of stem cells (Harrison, *Hematopoietic Cell Transplantation*):

Source	Collection	Engraftment	GVHD	Notes
Bone marrow	Iliac-crest aspiration (10–15 mL/kg); $1.5-5 \times 10^8$ nucleated cells/kg	Reference	Lowest with unrelated donors	Original source
Peripheral blood (PBSC)	Leukapheresis after G-CSF $\pm$ plerixafor; aim $>2.5 \times 10^6$ CD34 ⁺ /kg	Fastest (~1 wk earlier)	More chronic GVHD (T-cell content)	Most commonly used
Umbilical cord blood	Cryopreserved units	~1 wk slower	Lowest (few T cells)	Tolerates HLA mismatch; double-cord units for adults

- Categories by donor relationship:

- **Autologous** — patient's own stored stem cells re-infused after high-dose therapy; **no** GVHD/rejection but **no graft-versus-tumour (GVT) effect** and risk of tumour-cell contamination.
- **Syngeneic** — identical twin (~1% of cases); no GVHD, no tumour contamination.
- **Allogeneic** — genetically non-identical donor; provides a **GVT effect** but risks GVHD and graft rejection.

- **HLA matching** (genes HLA-A, -B, -C, -D): odds that a full sibling matches = $\frac{1}{4}$; probability of an HLA-identical sibling = $1 - (0.75)^n$ (n = number of siblings). Matched unrelated donors are found for ~60% of patients via registries (>40 million donors). With HLA-identical siblings, graft rejection is 1–3% and severe acute GVHD ~15%. **Post-transplant high-dose cyclophosphamide** now permits **haploidentical** (single-haplotype-shared) transplantation.

Conditioning regimens and the transplant procedure

- The **preparative (conditioning) regimen** eradicates underlying disease and immunosuppresses the host to prevent graft rejection.
- **Myeloablative**: combinations of **busulfan**, **cyclophosphamide**, **melphalan**, **thiotepa**, **carmustine**, **etoposide**, **total-body irradiation (TBI)**.
 - **Reduced-intensity**: e.g., **fludarabine + melphalan** — significant but non-lethal myelosuppression; favoured in older/comorbid patients.
 - **Nonmyeloablative**: e.g., **fludarabine + 200 cGy TBI** — relies on the **GVT effect**.
- Disease-specific examples: SCID with a matched sibling needs **no conditioning**; aplastic anaemia — **cyclophosphamide + antithymocyte globulin (ATG)**; thalassaemia/sickle cell — **busulfan + cyclophosphamide**.
- **Engraftment**: marrow grafts reach 500 granulocytes/ μ L by ~day 22 (PBSC ~1 week faster, cord blood ~1 week slower). Innate immunity recovers in weeks; **adaptive (T- and B-cell) immunity**

takes 1–2 years. Donor chimerism is documented by sex-chromosome FISH or short-tandem-repeat analysis.

Clinical indications for stem cell transplantation

- ▶ **Non-malignant:** severe combined immunodeficiency (cure >90%), aplastic anaemia, β -thalassaemia major and sickle cell anaemia (HLA-identical sibling cure 80–90%), congenital marrow-failure and phagocyte disorders (Kostmann, chronic granulomatous disease, Wiskott-Aldrich, Chédiak-Higashi), osteopetrosis, selected storage diseases (Hurler, Gaucher), and increasingly **severe autoimmune disease** (a randomised trial showed survival benefit of HCT in severe scleroderma; trials ongoing in multiple sclerosis).
- ▶ **Malignant:** acute leukaemias (AML/ALL — allogeneic, guided by remission status and measurable residual disease), CML failing ≥ 2 tyrosine-kinase inhibitors, myelodysplasia (IPSS Int-2/high), myelofibrosis, lymphomas and Hodgkin disease (usually **autologous**), **multiple myeloma** (autologous as part of initial therapy), and **relapsed testicular germ-cell tumour** (autologous high-dose chemotherapy).

Disease	Allogeneic 3-yr survival	Autologous
Severe combined immunodeficiency	95%	—
Aplastic anaemia	98%	—
Thalassaemia	95%	—
AML (first remission)	57%	—
Multiple myeloma (initial)	—	80%
Hodgkin disease (2nd remission)	68%	89%

Complications of transplantation

- ▶ **Acute GVHD** (first ~3 months; peak ~4 weeks): triad of **maculopapular skin rash**, **cholestatic liver injury** (rising bilirubin), and **secretory diarrhoea**, graded I–IV. Prophylaxis = **calcineurin inhibitor** (cyclosporine/tacrolimus) + **methotrexate**, often with a third agent (mycophenolate, abatacept, or post-transplant cyclophosphamide). Treatment = **prednisone 1–2 mg/kg**; steroid-refractory disease responds to the JAK inhibitor **ruxolitinib**.
- ▶ **Chronic GVHD** (3 months–2 years; 20–50%): autoimmune-like — malar rash, sicca, arthritis, obliterative bronchiolitis, cholestasis. Steroid-resistant disease: **ibrutinib**, **ruxolitinib**, **belumosudil** (kinase inhibitors).
- ▶ **Regimen-related toxicity:** mucositis, **sinusoidal obstruction syndrome (SOS / veno-occlusive disease)** — tender hepatomegaly, ascites, jaundice; treated with **defibrotide**; haemorrhagic cystitis (prevent with MESNA); transplant-associated thrombotic microangiopathy (responds to **eculizumab**); late bronchiolitis obliterans, cataracts, infertility, hypothyroidism.
- ▶ **Infection** by phase: early neutropenic bacterial/Candida; intermediate **CMV**, **Aspergillus** (CMV prophylaxis with **letermovir** or pre-emptive ganciclovir); late encapsulated bacteria/VZV. Standard prophylaxis: levofloxacin, fluconazole/mould-active azole, **co-trimoxazole** for **Pneumocystis**, acyclovir.

- ▶ **Graft failure** and disease relapse — relapse after allograft may respond to **donor lymphocyte infusions** (CML response up to 75%).

Gene- and cell-based stem cell therapies (the modern frontier)

- ▶ **Why HSCs are the ideal gene-therapy target** (Harrison, *Gene and Cell-Based Therapy*): they persist for life, so genetic modification of autologous HSCs gives a durable, **HLA-matching-free, GVHD-free** cure. Transgene must integrate (lentiviral) or the target locus be edited; myeloablative conditioning is still needed.
- ▶ **Ex vivo gene-addition products (autologous HSCs)**: *Strimvelis* (retroviral, ADA-SCID), *Zynteglo* (lentiviral β^A -T87Q globin, transfusion-dependent β -thalassaemia/sickle cell disease), *Skysona* (cerebral adrenoleukodystrophy, ABCD1), *Libmeldy* (metachromatic leukodystrophy, ARSA). The **X-linked SCID** trials proved gene therapy could cure but revealed **insertional mutagenesis** (LMO-2 activation $\rightarrow$ T-ALL in 5/20 children), prompting the shift to safer lentiviral vectors.
- ▶ **Ex vivo gene editing**: *Casgevy* (exagamglogene autotemcel) — CRISPR/Cas9 inactivation of the **BCL11A** erythroid enhancer in autologous CD34⁺ cells, de-repressing **γ -globin/HbF** to treat sickle cell disease and β -thalassaemia ($\approx$ 29/31 patients free of vaso-occlusive crises).
- ▶ **CAR-T cell therapy**: autologous T cells engineered with a **chimeric antigen receptor** (antibody scFv + transmembrane + costimulatory **CD28 or 4-1BB** + CD3 ζ). Approved anti-**CD19** products (Kymriah, Yescarta, Tecartus, Breyanzi) for B-ALL and large-cell/mantle-cell lymphoma, and anti-**BCMA** products (Abecma, Carvykti) for myeloma — >80% complete-response rates in refractory B-ALL. Key toxicities: **cytokine release syndrome** (treat with **tocilizumab** $\pm$ steroids), **ICANS/neurotoxicity** (dexamethasone), B-cell aplasia/hypogammaglobulinaemia, and a boxed-warning risk of secondary T-cell malignancy.
- ▶ **Other cell therapies**: oncolytic virus *talimogene laherparepvec* (melanoma) and dendritic-cell vaccine (sipuleucel-T) for prostate cancer.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hematopoietic hierarchy**: central Hematopoietic stem cell with a curved *self-renewal* arrow $\rightarrow$ **Multipotent progenitor** branching into **Common lymphoid progenitor** ($\rightarrow$ B cell, T cell, NK cell) and **Common myeloid progenitor** ($\rightarrow$ **Granulocyte-monocyte progenitor** $\rightarrow$ monocyte/granulocyte; $\rightarrow$ **Megakaryocyte-erythroid progenitor** $\rightarrow$ platelets, RBCs). Annotate decreasing self-renewal and increasing proliferation/differentiation along the axis.
- ▶ **CAR vs native T-cell receptor**: label VH and VL (scFv antigen-binding domain), spacer, transmembrane (TM) domain, costimulatory domain (CD28 or 4-1BB), CD3 ζ signalling chain; alongside a native TCR $\alpha\beta$ chains recognising **antigenic peptide–MHC I** through the CD3 complex.

Clinical / Diagnostic significance

- ▶ Determine **HLA type early** in candidates (e.g., all AML patients) to enable timely donor search.

- ▶ **Autologous** transplant/gene therapy avoids GVHD and donor matching but lacks a GVT effect; **allogeneic** offers GVT at the cost of GVHD — the central therapeutic trade-off.
- ▶ Recognise and grade **GVHD** (skin/liver/gut) and monitor for **SOS, TMA, CMV reactivation, and PJP** — each has specific therapy (defibrotide, eculizumab, letermovir/ganciclovir, co-trimoxazole).
- ▶ Gene-edited and CAR-T recipients require **long-term surveillance** — lifelong monitoring for secondary malignancy after CAR-T, and 15-year insertion-site monitoring for integrating-vector HSC products.

High-yield exam pointers

- ▶ Two cardinal stem-cell properties: **self-renewal + differentiation**; achieved by **asymmetric division**.
- ▶ HSC markers: **CD34, CD90 (Thy-1), CD117 (c-Kit), CD133, CD110 (c-Mpl)**.
- ▶ Mobilisation = **G-CSF + plerixafor (CXCR4 antagonist)**; target autologous dose $>2.5 \times 10^6$ **CD34⁺ cells/kg**.
- ▶ HLA-identical sibling probability = $1 - (0.75)^n$; **post-transplant cyclophosphamide** enables **haploidentical** transplant.
- ▶ Conditioning intensity: myeloablative > reduced-intensity (**fludarabine + melphalan**) > nonmyeloablative (**fludarabine + 200 cGy TBI**).
- ▶ Acute GVHD = **skin + liver + gut**; first-line **prednisone**, steroid-refractory **ruxolitinib**. Chronic GVHD steroid-refractory: **ibrutinib/ruxolitinib/belumosedil**.
- ▶ **SOS** → **defibrotide**; **TMA** → **eculizumab**; **CMV** → **letermovir/ganciclovir**.
- ▶ **Casgevy** edits **BCL11A** to raise **HbF** in sickle cell disease/ β -thalassaemia; **X-linked SCID** trial caused **LMO-2 insertional T-ALL**.
- ▶ CAR-T costimulatory domains = **CD28 or 4-1BB**; CRS treated with **tocilizumab**.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Hematopoietic Stem Cells" (David T. Scadden, Dan L. Longo); "Hematopoietic Cell Transplantation" (Frederick R. Appelbaum); "Gene and Cell-Based Therapy in Clinical Medicine" (Katherine A. High, Marcela V. Maus).
- ▶ *Coverage note:* The Harrison corpus covers HSC biology, hematopoietic cell transplantation, and gene-/cell-based (CAR-T, gene-editing) therapy in depth. Coverage of **embryonic stem cell, iPSC, and mesenchymal stem cell** therapeutics is limited, as these remain largely investigational; the classification of stem cells by potency given above is standard, universally accepted textbook medicine. No dedicated specialty text or CMDT chapter was specified for this topic.



Evidence-based medicine

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

Definition / Introduction — Evidence-based medicine (EBM) is the conscientious, explicit and judicious integration of the **best available external clinical research evidence** with **individual clinical expertise** and the **patient's values and preferences** to make decisions about the care of individual patients. It updates the traditional model of clinical medicine (knowledge + intuition + judgement) by placing far greater emphasis on the *processes* by which clinicians obtain the most up-to-date and relevant research to determine for themselves whether an intervention alters disease course or improves length/quality of life. As described by its founding proponents at *McMaster University* in the early 1990s, EBM is practised as a structured, repeatable cycle of well-defined steps — classically summarised as the "5 A's" (Ask, Acquire, Appraise, Apply, Assess).

The EBM cycle — the five steps ("5 A's")

Step	"A"	Core task	Key tools
1	Ask	Convert the clinical problem into a focused, answerable question	PICO / PICOT framework
2	Acquire	Search the literature/online databases efficiently for the best external evidence	MEDLINE, EMBASE, Cochrane Library, DARE
3	Appraise	Critically appraise the evidence for validity, importance (magnitude) and applicability	Risk-of-bias checks, AMSTAR2, levels of evidence
4	Apply	Integrate the appraisal with clinical expertise and the patient's unique features and preferences	Shared decision-making, NNT/ARR
5	Assess	Evaluate one's own performance/outcome and record for future use (audit)	Audit, reflective record-keeping

- ▶ Harrison frames the cycle as **four key steps** (formulate the question → search literature/databases → appraise validity & relevance → integrate with the unique patient and their preferences); the widely taught **fifth step (self-audit / "Assess" / recording for future use)** completes the loop. Both framings are reproduced below.

Step 1 — ASK: frame an answerable clinical question

- ▶ Asking a **well-built clinical question** generated from a real patient encounter is arguably the **single most important step** — a sharp question makes searching and appraisal far easier and forces the clinician to define the patient, intervention and outcomes precisely.
- ▶ Use the **PICO** acronym (a fifth element, *Time-frame*, gives **PICOT**):
 - **P** — *Patient / Problem* (e.g., immunocompetent child with cutaneous warts).
 - **I** — *Intervention* (the test, drug or exposure of interest).
 - **C** — *Comparator* (placebo/vehicle or an alternative; optional).
 - **O** — *Outcome* (a clinically important, patient-relevant endpoint).
 - **T** — *Time-frame* over which the outcome is judged.

- Questions are categorised by domain — **therapy, diagnosis, prognosis, aetiology/harm, and prevention** — because the question type dictates which study design is the "best evidence."

Step 2 — ACQUIRE: search for the best external evidence

- Conduct a **predefined, reproducible, explicit search** of the literature and online databases (MEDLINE, EMBASE, the *Cochrane Database of Systematic Reviews*, DARE) rather than relying on memory or a single textbook.
- Searching the world's literature and appraising it is time-consuming and demands skills most busy clinicians lack; hence the pragmatic shortcut of seeking a recent, high-quality **systematic review** that has already synthesised the primary studies (the *Cochrane* reviews are the prototype).
- Pre-appraised, pre-synthesised resources (systematic reviews, guidelines, evidence summaries) sit at the top of the practical search strategy.

Step 3 — APPRAISE: critically appraise the evidence

Appraisal asks three questions: **Are the results valid? What are the results (importance/magnitude)? Will they help my patient (applicability)?** This rests on the **hierarchy of evidence**, where the strength of evidence depends on the *type of question* asked.

Level	Therapy / harm question — best evidence
1a	Systematic review of multiple RCTs with homogeneity
1b	Individual RCT with narrow confidence intervals
1c	" All-or-none " effect (e.g., streptomycin for TB meningitis, insulin for diabetes)
2a/2b	Cohort studies (with homogeneity / individual cohort or low-quality RCT)
2c	" Outcomes " research (cost–benefit, cost–effectiveness, cost–utility)
3a/3b	Case–control studies
4	Case series (and poor-quality cohort/case–control studies)
5	Expert opinion without explicit appraisal; bench research; logical deduction

- (*Oxford Centre for Evidence-Based Medicine levels.*) For **diagnosis** questions, the best evidence is an **independent, blind comparison** of an appropriate spectrum of consecutive patients against a reference ("gold") standard; for **rare harms**, cohort/case–control studies, post-marketing surveillance and pharmacovigilance are most useful.
- **Study quality outranks design label**: a well-conducted cohort study can be more reliable than a small, poorly conducted RCT. The best therapeutic evidence comes from large, fully masked RCTs with **concealed allocation** and **intention-to-treat** analysis.
- **Systematic reviews & meta-analysis** are regarded by many as the apex of the hierarchy because they comprehensively and reproducibly summarise the evidence; meta-analysis can reveal a true benefit that individually underpowered trials missed (classically, the benefit of **streptokinase/thrombolysis in acute MI** was evident by cumulative meta-analysis a decade before large trials/guidelines confirmed it). They are *not* infallible — they cannot remedy

deficient primary data and should include **unpublished trials** to avoid **publication bias**; tools such as AMSTAR2 appraise their quality.

Tools of appraisal — quantifying test performance and treatment effect

- ▶ **Diagnostic test metrics** — *sensitivity* (detection of diseased), *specificity* (detection of non-diseased), and ROC curves illustrating their trade-off.
- ▶ **Bayes' rule / post-test probability** — the post-test probability of disease is derived from the **pre-test probability** (prevalence/clinical context), **sensitivity** and **specificity**, summarised by the **likelihood ratio (LR)**:
 - **LR positive** = sensitivity / (1 – specificity); **LR negative** = (1 – sensitivity) / specificity.
 - An LR+ >10 markedly raises (rules *in*) the probability of disease; a very low LR– rules it *out*. The **Bayes nomogram** (Fig. 4-2) connects pre-test probability + LR to read off post-test probability.
- ▶ **Treatment-effect metrics** (essential for the "Apply" step):
 - **Absolute Risk Reduction (ARR)** = control event rate – treatment event rate.
 - **Relative Risk Reduction (RRR)** = ARR ÷ control event rate.
 - **Number Needed to Treat (NNT)** = 1 / ARR — e.g., a therapy cutting 5-year mortality from 12% → 8% gives ARR = 4% and NNT = 25. The same relative benefit applied to a lower-risk group (6% → 4%) gives ARR 2% and NNT 50 — illustrating that absolute benefit falls as baseline risk falls.
 - **Odds ratio / relative risk** are the usual summary measures of relative benefit; clinicians must always also examine the *absolute* benefit and harms.

Step 4 — APPLY: integrate evidence with expertise and patient values

- ▶ Integrate the appraised evidence with the **clinician's own expertise** and the **individual patient's circumstances, comorbidities and preferences** — the "average" trial patient may not resemble the patient in front of you (external validity/generalisability).
- ▶ Ask: *Can these results be applied to my patient? Were all clinically important outcomes considered? Do the benefits outweigh the harms and costs?*
- ▶ **Clinical practice guidelines** (Institute of Medicine 1990: "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances") operationalise EBM but are meant to **assist, not dictate** — guideline-level evidence alone is never sufficient for an individual decision (notably, <15% of cardiovascular guideline recommendations rest on the highest level of trial evidence). This is the locus of **shared decision-making**.

Step 5 — ASSESS: audit and record

- ▶ Evaluate your own performance in executing steps 1–4 and the patient's outcome; **record the information for future use** so the appraised answer can be reused efficiently. This closes the loop and underpins clinical **audit and quality improvement** — guideline-derived "best practices" become **quality indicators** (e.g., proportion of acute-MI patients given aspirin on admission; proportion of HFrEF patients on an ACE inhibitor).

Limitations and threats to EBM (examiner favourites)

- ▶ **Limitations:** publication bias; poor methodological quality of many trials; lack of evidence in many areas; reliance on **summary (group) statistics** that mask individual responses.
- ▶ **Threats:** data-driven and sponsor-funded systematic reviews, selective outcome reporting, non-publication of negative trials, "spin," ghost-writing.
- ▶ EBM is an **ideal, not a finished tool**: most clinical problems will never be tested in an RCT, so excellent clinical reasoning plus respect for patient preferences remain paramount.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Evidence pyramid (hierarchy of evidence):** a triangle, broad base to narrow apex labelled bottom-to-top — *In-vitro/bench research* → *Animal research* → *Ideas/editorials/expert opinion* → *Case reports* → *Case series* → *Case-control studies* → *Cohort studies* → *Randomised controlled trials* → *Systematic reviews & meta-analyses (apex)*.
- ▶ **The EBM cycle (5 A's):** a circular loop of five boxes with arrows returning to the start — *Ask (PICO)* → *Acquire (search)* → *Appraise (validity, importance, applicability)* → *Apply (integrate with expertise + patient values)* → *Assess (audit/record)* → *back to Ask*.

Clinical / Diagnostic significance

- ▶ Provides a **reproducible, teachable framework** for translating a bedside problem into an evidence-supported decision, reducing reliance on anecdote and cognitive bias (anchoring, premature closure).
- ▶ Quantitative outputs (LR, post-test probability, NNT/ARR) let clinicians **calibrate testing and treatment thresholds** to an individual's baseline risk and to weigh benefit against harm and cost.
- ▶ Anchors **guideline development, clinical audit and quality indicators**, and frames **shared decision-making** by making the strength and limits of evidence explicit to the patient.

High-yield exam pointers

- ▶ EBM = best external evidence + clinical expertise + patient values/preferences; originated at *McMaster University*, early 1990s.
- ▶ Remember the 5 A's: **Ask** → **Acquire** → **Appraise** → **Apply** → **Assess** (Harrison lists the first four; the fifth is self-audit/recording).
- ▶ Step 1 question structured as **PICO(T)**; categorise by therapy/diagnosis/prognosis/harm/prevention.
- ▶ Hierarchy/best design by question: **therapy** → **RCT**; **diagnosis** → **cross-sectional study vs gold standard**; **prognosis** → **cohort**; **rare harm** → **case-control / pharmacovigilance**.
- ▶ **Systematic review/meta-analysis** = **apex**; *Cochrane* is the prototype; beware **publication bias** (include unpublished/negative trials); appraise with **AMSTAR2**.
- ▶ **NNT** = $1/ARR$; **LR+** = $\text{sensitivity}/(1 - \text{specificity})$, **LR+** > 10 strongly rules in disease; use the **Bayes nomogram** for post-test probability.
- ▶ Quality can trump design: a good cohort study may beat a poor RCT; demand **concealed allocation + intention-to-treat**.

- ▶ Guidelines (IOM 1990 definition) **assist, not dictate**; <15% of CV recommendations rest on top-level evidence — individualise.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Decision-Making in Clinical Medicine" (the four key EBM steps; sources of evidence — clinical trials, registries, RCTs, meta-analysis; Bayes' rule, sensitivity/specificity, likelihood ratios, post-test probability; ARR/NNT; clinical practice guidelines and quality indicators).
- ▶ **Rook's Textbook of Dermatology, 10e** — "Principles of Evidence-based Dermatology" (used for the general EBM framework: the explicit **five-step cycle**, **PICO/PICOT**, the **hierarchy/levels of evidence** (Oxford CEBM), NNT, AMSTAR2, and the limitations/threats to EBM — these principles are generic to internal medicine).
- ▶ *Coverage note:* The RGUHS-suggested Harrison chapter covers the **content** of EBM richly but presents the cycle as **four steps** rather than the canonical **five-step "5 A's"**; the five-step structure and PICO/levels-of-evidence detail were grounded in Rook's general EBM chapter. The "5 A's" labelling (Ask/Acquire/Appraise/Apply/Assess) and **GRADE-style certainty rating** are universally accepted standard EBM terminology used here to organise the answer.



Internal capsule — structure and blood supply

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

Definition / Introduction — The **internal capsule** is a thick, compact, V-shaped (boomerang-shaped) sheet of **projection white matter** that carries virtually all the afferent (thalamocortical) and efferent (corticofugal) fibres travelling between the cerebral cortex and the brainstem/spinal cord. On a horizontal section it lies wedged between the **caudate nucleus and thalamus medially** and the **lentiform nucleus (putamen + globus pallidus) laterally**, with its apex (genu) pointing medially. Superiorly it fans out into the **corona radiata**; inferiorly it condenses into the **crus cerebri (cerebral peduncle)**. Because an enormous volume of motor and sensory traffic is funnelled through a small territory fed by tiny perforating end-arteries, a lesion barely a few millimetres across (a *lacune*) can produce a dense contralateral hemiplegia — making this anatomy of major clinical importance.

Gross anatomy, relations and subdivisions

- ▶ **Course:** continuous above with the **corona radiata** (subcortical white matter) and below with the **crus cerebri**; medially it borders the diencephalon, laterally the basal ganglia.
- ▶ On a horizontal (axial) section the capsule has five named parts; on a sagittal view the retrolenticular and sublenticular components are best appreciated:
 - **Anterior limb** — lies between the **head of the caudate** (medially) and the **lentiform nucleus** (laterally).
 - **Genu** — the bend/apex; relates to the lateral wall of the third ventricle; abuts the ICA-derived perforators.

- **Posterior limb** — lies between the **thalamus** (medially) and the **lentiform nucleus** (laterally); the largest and clinically most important segment.
- **Retrolenticular part** — fibres lying *behind* the lentiform nucleus.
- **Sublenticular part** — fibres passing *beneath* the lentiform nucleus toward the temporal lobe.

Fibre content of each part

Part	Principal fibre tracts	Functional traffic
Anterior limb	Anterior (frontal) thalamic radiation; frontopontine fibres	Prefrontal–dorsomedial/anterior thalamic loops; frontal → pontine relay
Genu	Corticobulbar (corticonuclear) fibres; corticopontine fibres to facial & hypoglossal nuclei	Supranuclear control of bulbar/cranial-nerve motor nuclei
Posterior limb	Corticospinal (pyramidal) fibres, somatotopically arranged; superior thalamic radiation (sensory); corticorubral, corticoreticular fibres	Voluntary limb movement; thalamocortical somatosensory relay
Retrolenticular part	Optic radiation (geniculocalcarine fibres); posterior thalamic radiation	Vision (LGB → calcarine cortex)
Sublenticular part	Auditory (acoustic) radiation; temporopontine fibres	Hearing (MGB → Heschl's gyrus)

- *Brazis* confirms the corpus-derived correlates: **corticospinal fibres run in the posterior limb**, the **corticobulbar/corticopontine fibres to facial and hypoglossal nuclei are concentrated in the genu**, the **superior thalamic radiation** (light-touch/pin sensation) travels in the posterior limb, and the **geniculocalcarine (optic) fibres** lie in the retrolenticular white matter.

Blood supply

The capsule is perfused almost entirely by small, deep **perforating (penetrating) end-arteries** with little collateral overlap — hence its vulnerability to lacunar infarction in hypertension and small-vessel disease.

Part of capsule	Arterial supply (parent vessel)
Anterior limb	Medial lenticulostriate branches / recurrent artery of Heubner from the A1 (precommunal) segment of the ACA; deep A1 perforators
Genu	Penetrating lenticulostriate perforators (single-vessel occlusion → <i>capsular genu syndrome</i>); classically also direct small branches of the internal carotid artery
Posterior limb	Superior part — lateral lenticulostriate arteries from the M1 segment of the MCA; inferior/main part — anterior choroidal artery (branch of the ICA)
Retrolenticular part	Anterior choroidal artery (with contribution from the posterior choroidal artery of the PCA)
Sublenticular part	Anterior choroidal artery

- ▶ **Recurrent artery of Heubner (medial striate artery):** arises from the lateral aspect of the ACA (A1/proximal A2) and supplies the **anteroinferior limb of the internal capsule, anterior putamen and caudate, and the tip of the outer globus pallidus.** (Harrison: A1 deep penetrators supply the anterior limb, anterior perforated substance, amygdala, anterior hypothalamus and inferior head of caudate.)
- ▶ **Lateral lenticulostriate arteries:** penetrating branches of the proximal MCA (M1) supply the putamen, outer globus pallidus, posterior limb of the internal capsule, adjacent corona radiata and most of the caudate; *Brazis* adds that they feed the superior portion of both the anterior and posterior limbs.
- ▶ **Anterior choroidal artery (AChA):** arises from the internal carotid artery distal to the posterior communicating artery; supplies the posterior limb of the internal capsule, the retrolenticular white matter (through which the geniculocalcarine fibres pass), the optic tract, lateral geniculate body, midbrain and choroid plexus of the temporal horn. It is vulnerable to iatrogenic occlusion during clipping of ICA aneurysms.

Somatotopic organisation (high-yield)

- ▶ Corticospinal fibres in the posterior limb are arranged **antero-posteriorly: face → arm → trunk → leg.**
- ▶ *Harrison:* ischaemia at the genu causes **facial weakness first**, then arm, then leg, as the infarct extends **posteriorly** within the capsule.
- ▶ *Brazis:* at superior capsular levels the **face/bulbar muscles** are affected by lesions of the **genu or anterior posterior limb**, whereas **more posterior lesions cause arm and leg weakness.**
- ▶ A "parathalamic rim" of the posterior limb carries the sensory tracts; small lacunes that spare this rim produce a **pure motor** deficit.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Horizontal (axial) section of internal capsule** (lentiform nucleus, caudate head, thalamus drawn around a V-shaped capsule). Label: *Anterior limb, Genu, Posterior limb, Retrolenticular part, Sublenticular part; Head of caudate nucleus, Putamen, Globus pallidus (lentiform), Thalamus; fibre content — frontopontine/anterior thalamic radiation (anterior limb), corticobulbar (genu), corticospinal + superior thalamic radiation (posterior limb), optic radiation (retrolenticular), auditory radiation (sublenticular); somatotopy face→arm→leg in posterior limb.*
- ▶ **Diagram 2 — Blood supply / coronal vascular territory.** Label: *Anterior limb → recurrent artery of Heubner (ACA-A1) + medial lenticulostriates; Genu → lenticulostriates/ICA branches; Posterior limb (superior) → lateral lenticulostriates (MCA-M1); Posterior limb (inferior) + retrolenticular → anterior choroidal artery (ICA).*

Clinical / Diagnostic significance

- ▶ **Pure motor hemiparesis** — the commonest lacunar syndrome; infarct in the **posterior limb of the internal capsule** (or corona radiata/basis pontis) → contralateral face-arm-leg weakness with little/no sensory loss (*Harrison, Brazis*).

- ▶ **Ataxic hemiparesis and dysarthria–clumsy hand syndrome** — lacunes of the **posterior limb** or **genu/anterior limb** (or basis pontis) respectively.
- ▶ **Sensorimotor stroke** — posteroventral thalamus + adjacent **posterior limb**.
- ▶ **Capsular genu syndrome** — contralateral facial and lingual paresis with dysarthria, mastication–palatal–pharyngeal weakness; bilateral genu lesions may cause cognitive/behavioural change.
- ▶ **Capsular warning syndrome** — clustering TIAs affecting face, arm and leg from threatened occlusion of a **single lenticulostriate artery**, heralding a completed capsular infarct.
- ▶ **Anterior choroidal artery syndrome (Foix)** — the classic triad of contralateral **hemiplegia** (**posterior-limb corticospinal interruption**), **hemianaesthesia** (**superior thalamic radiation**), and **homonymous hemianopia** (**optic tract/LGB/optic radiation**), often with macular/horizontal-meridian sparing.
- ▶ **Artery of Heubner infarction** — contralateral **face and arm weakness without sensory loss** (anterior-limb + anterior putamen).
- ▶ **Investigation: MRI with diffusion-weighted imaging (DWI)** is the most sensitive for acute lacunes; perforators are too small to be seen on CT/CT-angiography. Hypertension and age are the principal risk factors (lipohyalinosis/microatheroma of penetrators).

High-yield exam pointers

- ▶ Internal capsule = compact **projection fibres**, continuous above with **corona radiata**, below with **crus cerebri**; five parts — anterior limb, **genu**, posterior limb, retrolenticular, sublenticular.
- ▶ **Corticospinal fibres** → **posterior limb**; **corticobulbar** → **genu**; **optic radiation** → **retrolenticular**; **auditory radiation** → **sublenticular**.
- ▶ **Somatotopy** of posterior limb: **face (anterior)** → **arm** → **leg (posterior)**.
- ▶ Blood supply summary: **Anterior limb** = **recurrent artery of Heubner (ACA)**; **Posterior limb** = **lateral lenticulostriates (MCA)** + **anterior choroidal artery (ICA)**; **Retrolenticular/sublenticular** = **anterior choroidal artery**.
- ▶ A tiny **lacune** in the posterior limb can cause a **dense hemiplegia** — disproportionate deficit for lesion size.
- ▶ **Pure motor hemiparesis** = the signature capsular lacunar syndrome; lenticulostriate occlusion.
- ▶ **Anterior choroidal artery triad** = **hemiplegia** + **hemianaesthesia** + **hemianopia**; high risk of **iatrogenic occlusion during ICA aneurysm clipping**.
- ▶ These are **perforating end-arteries** with poor collaterals → **hypertension/age** drive lacunar disease; **DWI-MRI** is the key test.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Introduction to Cerebrovascular Diseases" (lenticulostriate territory; ACA-A1, MCA-M1 and anterior choroidal artery supply of the internal-capsule limbs) and "Ischemic Stroke" (lacunar/small-vessel syndromes; posterior-limb and genu correlations).
- ▶ **Brazis, Masdeu & Biller — *Localization in Clinical Neurology*** — "Vascular Syndromes of the Forebrain, Brainstem, and Cerebellum" (recurrent artery of Heubner, anterior choroidal artery, lenticulostriate territories, capsular genu and anterior-choroidal syndromes, lacunar-infarction table) and "Localization of Lesions Affecting the Cerebral Hemispheres" (capsular somatotopy, parathalamic sensory rim, corticobulbar/corticospinal fibre course).

Coverage note: The corpus (Harrison + Brazis) covers the **blood supply, fibre correlates and lacunar/clinical syndromes** in depth and is the primary grounding here. The fine **descriptive neuroanatomy of fibre content** (anterior thalamic radiation, frontopontine, auditory radiation in the sublenticular part) is given as **universally accepted standard neuroanatomy** (Gray's/Snell), consistent with and partly confirmed by the Brazis text; no specifics have been fabricated.



Temperature regulation

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

Definition / Introduction — Thermoregulation is the homeostatic process by which the body maintains its **core temperature** within a narrow physiological range (36.5–37.5°C / 97.7–99.5°F) despite wide swings in environmental temperature and metabolic activity. It is governed by the **hypothalamus**, which acts as a biological thermostat with a defined "**set point**," balancing **heat production** against **heat loss**. A regulated upward shift of this set point produces **fever**, whereas failure of heat dissipation with an *unchanged* set point produces **hyperthermia** — a distinction that is clinically and therapeutically pivotal.

Normal body temperature, variation and measurement

- ▶ **Normal core range:** 36.5–37.5°C; mean **oral temperature** 36.6°C (95% CI 35.7–37.3°C) in a study of >35,000 adults. A temperature >37.7°C (>99.9°F) — the 99th percentile for healthy individuals — defines **fever**.
- ▶ **Diurnal rhythm:** lowest at 8 a.m., highest at 4 p.m.; also lower in summer, higher in winter.
- ▶ **Physiological modifiers:** temperature falls ~0.02°C per 10-year increase in age; African-American women run **0.052°C higher** than white men; cancer raises baseline ~0.02°C, hypothyroidism lowers it ~0.01°C.
- ▶ **Menstrual cycle:** a.m. temperature is low for the 2 weeks before ovulation, then rises ~0.6°C (1°F) at **ovulation** and stays elevated through the luteal phase until menses.
- ▶ **Site corrections (high-yield):**

Site	Relationship to oral / core
Oral	Reference; lower if mouth-breathing (tachypnoea)
Rectal	~0.4°C (0.7°F) higher than oral
Lower oesophageal	Closely reflects true core temperature
Tympanic membrane (unadjusted mode)	~0.8°C (1.6°F) lower than rectal; more variable

Hypothalamic control and the "set-point" model

- ▶ The **preoptic anterior hypothalamus** and **posterior hypothalamus** integrate two afferent inputs: (1) **peripheral** signals from cutaneous **warmth/cold receptors** via peripheral nerves, and (2) **central** signals from the **temperature of blood** bathing the hypothalamic neurons.
- ▶ The **thermoregulatory centre** compares these inputs against the **set point** and drives efferent responses to keep blood temperature matched to that setting — analogous to a **home thermostat**.
- ▶ In a thermoneutral environment, basal **metabolism produces more heat than is needed**; the hypothalamus continuously balances this excess heat production (muscle, liver) against dissipation (skin, lungs).
- ▶ A standing concept: a natural "**thermal ceiling**" (~106°F) appears to be defended by central **antipyretic neuropeptides**, so most infective fevers rarely exceed this without CNS involvement.

Heat balance — production vs loss (effector mechanisms)

- ▶ **Heat-gain / conservation effectors** (triggered when actual temperature is *below* set point, i.e., the chill/rigor phase of rising fever):
 - **Cutaneous vasoconstriction** — vasomotor-centre neurons shunt blood from skin of hands/feet to the core, reducing radiant loss; the patient *feels cold*.
 - **Shivering thermogenesis** — increased heat production from skeletal muscle.
 - **Non-shivering thermogenesis** — increased metabolic heat from the **liver** (and, in standard physiology, brown adipose tissue — see Coverage note).
 - **Behavioural** — putting on clothing/bedding to reduce heat loss.
- ▶ **Heat-loss effectors** (triggered when actual temperature is *above* set point — e.g., when the set point is reset downward by antipyretics, the defervescence/flush phase):
 - **Cutaneous vasodilation and sweating** (evaporative loss).
 - **Behavioural** — removal of clothing.
- ▶ During fever, body temperature typically rises by 1–2°C; these conservation and production processes continue until blood temperature reaches the new febrile "thermostat setting," then are held there by normal afebrile balance mechanisms.

Fever versus hyperthermia (must distinguish)

Feature	Fever	Hyperthermia
Hypothalamic set point	Raised (e.g., 37→39°C)	Unchanged / normal

Feature	Fever	Hyperthermia
Mechanism	Pyrogen-driven; regulated rise	Uncontrolled rise exceeding heat-loss capacity
Pyrogenic molecules	Present (cytokines, PGE2)	Absent
Typical cause	Infection, inflammation, malignancy	Exogenous heat exposure / excess endogenous heat production (exertion, drugs blocking sweating, heat stroke)
Skin	May be cold (vasoconstriction)	Hot but characteristically dry (in heat stroke / anhidrotic drugs)
Response to antipyretics	Responds (aspirin/acetaminophen lower it)	Does NOT respond
Urgency	Usually benign, self-limited	Can be rapidly fatal

- ▶ **Hyperpyrexia:** fever $>41.5^{\circ}\text{C}$ ($>106.7^{\circ}\text{F}$) — seen in severe infection and especially CNS haemorrhage.
- ▶ **Hypothalamic fever:** rare regulated set-point elevation from local **trauma, haemorrhage, tumour, or intrinsic hypothalamic malfunction** — but most patients with hypothalamic damage are paradoxically **subnormal**, not supranormal.

Pathogenesis of fever — resetting the set point upward

- ▶ **Exogenous pyrogens:** microbial products/toxins. Classic example is **lipopolysaccharide (endotoxin)** of gram-negative bacteria (fever at 2–3 ng/kg IV in humans). Gram-positive toxins act as **superantigens** (e.g., TSST-1, staphylococcal enterotoxins, streptococcal pyrogenic exotoxins; fever at 1–10 µg/kg).
- ▶ **Pyrogenic cytokines** (formerly "endogenous pyrogens"): small proteins (10–20 kDa) — IL-1, IL-6, TNF, interferons, ciliary neurotropic factor — released from **monocytes/macrophages and endothelial cells**. IL-1 and TNF produce fever at 10–100 ng/kg; IL-6 requires 1–10 µg/kg. Fever can also arise *without* infection (pericarditis, trauma, stroke, immunisation).
- ▶ **Final common pathway — PGE2:** cytokines (and direct Toll-like receptor/IL-1 receptor activation) act on the **hypothalamic endothelium** near the **circumventricular organ — organum vasculosum of the lamina terminalis** — raising **prostaglandin E2 (PGE2)**. PGE2 (chiefly via the **EP-3 receptor**, essential for fever) stimulates glial release of **cyclic AMP**, which acts as the neurotransmitter that **elevates the thermoregulatory set point**.
- ▶ Peripheral PGE2 induced in tissues accounts for the **myalgias and arthralgias** of fever.

Antipyresis — restoring the set point downward

- ▶ Fever is reduced by lowering the elevated set point, achieved by **reducing hypothalamic PGE2**.
- ▶ **Cyclooxygenase (COX) inhibitors** are the principal antipyretics; potency correlates with inhibition of **brain COX**. **Aspirin and acetaminophen** are equally effective; NSAIDs (**ibuprofen**) and COX-2 inhibitors are also excellent antipyretics.
- ▶ **Acetaminophen** is a poor peripheral COX inhibitor (minimal anti-inflammatory action) but in the brain is oxidised by **cytochrome P450** to an active COX-inhibiting form (with proposed

COX-3 inhibition); it is the **preferred** antipyretic given the platelet/GI effects of aspirin and NSAIDs.

- ▶ In children, use **acetaminophen or ibuprofen** — aspirin risks **Reye syndrome** with certain viral infections.
- ▶ **Glucocorticoids** act at two levels: inhibit **phospholipase A2** (less arachidonic-acid substrate for PGE2) and block **transcription of pyrogenic cytokine mRNA**.
- ▶ Chronic high-dose antipyretics do **not** lower *normal* core temperature — confirming PGE2 has **no role in normal thermoregulation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — "Chronology of fever induction" (Harrison Fig 20-1):** vertical flow with labels — *Infection, microbial toxins, mediators of inflammation, immune reactions* → *Monocytes/macrophages, endothelial cells* → *Pyrogenic cytokines (IL-1, IL-6, TNF, IFN)* → *Circulation* → *Hypothalamic endothelium* → *PGE2* → *cyclic AMP* → *Elevated thermoregulatory set point* → *Heat conservation, heat production* → *Fever*.
- ▶ **Diagram 2 — Hypothalamic "thermostat" balance:** central box *Hypothalamic set point* with afferents labelled *Skin warmth/cold receptors* and *Temperature of blood*; left arm *Heat production / conservation* (labels: *vasoconstriction, shivering, non-shivering thermogenesis, behaviour*); right arm *Heat loss* (labels: *vasodilation, sweating, behaviour*). Show set point shifting up = **fever**, set point normal but load > loss = **hyperthermia**.

Clinical / Diagnostic significance

- ▶ **Therapeutic crux:** confirm fever vs hyperthermia — hyperthermia (heat stroke, neuroleptic malignant/serotonin syndrome, malignant hyperthermia) is an emergency, does **not** respond to antipyretics, and needs **physical/external cooling** rather than COX inhibitors.
- ▶ **Metabolic cost:** every 1°C above 37°C raises oxygen consumption by ~13% — hence the rationale to treat fever in cardiac, pulmonary or neurologically compromised patients.
- ▶ **Temperature–pulse dissociation (relative bradycardia):** typhoid, brucellosis, leptospirosis, drug fever, factitious fever.
- ▶ **Blunted febrile response** (may have serious infection *without* fever): neonates, elderly, chronic liver/renal failure, and patients on **glucocorticoids or anticytokine therapy** — septic shock may even cause **hypothermia**.
- ▶ **Investigations:** CBC with manual differential (band forms, toxic granulations, Döhle bodies suggest bacterial infection), **CRP and ESR** for occult inflammation; circulating cytokine levels are not clinically useful.

High-yield exam pointers

- ▶ Control centre = **hypothalamus**: preoptic anterior (heat-loss) + posterior hypothalamus integrating **skin receptor** and **blood-temperature** inputs against a **set point**.
- ▶ Normal core 36.5–37.5°C; fever >37.7°C; **hyperpyrexia** >41.5°C.
- ▶ Rectal +0.4°C over oral; tympanic (unadjusted) –0.8°C below rectal; oesophageal ≈ core.

- ▶ **Fever = raised set point; hyperthermia = normal set point, failed heat loss** — only fever responds to antipyretics.
- ▶ Final mediator of fever = **PGE2** acting via **EP-3 receptor** near the **OVL**; COX inhibitors are antipyretic.
- ▶ Rising fever = **vasoconstriction + shivering** (feels cold); defervescence = **vasodilation + sweating** (flush).
- ▶ **Acetaminophen preferred**; aspirin avoided in children (**Reye syndrome**); glucocorticoids inhibit **PLA2** + cytokine transcription.
- ▶ **+13% O₂ consumption per 1°C**; relative bradycardia in typhoid/brucellosis/leptospirosis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 20 "Fever"** (Dinarello & Surana): thermoregulation, hypothalamic set-point, normal temperatures and measurement, fever vs hyperthermia, pyrogen/cytokine/PGE2 pathogenesis, and antipyretic pharmacology.

Coverage note (gap flagged): Ch 20 is fever-centric; *pure thermoregulatory physiology* is covered only insofar as it underlies fever. The four physical mechanisms of heat exchange (**radiation, conduction, convection, evaporation**) and **brown adipose tissue** as the dedicated organ of non-shivering thermogenesis are universally accepted standard physiology but are **not detailed in Ch 20** (which cites skin/lung dissipation and hepatic non-shivering thermogenesis) — included here only as standard textbook physiology. Detailed hyperthermia syndromes and heat-stroke management belong to Harrison Ch 478 (referenced by Ch 20 but not provided for this answer).



Teratogenesis

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

Definition / Introduction — A **teratogen** is any agent (drug, chemical, physical factor, infectious organism or maternal metabolic state) that, acting during embryonic or fetal development, causes a permanent structural or functional abnormality in the conceptus. **Teratogenesis** is the process by which such abnormal development is initiated; the four classic manifestations are **death (abortion/stillbirth), structural malformation, intrauterine growth restriction (IUGR) and functional/behavioural deficit**. Only ~2–3% of major congenital anomalies are attributable to recognised drug/chemical teratogens, yet these are among the most *preventable* causes of birth defects, making preconception counselling a core internal-medicine responsibility for women of reproductive age.

Wilson's principles and the critical periods of development

The internist must grasp *when, to whom* and *how much* exposure produces harm — encapsulated in Wilson's six principles of teratology:

- ▶ **Genotype-dependence** — susceptibility depends on the genotype of the conceptus and how it interacts with the environment (e.g., slow vs fast hydroxylators, *MTHFR* polymorphisms).

- ▶ **Timing (developmental stage)** — susceptibility varies sharply with the stage of development at exposure (see critical periods below).
- ▶ **Mechanism-specific action** — each agent acts through a specific pathogenetic mechanism on developing cells/tissues.
- ▶ **Access depends on the agent** — manifestation requires the agent (or its metabolite) to reach the conceptus; this is governed by maternal absorption/metabolism and placental transfer (favoured by low molecular weight, lipid solubility, non-ionisation, low protein binding).
- ▶ **Four end-points** — the manifestations are *death, malformation, growth retardation and functional deficit*.
- ▶ **Dose-response** — severity and frequency rise with dose, from a *no-effect threshold* up to a wholly lethal level.

Critical periods (timing of exposure):

Stage	Timing (post-conception)	Dominant effect
Pre-implantation / blastogenesis	0–2 weeks	"All-or-none" — embryonic death and resorption, or complete recovery; structural defects uncommon
Embryonic period (organogenesis)	3–8 weeks	Maximum vulnerability to major structural malformations — organ-specific defects depending on what is forming
Fetal period	9 weeks–term	Functional deficits, growth restriction, minor anomalies (CNS, palate, teeth, external genitalia remain vulnerable)

This is why poor periconceptional glycaemic control in diabetes acts during the **critical first 5–8 weeks of embryonic growth**, increasing spontaneous abortion and congenital malformation, and why cytotoxic chemotherapy is *virtually never* given in the first trimester.

Mechanisms of teratogenesis

Teratogens converge on a limited number of cellular/molecular pathways:

- ▶ **Folate antagonism / impaired one-carbon metabolism** — antifolate and antiepileptic drugs (methotrexate, valproate, carbamazepine, phenytoin, trimethoprim) impair DNA synthesis and neural-tube closure → neural tube defects (NTDs) and orofacial clefts.
- ▶ **Disruption of the morphogen/retinoic-acid signalling pathway** — retinoids (isotretinoin) deregulate neural-crest migration → craniofacial, cardiac, thymic and CNS defects.
- ▶ **Neural-crest cell disruption** — impaired migration/apoptosis of crest cells underlies many craniofacial and conotruncal cardiac malformations (e.g., retinoids, alcohol).
- ▶ **Vascular disruption / hypoxia–ischaemia** — vasoconstriction or thrombosis interrupts blood supply to developing structures (limb-reduction and bowel-atresia patterns; cocaine, misoprostol).
- ▶ **Oxidative stress and free-radical injury** — reactive intermediates (e.g., of phenytoin, alcohol) damage embryonic macromolecules.

- ▶ **Receptor- or enzyme-mediated and endocrine disruption** — ACE-inhibitor/ARB blockade of the fetal renin–angiotensin system → renal tubular dysgenesis and oligohydramnios; androgens → virilisation; antithyroid drugs → fetal goitre/aplasia cutis.
- ▶ **Inhibition of cell proliferation / programmed cell death and impaired DNA synthesis** — cytotoxic chemotherapy, ionizing radiation.
- ▶ **Direct cytotoxic and tissue-tropic effects** — tetracycline chelates calcium in mineralising tissues (teeth, bone); aminoglycosides are cochleo-vestibulotoxic; intrauterine infection (e.g., rubella, CMV, Zika) directly destroys fetal tissue.

Major teratogenic agents and their characteristic effects

Agent	Characteristic effect on conceptus
ACE inhibitors / ARBs	Renal tubular dysgenesis, oligohydramnios, calvarial hypoplasia, IUGR, stillbirth and congenital anomalies — <i>contraindicated</i> in pregnancy
Warfarin	Fetal warfarin syndrome — <i>chondrodysplasia (chondromalacia) punctata</i> , nasal hypoplasia, stippled epiphyses; CNS injury and neonatal bleeding; avoid in 1st trimester (used only for mechanical valves; bridge to heparin at 36 weeks)
Valproate / other antiseizure drugs	NTDs (spina bifida), orofacial clefts, neurodevelopmental impairment — <i>discontinue before conception</i> ; prefer lamotrigine/levetiracetam
Phenytoin	<i>Fetal hydantoin syndrome</i> — digital/nail hypoplasia, facial dysmorphism, growth/cognitive deficit
Methimazole / carbimazole	<i>Aplasia cutis</i> , choanal/oesophageal atresia (crosses placenta more than PTU)
Isotretinoin / systemic retinoids	Retinoic-acid embryopathy — CNS, craniofacial (ear), cardiac and thymic defects; strict pregnancy-prevention programme
Methotrexate / aminopterin	Cranial dysostosis, limb defects, IUGR (aminopterin syndrome)
Lithium	Cardiac defects, classically <i>Ebstein's anomaly</i>
Tetracyclines	Deciduous-tooth discoloration and bone-growth inhibition (2nd–3rd trimester)
Aminoglycosides (streptomycin)	Eighth-nerve (cochleo-vestibular) ototoxicity, may be irreversible
Thalidomide	Limb-reduction defects — <i>phocomelia/amelia</i> (historical prototype teratogen)
Diethylstilbestrol (prenatal)	Vaginal clear-cell adenocarcinoma and genital-tract anomalies in exposed daughters
Alcohol	Fetal alcohol spectrum disorder — IUGR, microcephaly, characteristic facies, intellectual disability
Cytotoxic chemotherapy / ionizing radiation	First-trimester exposure → abortion and malformation; both generally avoided

Agent	Characteristic effect on conceptus
Infections (TORCH)	<i>Rubella</i> (cataract, cardiac, deafness), <i>CMV</i> (microcephaly, intracranial calcification, chorioretinitis), <i>Zika</i> (severe microcephaly, CNS malformation, fetal death), toxoplasma, syphilis, VZV, HSV

Risk factors for teratogenesis

- ▶ **Drug/medication exposure** — particularly the high-risk drugs above; polypharmacy and self-medication in early, often unrecognised, pregnancy.
- ▶ **Maternal disease/metabolic state** — *pregestational diabetes* with poor periconceptional control, *obesity*, untreated maternal PKU, and thyroid disease all raise the malformation rate.
- ▶ **Maternal infection** — primary first-trimester rubella, CMV, Zika, toxoplasmosis, syphilis.
- ▶ **Physical agents** — therapeutic/diagnostic *ionizing radiation* and sustained maternal *hyperthermia*.
- ▶ **Environmental/recreational toxins** — alcohol, tobacco, organic mercury (Minamata), lead, certain solvents.
- ▶ **Nutritional deficiency** — periconceptional *folate deficiency* (and antifolate drug use) — the lower the maternal folate, the greater the NTD risk.
- ▶ **Genetic susceptibility of the conceptus and timing/dose of exposure** (per Wilson's principles).
- ▶ **Advanced maternal age** — chiefly increases chromosomal (aneuploidy) risk rather than environmental teratogenesis.

Prevention and preconception counselling

Prevention is overwhelmingly *preconceptional and primary*:

- ▶ **Periconceptional folic acid** — **0.4 mg/day** before and at conception (continued through the first 12 weeks) reduces NTDs (anencephaly, meningomyelocele, encephalocele, spina bifida) by ~80% and also lowers cleft-palate/lip risk; **high-risk women** (previous NTD-affected fetus, diabetes, sickle-cell disease, on antiepileptic drugs) need **4–5 mg/day**. Population-level **food fortification** addresses poor supplement compliance.
- ▶ **Preconception optimisation of maternal disease** — tight glycaemic control before conception in diabetes; review and *switch teratogenic drugs* (stop ACE-I/ARB, valproate, warfarin, isotretinoin, statins; substitute pregnancy-compatible agents) ideally before conception.
- ▶ **Rational, lowest-effective-dose prescribing** in any woman of reproductive potential; treat the mother adequately (untreated maternal disease may itself harm the fetus).
- ▶ **Pregnancy-prevention programmes** for proven teratogens — e.g., the regulated isotretinoin programme: two negative pregnancy tests before initiation and a negative test before every refill, with mandated contraception.
- ▶ **Drug-safety classification** — the former FDA **pregnancy categories A, B, C, D, X** (X = contraindicated) have largely been replaced by the **2015 Pregnancy & Lactation Labeling Rule (PLLR)** narrative format.

- ▶ **Immunisation** — ensure rubella and varicella immunity *before* pregnancy (MMR ≥ 3 months pre-conception); give influenza, COVID-19 and Tdap in pregnancy. Antenatal screening for rubella, syphilis, hepatitis B/C, HIV.
- ▶ **Avoid teratogenic exposures** — abstain from alcohol/tobacco; minimise diagnostic ionizing radiation; counsel on travel to Zika-endemic areas.
- ▶ **Antenatal surveillance** — maternal serum screening, detailed anomaly ultrasound (and fetal echocardiography in high-risk groups) for early detection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **"Critical periods of human development" timeline** — a horizontal bar from fertilisation to term divided into: *Weeks 0–2 (pre-implantation = "all-or-none")*, *Weeks 3–8 (embryonic period = organogenesis = maximal structural-malformation risk, shown as solid red bars)*, *Weeks 9–38 (fetal period = functional defects/growth restriction, shown as lighter bars)*. Add organ-specific sensitivity bars labelled *CNS, heart, limbs, eyes, ears, teeth, palate, external genitalia*.
- ▶ **Wilson's-principles concept map** — central box *"TERATOGEN"* with arrows to the four outcome labels: *Death, Malformation, Growth retardation, Functional deficit*, and side labels *Genotype, Timing, Mechanism, Access/Placental transfer, Dose–response*.

Clinical / Diagnostic significance

- ▶ Establishing teratogenic causation requires consistent exposure during the relevant critical window, a recognisable pattern of anomalies, and a biologically plausible mechanism.
- ▶ A drug history must be taken in *every* woman of reproductive age; the highest-risk window (organogenesis) often precedes recognition of the pregnancy — hence preconception, not antenatal, intervention.
- ▶ Detection: maternal serum markers, **anomaly ultrasound**, fetal echocardiography, and amniocentesis/cordocentesis where indicated; congenital rubella confirmed by IgM on fetal blood, CMV/Zika by maternal serology/NAAT with serial ultrasound.
- ▶ Management pearls: substitute pregnancy-safe alternatives (labetalol/nifedipine for hypertension instead of ACE-I/ARB; LMWH instead of warfarin except mechanical valves; PTU in the first trimester for hyperthyroidism); supplement folic acid 4 mg/day with antiepileptic drugs; counsel on the option of therapeutic termination after high-risk first-trimester exposure.

High-yield exam pointers

- ▶ **Teratogen** = agent causing permanent structural/functional fetal abnormality; four end-points = *death, malformation, growth retardation, functional deficit*.
- ▶ **Organogenesis (weeks 3–8 post-conception) = period of maximum structural-malformation risk**; weeks 0–2 = "all-or-none"; fetal period = functional/growth effects.
- ▶ **Wilson's six principles**: genotype, timing, mechanism, access, four end-points, dose–response.
- ▶ **ACE-I/ARB** → renal dysgenesis/oligohydramnios/stillbirth; **warfarin** → chondrodysplasia punctata + nasal hypoplasia; **valproate** → NTDs; **isotretinoin** → retinoic-acid embryopathy; **lithium** → Ebstein's anomaly; **thalidomide** → phocomelia; **DES** → vaginal clear-cell

adenocarcinoma; **tetracycline** → stained teeth; **aminoglycoside** → VIII-nerve deafness; **methimazole** → aplasia cutis.

- ▶ **Folic acid 0.4 mg/day** (high-risk 4–5 mg/day) periconceptionally cuts NTDs ~80%.
- ▶ Prevention is *preconceptional*: optimise maternal disease, switch teratogenic drugs, ensure rubella/varicella immunity, avoid alcohol and unnecessary radiation.
- ▶ Old FDA categories A–B–C–D–X superseded by the PLLR (2015) narrative labelling.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Medical Disorders During Pregnancy" (drug management in pregnancy: ACE-I/ARB, warfarin, antithyroid drugs, valproate/antiseizure drugs, chemotherapy/radiation, TORCH infections, diabetes and obesity in pregnancy); "Megaloblastic Anemias / Vitamin B12 and Folic Acid" (folic acid and NTD prevention); "Disorders of the Skin" (isotretinoin teratogenicity and pregnancy-prevention programme); "Treatment and Prophylaxis of Bacterial Infections / antimicrobials in pregnancy" (tetracyclines, aminoglycosides); "Approach to the Patient with Cancer / cancer prevention" (diethylstilbestrol → vaginal clear-cell carcinoma; folic acid in prevention).
- ▶ **Coverage note:** Harrison 22e covers individual agent-specific teratogens and pregnancy drug-management well but does **not** contain a dedicated account of teratogenesis *mechanisms*, **Wilson's principles of teratology**, the formal **critical-period framework**, or the named dysmorphic syndromes (fetal hydantoin/warfarin syndromes, FAS, Ebstein with lithium, aminopterin syndrome, thalidomide-phocomelia) and the FDA category/PLLR scheme — these are presented from **universally accepted standard internal-medicine/teratology** and are flagged here for transparency. No specialty teratology textbook was listed in the spec corpus.



Therapeutic index

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

Definition / Introduction — The **therapeutic index (TI)** — also called the **therapeutic ratio** or, when expressed as a concentration range, the **therapeutic window** — is a quantitative measure of the *safety* of a drug. It expresses the separation between the dose (or plasma concentration) that produces the **desired therapeutic effect** and the dose (or concentration) that produces **toxicity**. A drug is "well-tolerated" when there is a **wide margin** between these two dose–response relations; conversely, when the curves lie close together the drug has a **narrow therapeutic index** and even small dosage increments may sharply increase the likelihood of harm. The concept therefore underpins rational dose selection, safety monitoring and the practice of therapeutic drug monitoring (TDM).

Quantitative basis — definitions and formulae

- ▶ Drug effects (both beneficial and adverse) follow a series of **quantal dose–response (cumulative frequency) curves**, where the proportion of a population showing a defined response is plotted against log dose/concentration (Fig. 71-1, Harrison).
- ▶ Three reference doses are read from these sigmoid curves:
 - **ED₅₀** (median *effective* dose) — dose producing the specified therapeutic effect in 50% of the population.
 - **TD₅₀** (median *toxic* dose) — dose producing a defined toxic effect in 50%.
 - **LD₅₀** (median *lethal* dose) — dose killing 50% (derived from animal/preclinical data).

Index	Formula	Meaning / use
Therapeutic Index (clinical)	$TI = TD_{50} / ED_{50}$	Higher ratio = safer drug
Therapeutic Index (preclinical)	$TI = LD_{50} / ED_{50}$	Animal data during drug development
Certain Safety Factor / Margin of Safety	$CSF = LD_1 / ED_{99}$ (or TD_1/ED_{99})	More reliable than TI; accounts for curve <i>slope</i> and overlap of extremes
Standard Safety Margin	$[(LD_1 - ED_{99})/ED_{99}] \times 100$	% dose increase from near-maximal efficacy to onset of lethality

- ▶ The TI is a **ratio with no units**; the larger the value, the greater the cushion between efficacy and toxicity.
- ▶ The plain TI (TD_{50}/ED_{50}) can be **misleading** when the two curves are not parallel, because it ignores the extremes of the population. The **certain safety factor** (LD_1/ED_{99}) corrects for this by comparing the dose that *just begins* to be toxic with the dose giving *near-maximal* benefit, and is the more clinically meaningful safety index.

Graphical representation (wide vs narrow ratio)

- ▶ **Wide therapeutic ratio:** the desired-effect and adverse-effect curves are **widely separated** — therapeutic doses carry a low probability of toxicity (e.g., penicillins, most modern antimicrobials).

- ▶ **Narrow therapeutic ratio:** the curves are **close / overlapping**, so the chance of toxicity at therapeutic doses is high; a **steep dose–response curve for adverse effects** is especially dangerous because a small dosage increment produces a large jump in toxicity risk.
- ▶ When a reproducible **concentration–effect** relationship exists, *plasma concentration* may be substituted for dose on the x-axis, which is the rationale for using measured drug levels (TDM) to steer therapy.

Narrow-therapeutic-index drugs and their target ranges

These agents require dose individualisation, level monitoring and caution with interactions/organ dysfunction.

Drug	Usual therapeutic range	Notes / monitoring caveat
Digoxin	HF 0.5–0.9 ng/mL; AF 0.5–2 ng/mL	Hypokalaemia potentiates toxicity; toxicity is a <i>clinical</i> diagnosis
Lithium	0.5–1.2 mmol/L	Thiazides/loop diuretics raise levels
Phenytoin	10–20 mg/L (5–10 in uraemia/hypoalbuminaemia); free target 0.5–2.0 mg/L	Capacity-limited (zero-order) kinetics; monitor <i>free</i> drug if low albumin/renal failure
Theophylline	5–15 mg/L (panic ≥30)	Clearance ↑ in smokers, ↓ in HF/cirrhosis
Valproic acid	50–100 mg/L (≤125 bipolar; panic >150)	Concentration-dependent protein binding
Carbamazepine	4–12 mg/L	Auto-induces own metabolism
Gentamicin	Peak 4–8 mg/L, trough <2 mg/L	Nephro-/oto-toxicity with high troughs
Vancomycin	Trough 10–20 mg/L	Trough-guided dosing; nephrotoxicity risk
Cyclosporine / Tacrolimus	CsA 100–300 ng/mL; Tac trough 8–12 ng/mL	Whole-blood (EDTA) trough; concentration-related nephrotoxicity
Warfarin	(INR-guided, not level)	Numerous CYP2C9/VKORC1 and drug interactions

Therapeutic window and therapeutic drug monitoring (TDM)

- ▶ The **therapeutic window** is the **concentration range** lying *above* the minimum effective concentration but *below* the toxic threshold; TDM aims to keep plasma levels within it.
- ▶ TDM is most valuable for drugs with: a **narrow therapeutic index**, a good **concentration–effect correlation**, **no easily measured clinical endpoint**, and **wide pharmacokinetic variability** — typically anticonvulsants, antiarrhythmics, anti-rejection agents and certain antibiotics (Harrison).
- ▶ **Timing matters:** for most maintenance dosing, sample at **trough** (just before the next dose at steady state) to confirm maintained efficacy — e.g., anticonvulsants and **vancomycin** (trough used because sustained high levels risk nephrotoxicity). When **peak**-related toxicity is the concern (e.g., QT prolongation with **sotalol/dofetilide**), the ECG/level is checked **~1–2 h post-dose** at steady state.

- ▶ **Steady state** is reached in ~4–5 **elimination half-lives**; a level drawn before steady state under-reads the eventual value. A **loading dose** speeds attainment of effect but does *not* change the time to true steady state.
- ▶ **First- vs zero-order kinetics**: in first-order elimination, doubling the dose doubles the steady-state level (linear, predictable). For **zero-order (saturable)** drugs — **phenytoin, aspirin, fluoxetine, ethanol** — a small dose increase causes a **disproportionate, sometimes toxic, rise** in concentration; this *functionally narrows* the therapeutic index and mandates small increments.

Factors that narrow or shift the therapeutic index

- ▶ **Altered clearance**: renal disease (digoxin, **dofetilide**, **sotalol** → QT/arrhythmia), hepatic disease (↑ oral bioavailability of high first-pass drugs — morphine, midazolam, nifedipine), heart failure/shock (contracted volume of distribution → higher plasma/CNS levels).
- ▶ **Altered protein binding**: only **free (unbound)** drug is active; in renal/hepatic disease or hypoalbuminaemia a fall in binding from 99→98% **doubles** free drug — hence free-level monitoring for phenytoin/valproate.
- ▶ **Drug interactions**: CYP and P-glycoprotein **inhibitors** (amiodarone, azoles, macrolides, cimetidine) raise levels of narrow-index substrates (warfarin, digoxin, dabigatran), while **inducers** (rifampin, carbamazepine, phenytoin, St John's wort) lower them — both pushing the patient outside the window.
- ▶ **"High-risk pharmacokinetics"**: when an active narrow-index drug relies on a **single elimination pathway**, any genetic, disease or drug-interaction block of that pathway causes marked, sometimes toxic, accumulation.
- ▶ **Extremes of age & genetics**: the elderly (polypharmacy, reduced organ function) and pharmacogenomic variants (e.g., **CYP2C9/VKORC1** for warfarin, **TPMT** for thiopurines) effectively shrink the safe margin.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two stacked quantal dose–response graphs** (x-axis = *log dose/concentration*, y-axis = *cumulative % of population responding*). On EACH panel draw two sigmoid curves: a left "Desired/therapeutic effect" curve and a right "Adverse/toxic effect" curve.
 - **Top panel — Wide therapeutic ratio**: curves *widely separated*. Label ED_{50} and TD_{50} ; show the wide gap.
 - **Bottom panel — Narrow therapeutic ratio**: curves *close/overlapping* with a steep toxicity curve. Labels: ED_{50} , TD_{50} (or LD_{50}), **Therapeutic window/index** = TD_{50}/ED_{50} , **Margin of safety** = LD_1/ED_{99} , and arrows marking *minimum effective concentration* and *minimum toxic concentration*.

Clinical / Diagnostic significance

- ▶ **Drug selection & dosing**: prefer wide-TI drugs where possible; for narrow-TI agents, "**start low, go slow**," use the smallest effective dose and titrate against levels or a clinical endpoint.
- ▶ **TDM** converts an abstract index into bedside practice — confirming adherence, diagnosing toxicity vs under-dosing, and guiding dose in renal/hepatic impairment.

- ▶ **Adverse drug reactions:** narrow-TI drugs are over-represented among the commonest culprits of ADR-related hospital admission (digoxin, warfarin, NSAIDs, opiates). **Type A** (dose-dependent, exaggerated pharmacology) reactions are the ones predicted by a low TI; **Type B** (idiosyncratic, dose-independent) reactions are *not* captured by the TI.
- ▶ **Drug development & regulation:** the preclinical LD_{50}/ED_{50} in animals is an early safety screen; a low TI demands tighter clinical-trial monitoring and may preclude approval.
- ▶ **Antidotes/rescue tied to the index:** digoxin-specific Fab (Digibind) for digoxin toxicity, leucovorin/glucarpidase rescue for methotrexate, and N-acetylcysteine for paracetamol all reflect the consequences of crossing a narrow window.

High-yield exam pointers

- ▶ $TI = TD_{50}/ED_{50}$ (clinical) or LD_{50}/ED_{50} (animal) — higher = safer; it is a **unitless ratio**.
- ▶ The **certain safety factor** (LD_1/ED_{99}) / standard safety margin is **more reliable** than TI because it accounts for curve slope and the extremes of the population.
- ▶ **Therapeutic window** = the *concentration range* above minimum effective and below toxic level; basis of TDM.
- ▶ Classic narrow-TI drugs: digoxin, lithium, warfarin, phenytoin, theophylline, aminoglycosides, vancomycin, cyclosporine/tacrolimus, antiarrhythmics, methotrexate.
- ▶ **Zero-order (saturable) kinetics** (phenytoin, aspirin, ethanol, fluoxetine) cause disproportionate level rises → behave as narrow-window drugs.
- ▶ Sample at **trough** for efficacy/most anticonvulsants and vancomycin; at **peak** (1–2 h) when peak toxicity (sotalol/dofetilide QT) is feared; interpret only at **steady state** (~4–5 half-lives).
- ▶ **Hypokalaemia worsens digoxin toxicity**; monitor **free phenytoin** in hypoalbuminaemia/renal failure; enzyme **inhibitors/inducers** and renal/hepatic disease shift the window.
- ▶ A **steep adverse-effect dose–response curve** is the single most dangerous feature — small dose rises cause large toxicity jumps.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Clinical Pharmacology" (Roden): therapeutic ratio/index/window concept and Fig. 71-1; dose–response relations; TDM, trough vs peak sampling (vancomycin, sotalol/dofetilide); first- vs zero-order kinetics; steady state and loading dose; high-risk pharmacokinetics; protein binding and free drug; Type A vs Type B ADRs; effects of renal/hepatic disease and drug interactions.
- ▶ **CMDT 2026** — **Appendix: Therapeutic Drug Monitoring (Table e5–1)**: therapeutic concentration ranges, half-lives and monitoring caveats for digoxin, lithium, phenytoin, theophylline, valproate, carbamazepine, gentamicin, vancomycin, cyclosporine/tacrolimus and methotrexate.
- ▶ **Coverage note:** Harrison presents the therapeutic index *qualitatively* (therapeutic ratio/window with the dose–response figure). The *quantitative* formulae — $TI = TD_{50}/ED_{50}$ (or LD_{50}/ED_{50}), the certain safety factor = LD_1/ED_{99} and standard safety margin — are universally accepted standard pharmacology (Goodman & Gilman / KDT / Katzung) included here for completeness, as the corpus chapter does not state these ratios explicitly.

**Organ transplant rejection**

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

Definition / Introduction — *Rejection* is the immune-mediated injury of a transplanted allograft caused by the recipient's recognition of donor **alloantigens** (chiefly mismatched HLA molecules) as foreign. It is classified by **tempo** (hyperacute, accelerated, acute, chronic) and by the **dominant effector arm** (T cell-mediated/cellular vs antibody-mediated/humoral). Understanding the pathogenesis underpins HLA matching, cross-matching, desensitization, and the entire framework of immunosuppression that has made transplantation the treatment of choice for end-stage organ failure.

Immunological basis — the alloimmune response

- ▶ **The target** — **HLA/MHC**: The major histocompatibility antigens are encoded on the short arm of **chromosome 6** (the HLA region). **Class I** (HLA-A, B, C) is expressed on all nucleated cells and presents to **CD8+** cells; **Class II** (HLA-DR, DQ, DP) is expressed on antigen-presenting cells (APCs) and presents to **CD4+** cells. HLA is highly **polymorphic**, so it becomes the principal immunologic target when mismatched. The number of mismatches at A, B and DR loci correlates with graft loss. ABO blood-group antigens and "minor" (non-HLA) antigens (e.g., endothelial antigens, the **LIMS-1** locus) provide additional targets.
- ▶ **Allorecognition** — **two pathways (Fig. 325-1)**:
 - **Direct pathway** — recipient T cells recognise *intact* donor MHC on **donor (passenger)** APCs: CD8 T cells recognise donor class I; CD4 T cells recognise donor class II. This drives early, vigorous acute rejection.

- **Indirect pathway** — donor MHC is shed, processed and presented as **peptides by recipient (self) APCs** to CD4 T cells. This mirrors normal physiologic antigen recognition and sustains **chronic rejection and antibody production**.
- ▶ **Two-signal T-cell activation:** Signal 1 = TCR binding to alloantigen–MHC; **Signal 2 (costimulation)** = CD28 on the T cell engaging CD80/CD86 on the APC. Both signals activate **calcineurin**, upregulating IL-2 and IFN- γ ; IL-2 acts via the **mTOR (target of rapamycin)** pathway to drive clonal proliferation — the molecular targets of CNIs, belatacept and mTOR inhibitors respectively.
- ▶ **Two effector arms:** T cell–mediated (CD8 cytotoxic killing + CD4-driven cytokine inflammation) and **antibody-mediated** (follicular helper T cells [T_{fh}] → B-cell/plasma-cell differentiation → **donor-specific antibody [DSA]** → complement-dependent and -independent endothelial injury, marked by C4d deposition).

Classification of rejection by tempo and mechanism

Type	Onset	Dominant mechanism	Key pathology	Reversibility
Hyperacute	Minutes–hours	Preformed anti-donor antibody (ABO / anti-HLA class I) + complement	Vascular thrombosis, fibrinoid necrosis, cortical infarction	Irreversible — graft loss; prevent by cross-match
Accelerated	2–5 days	Anamnestic (memory) T-cell + antibody response in a sensitised recipient	Vascular + cellular injury	Often refractory to treatment
Acute — cellular (TCMR)	Days–weeks to months	Recipient CD4/CD8 T cells vs donor HLA	Interstitial mononuclear infiltrate, tubulitis, endothelialitis (Banff)	Usually reversible with steroids $\pm$ ATG
Acute — antibody-mediated (AMR)	Days–weeks	De novo / preformed DSA + complement	C4d+ peritubular capillaries, capillaritis, glomerulitis	Harder to treat; plasmapheresis, IVIG, rituximab
Chronic	Months–years	Combined indirect alloimmunity, chronic active AMR, non-immune injury	Interstitial fibrosis, tubular atrophy, vasculopathy (intimal proliferation), glomerulopathy	Largely irreversible ; slowly progressive

Pathogenesis of each type

- ▶ **Hyperacute rejection:** Caused by **preformed circulating antibodies** against donor antigens — natural anti-ABO isohaemagglutinins or **anti-HLA** antibodies from prior **transfusion, pregnancy, prior transplant**, or (rarely) vaccination/infection. Antibody binds graft endothelium, fixes complement, and triggers a fulminant **vasculitic thrombotic** event with immediate, irreversible graft loss. A **positive cytotoxic cross-match** (recipient serum + donor T lymphocytes) predicts it and is **the only widely accepted absolute immunologic contraindication** to transplantation. Now largely *abolished* by routine ABO matching and cross-matching.

- ▶ **Accelerated rejection:** A rapid (2–5 day) anamnestic response in a **presensitised** recipient — secondary exposure to a previously primed antigen produces an immune response often **refractory to conventional treatment**. (A standard recognised category; Harrison emphasises the underlying mechanism of prior sensitisation rather than the eponymous label.)
- ▶ **Acute T cell-mediated (cellular) rejection (TCMR):** Recipient T cells respond to donor HLA. CD4+ cells recognise class II (HLA-DR) mismatch, proliferate and release proinflammatory cytokines; CD8+ cytotoxic cells recognise class I (HLA-A, -B) and lyse donor target cells via **perforin/granzyme B** and direct contact. Histology = immune-cell infiltration of the **interstitial, tubular and vascular** compartments (graded by the **Banff** classification). Clinically a **rise in serum creatinine** ± reduced urine output; treated with high-dose **methylprednisolone (0.5–1 g/day × 3 days)**, with ATG for steroid-resistant cases.
- ▶ **Acute antibody-mediated rejection (AMR):** Donor antigens drain to recipient lymph nodes, activating T_{fh} cells that drive B cells into **antibody-secreting plasma cells**. The resulting DSA (anti-HLA and non-HLA) deposit in the graft, injuring endothelium through complement-dependent and -independent routes. Diagnostic triad: (1) **C4d deposition** in peritubular capillaries/GBM, (2) **histologic microvascular injury** (capillaritis/glomerulitis), and (3) **circulating DSA**. Treatment is challenging — **plasmapheresis, IVIG, anti-CD20 (rituximab)** to deplete B cells, and **bortezomib** to target plasma cells.
- ▶ **Chronic rejection / chronic allograft dysfunction:** A slow, largely irreversible decline driven by **chronic active AMR**, indirect alloimmunity, and non-immune insults (CNI nephrotoxicity, hypertension, recurrent disease). Pathology = **interstitial fibrosis, tubular atrophy, transplant vasculopathy** (intimal proliferation, medial hypertrophy) and **glomerulopathy**. In the liver, the equivalent is **ductopenia** — the "**vanishing bile duct syndrome**" (progressive cholestasis, focal necrosis, vascular intimal fibrosis/foam cells), commoner after transplant for autoimmune liver disease and with limited reversibility.

Diagnosis and grading

- ▶ **Allograft biopsy is the gold standard** for distinguishing acute TCMR from AMR and from non-rejection causes (acute tubular injury, CNI toxicity, **BK polyomavirus** nephropathy, recurrent glomerular disease).
- ▶ **Banff classification** grades cellular rejection by the compartments infiltrated; **C4d immunostaining** of peritubular capillaries is the footprint of complement activation in AMR.
- ▶ **Immunologic work-up:** **Panel-reactive antibody (PRA)** quantifies sensitisation; **cytotoxic vs flow-cytometric cross-match** (more sensitive, detects anti-HLA IgG); **epitope matching** (especially class II DQ) refines risk.
- ▶ **Emerging non-invasive biomarkers:** donor-derived **cell-free DNA**, urinary chemokine **CXCL9**, urine exosome profiling — adjuncts to (not replacements for) biopsy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Allorecognition pathways** (redraw Fig. 325-1): Label — *Donor APC* (MHC I + MHC II), *Recipient (self) APC*, *Direct pathway* (CD8 T cell → donor MHC I; CD4 T cell → donor MHC II), *Indirect pathway* (self-APC presenting processed allopeptide on MHC II to CD4 T cell), *Th1/Th2/Th17*, *Tfh* → *naïve B cell* → *plasma cell* → *antibody-mediated rejection*, *Cytotoxic CD8 T cell* → *perforin/granzyme B* → *cellular rejection and organ damage*.
- ▶ **Timeline bar of rejection types**: a horizontal time axis labelled — *Minutes–hours* = *Hyperacute* (*preformed Ab*), *2–5 days* = *Accelerated* (*sensitised*), *Days–weeks–months* = *Acute* (*TCMR / AMR*), *Months–years* = *Chronic* (*fibrosis, vasculopathy*); annotate dominant mechanism and reversibility above each band.

Clinical / Diagnostic significance

- ▶ **Prevention starts before surgery**: ABO compatibility, HLA typing (now molecular/genomic), and a negative cross-match. **Desensitization** (plasmapheresis + IVIG ± rituximab) and **kidney paired donation** allow safe transplantation of sensitised candidates.
- ▶ **Immunosuppression** is lifelong (except identical twins). **Induction** = depleting (ATG, alemtuzumab/anti-CD52) or non-depleting (**basiliximab**, anti-IL-2R α) agents; **Maintenance** = a **calcineurin inhibitor** (**tacrolimus/cyclosporine**) + **antimetabolite** (**mycophenolate**) ± steroids, with **mTOR inhibitors** (**sirolimus/everolimus**) or **belatacept** (CTLA-4-Ig blocking CD28 costimulation; BENEFIT trial) as alternatives.
- ▶ **Treatment of established rejection**: TCMR → pulse methylprednisolone, then ATG if refractory; AMR → plasmapheresis + IVIG + rituximab ± bortezomib.
- ▶ **Complications of the immunosuppressed state**: time-dependent **opportunistic infection** (CMV, BK virus, *Pneumocystis*, fungal), and **malignancy** (skin/lip cancers, EBV-driven PTLD) — the balance against rejection must always be weighed.
- ▶ **Contrast — graft-versus-host disease (GVHD)**: the *reverse* of rejection. In allogeneic haematopoietic-stem-cell/bone-marrow transplantation, **immunocompetent donor T cells** **attack recipient (host) tissues** (skin, gut, liver), producing acute and chronic GVHD — host-versus-graft is rejection, graft-versus-host is GVHD.

High-yield exam pointers

- ▶ **Three classic types** = **Hyperacute**, **Acute**, **Chronic**; add **Accelerated** (*sensitised*) for completeness. Acute subdivides into **cellular** (TCMR) and **antibody-mediated** (AMR).
- ▶ **Hyperacute** = **preformed antibody** + **positive cytotoxic cross-match** = **only absolute immunologic contraindication**; occurs in minutes–hours; now largely abolished by cross-matching.
- ▶ **TCMR**: CD4 → class II, CD8 → class I; Banff-graded interstitial/tubular infiltrate; steroid-responsive.
- ▶ **AMR diagnostic triad**: **C4d+ peritubular capillaries**, **microvascular injury**, **circulating DSA**.
- ▶ **Direct allorecognition** drives early acute rejection; **indirect** drives chronic rejection and antibody formation.

- ▶ **Two-signal model:** TCR–MHC (signal 1) + CD28–CD80/86 (signal 2) → calcineurin → IL-2 → mTOR — the drug-target map.
- ▶ **Chronic rejection** = interstitial fibrosis, tubular atrophy, **transplant vasculopathy**; liver equivalent = **vanishing bile duct syndrome (ductopenia)**; largely irreversible.
- ▶ **HLA on chromosome 6:** class I = A, B, C; class II = DR, DQ, DP; mismatch number predicts graft survival.
- ▶ **GVHD is the mirror image of rejection** (donor T cells vs host), seen in allogeneic HSCT.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Kidney Transplantation" (Immunology of Rejection: hyperacute, T cell-mediated and antibody-mediated rejection, direct/indirect allorecognition, HLA matching, cross-matching, Banff/C4d/DSA, immunosuppression, chronic allograft injury); "Liver Transplantation" (allograft rejection — acute endothelialitis/bile-duct injury and chronic ductopenic *vanishing bile duct syndrome*); "Introduction to the Immune System" (type II cytotoxic and type IV delayed-type hypersensitivity mechanisms; MHC class I/II antigen presentation; GVHD references).

Coverage note: The corpus has **no single dedicated "transplantation immunology / rejection" chapter**; the richest, fully grounded source is the **Kidney Transplantation** chapter, supplemented by the **Liver Transplantation** and **immune-system** chapters. Specific *timings* (e.g., hyperacute minutes–hours, accelerated 2–5 days) and the **accelerated rejection** category are universally accepted standard internal-medicine teaching included to satisfy the full scope of the question; the chapters explicitly emphasise hyperacute, acute (cellular + AMR) and chronic rejection and the mechanism of prior sensitisation.



Genetic testing in pregnancy

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Prenatal genetic testing** is the application of cytogenetic, molecular and biochemical techniques during pregnancy to detect chromosomal abnormalities, single-gene (Mendelian) disorders and structural malformations in the fetus. It encompasses **screening** (population-level risk estimation: maternal serum markers, ultrasound, cell-free DNA) and **diagnostic** testing on fetal cells obtained by amniocentesis, chorionic villus sampling (CVS) or cordocentesis, plus **preimplantation genetic testing (PGT)** on IVF embryos. Because the information generated is sensitive, heritable and may inform decisions about continuation of pregnancy, it is inseparable from **genetic counselling** and a distinct set of **ethical, legal and social implications (ELSI)**.

Indications for genetic testing in pregnancy

Testing is offered when the *a priori* risk of a fetal genetic disorder is increased:

- ▶ **Advanced maternal age** (≥35 years) — rising risk of trisomies (21, 18, 13) with maternal age.

- ▶ **Abnormality of the fetus on ultrasound** — structural malformations or soft markers prompting karyotype/microarray.
- ▶ **Increased risk on the maternal serum screen** — an abnormal "*quad*" test (α -fetoprotein, β -human chorionic gonadotropin, inhibin-A, unconjugated estriol) or first-trimester combined screen.
- ▶ **Family history of a chromosomal abnormality** or a known **balanced parental translocation** (a recognised recurrence-risk situation, e.g. translocation Down syndrome).
- ▶ **A Mendelian disorder amenable to genetic testing** — known familial pathogenic variant (e.g. cystic fibrosis, thalassaemia/haemoglobinopathy, fragile-X, Duchenne muscular dystrophy, Marfan/FBN1, homocystinuria).
- ▶ **Positive carrier screening** in one or both parents, **consanguinity**, or membership of an at-risk ethnic group (e.g. founder mutations).
- ▶ **Recurrent pregnancy loss / previous affected child / infertility undergoing IVF** (overlap with adult and preconceptional indications).

Note: The corpus also lists postnatal indications (multiple congenital anomalies, developmental delay, intellectual disability, autism, short stature, dysmorphism, disorders of sexual development) — useful to contrast prenatal vs paediatric indications in the answer.

Methods I — Sampling techniques (when and how fetal material is obtained)

Method	Timing (gestation)	Technique	Material / typical analysis
Cell-free DNA (cfDNA) screen (NIPT)	from ~10 weeks	Maternal venous blood — non-invasive	Fetal + maternal cfDNA; screens common chromosomal aneuploidies and fetal sex ; a <i>screen</i> , not diagnostic
Maternal serum screen / ultrasound	1st–2nd trimester	Non-invasive	Quad markers, nuchal translucency, anomaly scan — risk estimation
Chorionic villus sampling (CVS)	weeks 9–12	Trans-cervical or trans-abdominal biopsy of chorion	Cytogenetic + mutational analysis; <i>earliest</i> diagnostic test — relevant when termination is a consideration
Amniocentesis	~16 weeks	Aspiration of amniotic fluid	Cultured amniocytes for karyotype , FISH , mutational analysis
Percutaneous umbilical blood sampling (PUBS / cordocentesis)	from ~18 weeks	Aspiration of fetal blood	Late-gestation diagnosis (rapid karyotype, fetal anaemia/infection work-up)
Preimplantation genetic testing (PGT)	pre-implantation	Single cell from 4- to 8-cell embryo , or first polar body of the oocyte (with IVF)	Avoids therapeutic abortion; costly and labour-intensive

- ▶ **Non-invasive (screening)** = cfDNA, serum markers, ultrasound — no procedure-related fetal loss; abnormal results require **confirmation** by an invasive diagnostic test.
- ▶ **Invasive (diagnostic)** = CVS, amniocentesis, PUBS — definitive but carry a procedure-related risk.

Methods II — Laboratory analytic techniques

Once fetal cells/DNA are obtained, the genome is interrogated at three levels:

- ▶ **Cytogenetics — chromosome level:** *karyotype* analysis (numerical and large structural abnormalities), **fluorescence in situ hybridisation (FISH)** for targeted aneuploidy/microdeletions.
- ▶ **Cytogenomics — sub-microscopic level:** **chromosomal microarray / array-based testing** for copy-number variants (deletions/duplications), and **multiplex ligation-dependent probe amplification (MLPA)** for single-exon deletions/duplications.
- ▶ **Molecular — sequence level:** PCR amplification from minute DNA samples, **direct (Sanger) DNA sequencing** for known single-gene disorders and prenatal diagnosis, and **next-generation / massively parallel sequencing — targeted gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS)** for undiagnosed syndromes.
- ▶ **Analysis of cfDNA ("liquid biopsy")** from a maternal sample provides minimally invasive screening for fetal chromosomal abnormalities and sex.
- ▶ The optimal family strategy is to **test an affected family member first** to identify the pathogenic variant, then offer **targeted variant testing** to the fetus/at-risk relatives.

Ethical issues involved

Prenatal genetic testing raises ethical, legal and social concerns that the candidate must be able to enumerate:

- ▶ **Genetic privacy & non-discrimination:** Genetic data is sensitive and should not be accessed without **explicit consent**; disclosure risks **discrimination by insurers or employers**. The U.S. **Genetic Information Nondiscrimination Act (GINA, 2008)** protects *asymptomatic* individuals in health insurance and employment but **does not protect the symptomatic individual** and **does not cover disability, long-term-care or life insurance**; the Affordable Care Act (2014) partly fills this gap.
- ▶ **Informed consent & non-directive counselling:** Couples must understand what the test can and cannot determine, its limitations, the possibility of inconclusive results, and the implications for the fetus and other relatives. Counselling is **non-directive** and supports **reproductive autonomy** — the decision (including continuation vs termination of pregnancy) rests with the parents.
- ▶ **Termination of pregnancy:** Earlier diagnosis (CVS) is valued *because* it allows earlier decision-making; this links prenatal testing to the morally contested issue of **selective termination** and concerns about devaluing disability.
- ▶ **Incidental / secondary findings:** Comprehensive sequencing (WES/WGS) may reveal **medically actionable** conditions but also **untreatable** disorders and **variants of uncertain significance (VUS)** unrelated to the test indication — a recognised ethical dilemma causing anxiety.

- ▶ **Uncertainty & psychosocial harm:** "Excluding a specific disorder is never equivalent to the assurance of a normal child"; results generate **anxiety, despair and survivor guilt**, and most adult-onset results are only *predictive* of risk, not deterministic.
- ▶ **Testing of children for adult-onset disease:** Professional bodies caution against testing for adult-onset disorders in childhood where no childhood intervention exists, to preserve the **future child's right to decide** (exceptions: MEN-2 → prophylactic thyroidectomy; FAP → colonoscopy from 10–15 yr).
- ▶ **Direct-to-consumer (DTC) testing:** Variable validity, inadequate counselling, confidentiality and **regulatory** concerns (CLIA/CAP accreditation; ACMG position statement).
- ▶ **Equity — the "genomics divide":** High cost may widen global inequities; WHO initiatives aim to attenuate these.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Prenatal testing timeline (gestation in weeks on a horizontal axis).** Labels: *cfDNA / NIPT (~10 wk)*, *CVS — chorionic villus sampling (9–12 wk, trans-cervical/trans-abdominal)*, *First-trimester combined screen (nuchal translucency)*, *Maternal serum "quad" screen (2nd trimester)*, *Amniocentesis (~16 wk, amniotic fluid)*, *Anomaly ultrasound (~18–20 wk)*, *PUBS / cordocentesis (≥18 wk, fetal blood)*; annotate **Non-invasive (screening)** vs **Invasive (diagnostic)**.
- ▶ **Diagram 2 — Three-tier methods pyramid.** Labels: base *Chromosome level: karyotype, FISH*; middle *Cytogenomic: chromosomal microarray (CNV), MLPA*; apex *Molecular: PCR, Sanger sequencing, NGS panels / WES / WGS, cfDNA*.

Clinical / Diagnostic significance

- ▶ Distinguishes a **screening** result (cfDNA, serum, ultrasound — gives a risk) from a **diagnostic** result (CVS/amniocentesis/PUBS — confirms or excludes) — abnormal screens **must** be confirmed invasively before irreversible decisions.
- ▶ **CVS earlier than amniocentesis** is decisive when termination is being considered; **PUBS** is reserved for late gestation and fetal blood disorders/infection.
- ▶ In **Down syndrome**, cytogenomic analysis is performed even with simple trisomy 21 to detect an **unbalanced translocation**, because a parent with a **balanced translocation** carries a substantial recurrence risk.
- ▶ **PGT with IVF** allows selection of unaffected embryos, avoiding therapeutic abortion, for couples with a known familial pathogenic variant.
- ▶ Every prenatal test must be wrapped in **pre-test counselling, informed consent and post-test counselling**, with the option of **DNA banking** and onward testing of relatives.

High-yield exam pointers

- ▶ Amniocentesis ~16 wk; CVS weeks 9–12; PUBS/cordocentesis ≥18 wk; cfDNA from maternal blood (non-invasive).
- ▶ Quad test = AFP + β-hCG + inhibin-A + unconjugated estriol.
- ▶ Amniotic fluid cells → karyotype, FISH, mutational analysis.

- ▶ Three method tiers: **karyotype/FISH** → **microarray/MLPA** → **PCR/Sanger/NGS** (**panel**, **WES**, **WGS**).
- ▶ **GINA (2008)** protects *asymptomatic* people in health insurance/employment; **not** symptomatic, **not** life/disability/long-term-care insurance.
- ▶ Counselling is **non-directive**; respect **reproductive autonomy**; consent must cover **incidental findings & VUS**.
- ▶ "Excluding a disorder ≠ guarantee of a normal child."
- ▶ Test the **affected family member first** to find the variant, then do targeted fetal testing.
- ▶ **PGT** analyses a single cell from a 4–8-cell embryo or the first polar body.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (indications for testing, amniocentesis/CVS/PUBS/cfDNA timing and technique, quad test, preimplantation/preconceptual diagnosis, mutational-analysis methods, GINA and ethical issues).
- ▶ **Harrison's Principles of Internal Medicine, 22e** — "The Integration of Inherited Genetics into Clinical Practice" (methodologic approaches: karyotype/FISH/MLPA/microarray/PCR/NGS; pre- and post-test counselling, informed consent, DNA banking, testing children for adult-onset disease, DTC testing/ACMG, VUS, GINA limitations).
- ▶ **CMDT 2026** — "Genetic & Genomic Disorders" (Down syndrome: cytogenomic analysis to detect unbalanced translocation and recurrence risk; cfDNA for fetal sex-chromosome aneuploidy; prenatal diagnosis in single-gene disorders).

Coverage note: This is an internal-medicine corpus; it covers prenatal **methods and ethics** well but does not provide obstetric-grade detail (e.g. exact cfDNA/NIPT detection rates and false-positive rates, nuchal-translucency cut-offs, procedure-related miscarriage rates, or ACOG/ISPD screening protocols). Such figures should be drawn from a dedicated obstetrics/medical-genetics text. The principle that genetic counselling is **non-directive** is stated as universally accepted standard practice rather than verbatim from these chapters.



Complement system — pathways and effector actions

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

Definition / Introduction — The **complement system** is a major soluble effector arm of *innate immunity*: a cascade of ~30 plasma and membrane proteins (predominantly **serine proteases**, regulators and receptors) that are activated sequentially, each cleaving and activating the next. Activation proceeds via **four pathways** — three initiating routes (**classical**, **lectin/MBL**, **alternative**) that converge on cleavage of **C3**, and a shared **terminal pathway** that assembles the lytic **membrane attack complex (MAC)**. Its three cardinal effector functions are **opsonisation**, generation of **inflammatory anaphylatoxins**, and **cytolysis**, and it forms the principal molecular bridge linking innate to adaptive immunity.

The three initiating pathways and the common terminal pathway

Feature	Classical pathway	Lectin (MBL) pathway	Alternative pathway
Trigger	Antigen–antibody immune complexes (IgM, IgG1, IgG2, IgG3) bound to C1q	Microbial surfaces bearing terminal mannose groups	Spontaneous C3 "tick-over"; C3b deposited directly on microbes / "altered self" (tumour cells) — <i>antibody-independent</i>
Recognition / initiating proteins	C1 complex = C1q–C1r–C1s	MBL (a collectin) + MASP-1 and MASP-2 (substitute for C1q, C1r, C1s)	Factor D, factor B, C3; stabilised by properdin (factor P)
Early activation	C1s cleaves C4 → C4a + C4b and C2 → C2a + C2b	MASPs cleave C4 and C2 (identical to classical from here on)	Factor D cleaves factor B (bound to C3b) → Bb
C3 convertase	C4b2a	C4b2a	C3bBb (properdin-stabilised)
C5 convertase	C4b2a3b	C4b2a3b	C3bBb3b
Immunological role	Links adaptive → innate immunity via specific antibody	Pattern-recognition of carbohydrate (true innate)	Powerful amplification loop for any C3b deposited by any pathway

- ▶ All three routes converge at **C3 cleavage** ($C3 \rightarrow C3a + C3b$) and then on the **terminal pathway**: the C5 convertase cleaves $C5 \rightarrow C5a + C5b$; C5b sequentially recruits **C6, C7, C8 and multiple C9** (poly-C9) to form the **MAC (C5b-9)**, which inserts into the lipid bilayer of bacteria or target cells and causes **osmotic lysis**.
- ▶ The cascade is *enzymatic and amplifying* — a single convertase cleaves many C3 molecules, so a small trigger produces a large effector response. The components are mostly serine proteases acting in a defined order.

Effector actions of complement

Effector molecule(s)	Action	Immunological consequence
C3b (and C4b, C1q, iC3b)	Opsonisation — coats microbe/target	Binds phagocyte complement receptors (CR1/CD35, CR3) → enhanced phagocytosis and clearance
C3a, C5a (also weak C4a)	Anaphylatoxins	Mast-cell/basophil degranulation, ↑ vascular permeability, smooth-muscle contraction; C5a is a potent neutrophil chemoattractant and activator → acute inflammation
C5b-9 (MAC)	Cytolysis / membrane perturbation	Direct lysis of bacteria (esp. <i>Neisseria</i>) and of antibody-coated cells
C3b/C4b on immune complexes	Immune-complex solubilisation & clearance	ICs bound by erythrocyte CR1 (CD35) are ferried to liver/spleen reticulo-endothelial system for safe disposal
C3d-antigen on B cells	Immune adjuvant	C3d engages CR2 (CD21) on B cells, lowering the threshold for B-cell activation — couples innate sensing to antibody production

- In summary (Harrison): complement cleavage products **facilitate microbe/damaged-cell clearance** (C1q, C4, C3), **promote inflammation** (anaphylatoxins C3a, C5a), and **promote lysis** (MAC).

Regulation of complement (why self is spared)

Tight regulation prevents bystander injury to host tissue; loss of a regulator causes characteristic disease.

Regulator	Type	Function	Loss / dysfunction causes
C1 inhibitor (C1-INH)	Plasma serpin	Inactivates C1r/C1s, MASPs and kallikrein; limits bradykinin generation	Hereditary angioedema (↓C4, ↓C2)
Factor H	Plasma	Cofactor for factor I; decay of alternative C3 convertase	aHUS , C3 glomerulopathy; deficiency → haemolytic-uraemic syndrome
Factor I	Plasma protease	Cleaves/inactivates C3b and C4b	Pyogenic infections
DAF / CD55	GPI-anchored membrane	Accelerates decay of C3/C5 convertases; blocks C3-fragment binding	Lost in PNH
CD59 (protectin)	GPI-anchored membrane	Blocks MAC (C9) insertion	Lost in PNH → intravascular haemolysis
MCP / CD46	Membrane	Cofactor for factor I	aHUS

Impact on immunity — how complement shapes host defence

- **Frontline innate defence:** lyses and opsonises pathogens within minutes of exposure, before antibody is available; the lectin and alternative pathways need no prior immunity (true pattern-recognition / innate arms).

- ▶ **Bridge to adaptive immunity:** classical-pathway activation via **immune-complex binding to C1q links innate and adaptive systems** through specific antibody; C3d-coated antigen amplifies B-cell responses (CR2/CD21), so complement is also an *adjuvant* for antibody production.
- ▶ **Inflammation & leukocyte recruitment:** C5a and C3a recruit and activate neutrophils, mast cells and basophils (which bear C3a/C5a receptors), orchestrating acute inflammation.
- ▶ **Immune-complex homeostasis:** efficient IC clearance prevents tissue deposition; *early* complement deficiency → defective clearance → **immune-complex disease** (SLE-like syndromes, glomerulonephritis, vasculitis).
- ▶ **A double-edged sword:** the same effectors that protect can injure host tissue when dysregulated — e.g. complement-fixing (C1-binding) IgM/IgG mediates **type II cytotoxic** reactions (transfusion haemolysis, Goodpasture's, pemphigus vulgaris) and contributes to **type III immune-complex** injury.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The four pathways converging on C3 and the MAC.** Three parallel columns feeding a common stem. Labels: *Classical* (Ag–Ab complex → C1q–C1r–C1s → C4, C2 → C4b2a); *Lectin* (mannose → MBL + MASP-1/2 → C4, C2 → C4b2a); *Alternative* (microbial surface, C3 tick-over → factor B, factor D, properdin → C3bBb); arrows from all three to C3 → C3a + C3b; then C5 convertase → C5 → C5a + C5b → C6, C7, C8, C9 (poly-C9) = MAC (C5b-9) → cell lysis. Side annotations: C3a/C5a = anaphylatoxins (inflammation), C3b = opsonin (phagocytosis), MAC = lysis.
- ▶ **Diagram 2 — Membrane regulators in PNH.** RBC membrane with GPI-anchored CD55 (blocks C3 convertase) and CD59 (blocks MAC); show their loss after PIGA mutation → C3b deposition → MAC-mediated **intravascular haemolysis**; mark site of **eculizumab** (anti-C5) block.

Clinical / Diagnostic significance

- ▶ **Pattern of deficiency predicts the disease (Table 360-12):**
 - Early classical components (C1q, C1r, C1s, C4, C2) → **immune-complex syndromes** (SLE, SLE-like, GN, vasculitis) and pyogenic infection with encapsulated organisms (*S. pneumoniae*).
 - C3 / alternative pathway (C3, factor D) → severe pyogenic infections + immune-complex disease.
 - Properdin → invasive *Neisseria* infection; factor H/I → HUS / pyogenic infection.
 - Terminal/MAC components (C5–C8; rarely C9) → recurrent *Neisseria* (meningococcal) infections.
- ▶ **Acquired complement disorders:**
 - **Paroxysmal nocturnal haemoglobinuria (PNH):** acquired PIGA mutation blocks GPI-anchor synthesis → loss of CD55 + CD59 → MAC-mediated **intravascular haemolysis**, haemoglobinuria, thrombosis; Coombs-negative. Treated with **eculizumab/ravulizumab** (anti-C5); **pegcetacoplan** (anti-C3) also curbs C3d-mediated extravascular haemolysis.

- **Hereditary angioedema:** C1-INH deficiency → unopposed kallikrein/bradykinin → recurrent **non-pruritic, non-urticarial angioedema** with GI involvement; complement screen shows **low C4** (and C2).
- ▶ **Therapeutics targeting complement:** eculizumab/pezelimab (anti-C5) for PNH/aHUS/CHAPLE; C3-directed agents; recombinant C1-INH for HAE — illustrating complement as a druggable pathway.
- ▶ **Useful tests:** CH50 (screens the entire classical→terminal pathway; zero/very low suggests a complete component deficiency), AH50 (alternative pathway), and individual **C3/C4 levels** (low C4 with normal C3 favours classical-pathway/C1-INH problems; low C3 favours alternative-pathway activation).

High-yield exam pointers

- ▶ **Four pathways = classical + lectin + alternative (initiating) + terminal (common).** All converge on C3, then MAC (C5b-9).
- ▶ **C3 convertases:** classical/lectin = C4b2a; alternative = C3bBb (properdin-stabilised). C5 convertases: C4b2a3b and C3bBb3b.
- ▶ **Lectin pathway** uses MBL + MASP-1/MASP-2 in place of C1q/C1r/C1s; triggered by **mannose**.
- ▶ **Three effectors:** opsonisation (C3b), anaphylatoxins (C3a, C5a; C5a = **chemotactic**), lysis (MAC); plus immune-complex clearance (RBC CR1/CD35) and B-cell adjuvant (C3d–CR2/CD21).
- ▶ **Antibody isotypes fixing classical complement:** IgM (most potent) and IgG1, IgG2, IgG3 (via C1q); IgG4 and IgA **do not** fix classical complement.
- ▶ **Early-component deficiency** → SLE / immune-complex disease; **terminal (MAC) deficiency** → recurrent *Neisseria*.
- ▶ PNH = loss of GPI-anchored CD55 + CD59 (PIGA); treat with **anti-C5 eculizumab**.
- ▶ **Hereditary angioedema** = C1-INH deficiency, bradykinin-mediated, **low C4**, no urticaria.
- ▶ Complement is the key molecular **bridge between innate and adaptive immunity**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Introduction to the Immune System" (four pathways, MASP/MBL, C3/C5 convertase convergence, MAC, anaphylatoxins, opsonisation, immune-complex clearance, Table 360-12 Complement Deficiencies and Associated Diseases, antibody complement-fixation); "Mechanisms of Regulation and Dysregulation of the Immune System" (complement-targeting biologics — eculizumab/pezelimab); "Hemolytic Anemias" (PNH — CD55/CD59, PIGA, eculizumab/pegcetacoplan); "Urticaria, Angioedema, and Allergic Rhinitis" (C1-INH deficiency / bradykinin-mediated hereditary angioedema, low C4/C2).
- ▶ **Coverage note:** The precise **convertase subunit formulae** (C4b2a, C3bBb, C4b2a3b, C3bBb3b), the **CR2/CD21–C3d** B-cell adjuvant link, properdin's *stabilising* role, and the laboratory screens **CH50/AH50** are universally accepted standard immunology (Janeway/Abbas) used to complete the answer; Harrison states the pathway proteins (C1/C4/C2; factor D/B/C3; MBL/MASP) and effector outcomes but does not spell out every convertase formula verbatim.



Polymerase chain reaction and DNA sequencing

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

Definition / Introduction — The **polymerase chain reaction (PCR)** is a *nucleic acid amplification test* (NAAT) that amplifies a specific region of DNA in vitro into millions of copies using sequence-specific oligonucleotide primers and a thermostable DNA polymerase. **DNA sequencing** is the determination of the precise order of nucleotide bases (A, T, G, C) in a DNA segment, performed historically by the *Sanger (dideoxy chain-termination)* method and now predominantly by *next-generation (massively parallel) sequencing*. Together these molecular tools underpin modern diagnosis of inherited, infectious and neoplastic disease, allowing genetic testing and mutational analysis from minute amounts of DNA extracted from leukocytes, buccal cells, or even single cells.

Principle, requirements and components of PCR

- ▶ **Principle** — *exponential, primer-directed enzymatic amplification* of a target sequence; each cycle theoretically doubles the template, so n cycles yield $\approx 2^n$ copies (25–40 cycles produce millions to billions of copies).
- ▶ **Template** — the double-stranded DNA containing the region of interest (genomic, plasmid, or, after reverse transcription, cDNA).
- ▶ **Primers** — a pair of short single-stranded oligonucleotides (~18–25 bp) complementary to sequences flanking the target; they define specificity. *Even a single base-pair mismatch, particularly near the 3' end of the primer, may abolish amplification* (Harrison).
- ▶ **Thermostable DNA polymerase** — *Taq polymerase* (from the thermophilic bacterium *Thermus aquaticus*), which survives repeated high-temperature denaturation.

- ▶ dNTPs (the four deoxynucleotide building blocks), Mg^{2+} -containing buffer, and a programmable thermal cycler.
- ▶ A key strength is sensitivity: PCR enables genetic and mutational analysis with very small quantities of DNA, and DNA sequencing can be performed directly on PCR products.

The three steps of a PCR cycle

Step	Temperature (typical)	Event
1. Denaturation	~94–95 °C	Double-stranded template separates into two single strands
2. Annealing	~50–65 °C	Primers hybridise to their complementary flanking sequences
3. Extension (elongation)	~72 °C	<i>Taq</i> polymerase synthesises the new strand 5'→3' from each primer

- ▶ The cycle is repeated 25–40 times; an initial denaturation and a final extension flank the cycling. Product is detected by *agarose gel electrophoresis*, fluorescence (real-time PCR), or downstream sequencing.

Modifications / types of PCR

Variant	Key feature & use
Reverse-transcriptase PCR (RT-PCR)	RNA first converted to cDNA by reverse transcriptase, then amplified — used for RNA viruses (HIV, HCV, SARS-CoV-2, influenza) and fusion transcripts
Real-time / quantitative PCR (qPCR)	Fluorescent signal measured per cycle → <i>quantifies</i> template (e.g. HIV/HBV/HCV viral load); RT-qPCR combines both
Multiplex PCR	Several primer sets in one reaction → <i>syndromic panels</i> (respiratory, gastroenteritis, meningoencephalitis) detecting many pathogens at once
Nested PCR	Two sequential amplifications with internal primers → increased sensitivity/specificity (standard molecular biology)
Isothermal amplification (e.g. LAMP)	Amplifies at a single temperature without thermal cycling → point-of-care/field and resource-limited settings

DNA sequencing — Sanger (first-generation) method

- ▶ **Principle: dideoxy chain termination.** The denatured template, a primer, DNA polymerase, normal dNTPs and a small proportion of fluorescently-labelled **dideoxynucleotides (ddNTPs)** are combined.
- ▶ Because ddNTPs lack the 3'-hydroxyl group, their incorporation halts further chain elongation, generating a nested set of fragments terminating at every base position.
- ▶ Fragments are resolved by size on **capillary electrophoresis**; the fluorescent terminators are read off as a **chromatogram** (Harrison shows "*chromatograms of sequence analyses after amplification of genomic DNA by PCR*" — Fig. 479-10B).

- ▶ Sanger sequencing of PCR products remains the reference standard for *single-gene/targeted* mutation confirmation.

Next-generation (NGS) and third-generation sequencing

- ▶ Next-generation / massively parallel sequencing produces *millions of sequences concurrently*, far beyond the capacity of prior dye-terminator methods, with cost per genome falling steeply.
- ▶ Clinical formats:
 - Targeted gene panels — multiple candidate genes captured by hybridisation then deep-sequenced (locus-heterogeneous disorders, somatic tumour panels).
 - Whole-exome sequencing (WES) — all coding exons; used for undiagnosed/rare syndromes.
 - Whole-genome sequencing (WGS) — entire genome, including non-coding regions.
 - RNA sequencing (RNA-Seq) — gene fusions, aberrant expression.
- ▶ 16S ribosomal RNA gene sequencing identifies fastidious/unculturable bacteria; metagenomic ("shotgun") and cell-free DNA sequencing allow *unbiased* pathogen discovery (e.g. *Leptospira* DNA found in CSF → neuroleptospirosis confirmed by retrospective PCR). Long-read (third-generation) platforms resolve repeats, plasmids and structural variants.
- ▶ Caveats: NGS detects numerous **variants of uncertain significance (VUS)** and incidental (secondary) findings, demands heavy bioinformatics, and may miss copy-number variants if not specifically analysed.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — One PCR cycle:** draw double-stranded template; arrow to *Denaturation* (~94 °C) showing two separated single strands; *Annealing* (~55 °C) showing forward and reverse primers bound; *Extension* (~72 °C) with Taq polymerase synthesising new strands; loop arrow back labelled "*repeat ×25–40 → exponential 2ⁿ amplification.*" Label: **template, primers, Taq polymerase, dNTPs, 5'/3' ends.**
- ▶ **Diagram 2 — Sanger sequencing:** template + primer + DNA polymerase + dNTPs + labelled ddNTPs; show a ladder of chain-terminated fragments of increasing length; arrow to **capillary electrophoresis** and a four-colour **chromatogram** read 5'→3'. Label: **ddNTP (no 3'-OH), chain termination, fluorescent peaks A/T/G/C.**

Clinical / Diagnostic significance

- ▶ Infectious disease (NAAT-based):
 - *Tuberculosis* — PCR amplification of the **rpoB gene** identifies *M. tuberculosis* directly in sputum and simultaneously detects **rifampicin resistance** (Xpert-type NAAT-R); CMDT: NAAT sensitivity/specificity 85–97% in smear-positive specimens, resistance-marker specificity > 98%.
 - *HIV* — RT-qPCR **viral load** for diagnosis/monitoring; **genotypic resistance testing** is standard before therapy (e.g. the K103N reverse-transcriptase mutation predicts efavirenz resistance).

- *Hepatitis B/C, SARS-CoV-2, influenza* — PCR/RT-PCR for detection and treatment response; multiplex **respiratory viral panels**.
- *Antibiotic resistance* — **mecA** (PBP2A) PCR for **MRSA**; **van** genes for **VRE**; multiplex carbapenemase PCR (**KPC, NDM, OXA-48, IMP1, VIM**).
- ▶ **Inherited single-gene disorders**: PCR-based mutation panels detect **CFTR $\Delta F508$** (cystic fibrosis), **β -globin Glu6Val/E6V** (sickle cell), and **trinucleotide-repeat expansions** (fragile X, Huntington's CAG repeat), including premutation sizing. Used for carrier testing, **prenatal diagnosis** (amniocentesis/ CVS with FISH + mutational analysis), and non-invasive prenatal **cfDNA** screening for aneuploidy/fetal sex.
- ▶ **Oncology / haematology**: RT-PCR for **BCR-ABL1 [t(9;22)]** diagnoses and monitors CML/Ph⁺ ALL minimal residual disease; tumour **mutational profiling/NGS** identifies *actionable driver mutations* guiding targeted therapy; **liquid-biopsy cfDNA** for minimally invasive diagnosis and surveillance; **BRCA1/BRCA2** testing for hereditary cancer risk.
- ▶ **Pharmacogenomics**: genotyping guides drug choice and dosing.
- ▶ **Pitfalls**: interpret NAAT against **pre-test probability** (a negative result in high-probability TB does not exclude disease); risk of **contamination/false positives**; detection of a microbial sequence alone does not prove causation (Koch's postulates); allelic heterogeneity means a negative targeted panel does not exclude a mutation elsewhere.

High-yield exam pointers

- ▶ PCR = in-vitro amplification needing **template, two primers, Taq polymerase** (from *Thermus aquaticus*), dNTPs, **Mg²⁺**, **thermal cycler**.
- ▶ Three steps: **Denaturation** (~94 °C) → **Annealing** (~55 °C) → **Extension** (~72 °C); $\approx 2^n$ amplification over 25–40 cycles.
- ▶ RT-PCR for RNA (HIV, HCV, SARS-CoV-2); **qPCR** quantifies (viral load); **multiplex** = syndromic panels.
- ▶ **Sanger sequencing** uses **dideoxynucleotides (no 3'-OH)** → **chain termination**, read as a chromatogram; NGS = massively parallel (WES, WGS, panels).
- ▶ TB: **rpoB** PCR detects organism **and rifampicin resistance**; MRSA = **mecA**; VRE = **van** genes.
- ▶ Heme-onc: **BCR-ABL1** RT-PCR for CML/MRD; tumour NGS for **actionable mutations**; **cfDNA liquid biopsy**.
- ▶ Genetic: **CFTR $\Delta F508$** , sickle **E6V**, **fragile X / Huntington repeat expansions**; prenatal **cfDNA** (NIPT).
- ▶ **16S rRNA / metagenomic / cfDNA sequencing** identifies culture-negative and novel pathogens.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Principles of Human Genetics" (mutational analysis, Sanger chromatograms after PCR amplification, NGS/WES/WGS, targeted panels, repeat-expansion and single-gene examples, prenatal diagnosis) and "Microbial Genomics and Infectious Disease" (NAAT/PCR definitions, RT-PCR, multiplex syndromic panels, 16S rRNA and metagenomic/cfDNA sequencing, rpoB/TB, HIV genotyping K103N, mecA/MRSA, van/VRE, carbapenemase panels, MALDI-TOF context).
- ▶ **CMDT 2026** — "Pulmonary Disorders" (NAAT-TB and resistance-marker performance characteristics for tuberculosis).
- ▶ **Coverage note:** The corpus covers PCR and DNA sequencing as laboratory techniques only thinly (spec gap = true). The **step-level mechanism of PCR** (denaturation/annealing/extension temperatures, *Taq*/Thermus aquaticus) and the **dideoxy chain-termination basis of Sanger sequencing** are not described in mechanistic detail in Harrison/CMDT; these are included as universally accepted standard molecular biology. All disease examples, the rpoB/mecA/van/carbapenemase/HIV-genotype details, the NGS/16S/metagenomic content and the single-gene/repeat-expansion examples are directly grounded in the cited chapters.



Therapeutic drug monitoring

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Monitoring of drug therapy* is the systematic process of assessing whether a prescribed drug is producing the intended benefit while staying within a safe exposure range, so that the dose can be individualised. It is achieved by tracking **clinical endpoints**, **physiological/biochemical surrogate markers**, direct **plasma (serum/whole-blood) drug-concentration measurement** — *therapeutic drug monitoring (TDM)* — and increasingly by **pharmacogenomic testing**. The unifying rationale is the **therapeutic window** (therapeutic index/ratio): the separation between the concentration needed for efficacy and that producing toxicity. Where this window is narrow and a definable concentration–effect relationship exists, monitoring lets the clinician keep the drug above the minimum effective and below the toxic concentration.

Goals and the four modalities of monitoring (HOW)

- ▶ The desired goal of any drug therapy is to **maximise the likelihood of benefit while minimising the risk of adverse drug reactions (ADRs)**. Monitoring operationalises this for the individual patient, because outcome varies widely owing to pharmacokinetic and pharmacodynamic differences (genetics, organ dysfunction, drug interactions, adherence, age).
- ▶ **1. Clinical/symptomatic endpoints** — the simplest method: relief of pain or palpitations, seizure frequency, mood; the patient reports efficacy. Useful when effect is directly observable.
- ▶ **2. Physiological / biochemical surrogate markers** — objective, repeatable tests that track effect: blood pressure (antihypertensives), INR (warfarin), aPTT/anti-Xa (heparin), blood glucose and

HbA1c (insulin/oral hypoglycaemics), TSH (levothyroxine), LDL cholesterol (statins), QT interval on ECG (sotalol, dofetilide).

- ▶ **3. Plasma drug-concentration measurement (TDM)** — quantifying the drug itself; reserved for agents where concentration predicts effect/toxicity but no easy clinical surrogate exists (anticonvulsants, antirejection agents, antiarrhythmics, antibiotics).
- ▶ **4. Toxicity surveillance and pharmacogenomic testing** — periodic organ-function/haematology checks to catch dose-dependent toxicity, plus pre-emptive genotyping to predict variant responders.

WHEN do you monitor — indications and timing

- ▶ **Patient-side (clinical) indications to measure a drug level:** narrow therapeutic index drug; suspected **toxicity** that mimics the underlying disease (e.g. digoxin, lithium, phenytoin); **failure of efficacy** (to detect non-adherence, an interaction, or use of expired/degraded drug); suspected **non-adherence**, especially in chronic disease (hypertension, HIV) and multi-dose regimens; after a **dose change**, or after starting/stopping an interacting drug; in **organ dysfunction** (renal/hepatic) and at extremes of age; and for drugs with **saturable (zero-order) kinetics** such as phenytoin, where small dose increments cause disproportionate rises.
- ▶ **Pharmacokinetic timing — sample at steady state:** steady state is reached after ~4–5 **elimination half-lives** following initiation or any dose change; levels drawn earlier under-estimate the eventual concentration.
- ▶ **Trough vs peak:** for *efficacy and most chronic dosing*, draw a **trough** — the lowest concentration, **just before the next dose** at steady state (anticonvulsants, vancomycin, ciclosporin, tacrolimus). For drugs where **toxicity tracks the peak**, sample at the anticipated peak — e.g. evaluate the ECG/QT 1–2 h post-dose at steady state with sotalol/dofetilide; draw an **aminoglycoside peak** 30 min after the end of a 30–60 min infusion.
- ▶ **Drug-specific timing pitfalls:** digoxin must **not** be drawn within **6 h of an oral** (or 4 h of an IV) dose because distribution is incomplete; **lithium** is sampled at a standard **12 h post-dose**; **methotrexate** is checked at **48 h** to guide leucovorin rescue.

WHERE do you monitor — specimen, site and setting

- ▶ **Specimen/matrix:** most TDM uses **serum from a plain (red-top) tube**, drawn at trough. Two important exceptions are **ciclosporin and tacrolimus**, which partition into red cells and require **whole blood in an EDTA (lavender-top) tube**.
- ▶ **Free vs total drug:** only **unbound drug** is pharmacologically active. For highly protein-bound drugs in hypoalbuminaemia/uraemia (classically **phenytoin**, and **valproate**), measure the **free (unbound) concentration** — target free phenytoin **0.5–2 mg/L** — because total levels mislead.
- ▶ **Sampling site of effect:** plasma concentration is only a surrogate for concentration at the target. Where tissue and plasma levels diverge (e.g. **P-glycoprotein** excluding drug from brain at the blood–brain barrier; drug acting outside plasma), plasma TDM is **not** a reliable guide and clinical/physiological monitoring is preferred.
- ▶ **Clinical setting:** ranges from the **ward/ICU** (vancomycin and aminoglycoside levels, lithium, antiepileptics, immunosuppressants, anticoagulation) to the **outpatient/anticoagulation clinic**

(INR, HbA1c, TSH, BP) and **pharmacovigilance systems** (spontaneous ADR reporting, e.g. MedWatch) for population-level safety signals.

Which drugs need plasma-concentration monitoring (TDM) — criteria + ranges

A drug warrants plasma TDM when **most** of the following apply: narrow therapeutic index; good concentration–effect/toxicity correlation; wide inter-individual pharmacokinetic variability; **no easily measured clinical endpoint**; toxicity that resembles the disease being treated; or saturable kinetics. By contrast, drugs with a direct surrogate (warfarin→INR, heparin→aPTT, insulin→glucose) do **not** need level monitoring.

Drug	Effective (target) concentration	Sampling note
Digoxin	0.5–0.9 ng/mL (heart failure); 0.5–2 ng/mL (AF)	Trough; not within 6 h of oral dose; hypokalaemia potentiates toxicity
Lithium	0.5–1.2 mmol/L	12 h post-dose; thiazide/loop diuretics raise levels
Phenytoin	10–20 mg/L (5–10 in uraemia/hypoalbuminaemia); free 0.5–2 mg/L	Trough; zero-order (capacity-limited) kinetics
Valproate (total)	50–100 mg/L (50–125 for bipolar)	Total + free preferred in renal/liver disease
Carbamazepine	4–12 mg/L	Auto-induces own metabolism
Phenobarbital	10–40 mg/L	—
Theophylline	5–15 mg/L (panic ≥30)	Clearance ↑1.5–2× in smokers
Vancomycin	Trough 10–20 mg/L	Trough used for efficacy and to limit nephrotoxicity
Gentamicin / Tobramycin	Conventional peak 4–8 / 5–10 mg/L; trough <2 mg/L	Peak 30 min post-infusion; trough pre-dose
Amikacin	Peak 20–30 mg/L; trough <8 mg/L	Once-daily high-dose: peak ~60, trough <5
Ciclosporin	100–300 ng/mL (12-h trough)	Whole blood (EDTA)
Tacrolimus	Trough 8–12 ng/mL	Whole blood; CYP3A5-dependent dosing
Methotrexate	<0.1 µmol/L at 48 h	Higher → escalate leucovorin ; glucarpidase if renal failure

Surrogate monitoring, toxicity surveillance and pharmacogenomic ("pre-emptive") monitoring

- **Surrogate endpoints (no drug level needed):** *warfarin* → INR (target ~2–3); *unfractionated heparin* → aPTT (~1.5–2.5×) or anti-Xa; *insulin / sulfonylureas* → capillary glucose and HbA1c; *antihypertensives* → BP; *levothyroxine* → TSH; *statins* → LDL-C for efficacy.

- **Toxicity surveillance (organ-function/haematology):** serum creatinine/eGFR with aminoglycosides, vancomycin and digoxin (and dose-reduce renally cleared dofetilide/sotalolol to avoid QT prolongation); LFTs with valproate, methotrexate and anti-tubercular drugs; CBC with carbamazepine, methotrexate and clozapine; serum K⁺ with digoxin (hypokalaemia potentiates toxicity).
- **Pharmacogenomic testing** identifies variant responders *before or during* therapy:

Gene	Drug	Why test / action
TPMT / NUDT15	Azathioprine, 6-mercaptopurine	Loss-of-function → life-threatening myelosuppression; reduce dose/avoid
HLA-B*1502	Carbamazepine (Asian/Indian ancestry)	Avoid — risk of SJS/TEN
HLA-B*5701	Abacavir	Avoid — hypersensitivity reaction
HLA-B*5801	Allopurinol (Han Chinese/Korean/Thai)	Avoid — SJS/TEN
G6PD	Rasburicase, tafenoquine, primaquine	Deficiency → haemolysis/methaemoglobinaemia; use alternative
CYP2C19	Clopidogrel	Loss-of-function → poor bioactivation, more CV events
CYP2C9 / VKORC1	Warfarin	Predict lower maintenance dose (–1639G>A)
DPYD	5-FU, capecitabine	Deficiency → severe/fatal toxicity; reduce/avoid
UGT1A1*28	Irinotecan	Reduced glucuronidation → neutropenia, diarrhoea
SLCO1B1 (c.521T>C)	Simvastatin	↑ levels → statin myopathy

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Therapeutic window curve (after Harrison Fig. 71-1):** two overlapping sigmoid dose/concentration–response curves on the same axes — label "*Desired (therapeutic) effect*" (left curve) and "*Adverse effect / toxicity*" (right curve); shade the gap between them as the "**Therapeutic window / index**"; mark the *Minimum effective concentration* and *Minimum toxic concentration*; draw a *narrow window* inset where the curves nearly overlap (e.g. digoxin, lithium).
- ▶ **Steady-state accumulation curve (after Fig. 71-4):** concentration (y-axis) vs time in half-lives (x-axis) showing step-wise rise to a plateau; label "*Steady state at ~4–5 half-lives*", "*Trough — sample here (pre-dose)*", "*Peak*", and show a loading dose reaching the plateau sooner without changing the final steady state.

Clinical / Diagnostic significance

- ▶ Converts empirical prescribing into **individualised, dose-optimised therapy**, reducing both treatment failure and dose-dependent toxicity.
- ▶ For **first-order drugs**, the steady-state level is linearly proportional to dose — if you want to double the level, double the dose; this does **not** hold for **zero-order** drugs (phenytoin, aspirin, fluoxetine), where a small increment can produce a disproportionate, toxic rise.
- ▶ A measured level distinguishes the differential of a deteriorating patient: e.g. worsening features on **digoxin/lithium/phenytoin** may be toxicity rather than disease progression.
- ▶ **Failure of efficacy** with a sub-therapeutic level points to **non-adherence, a drug interaction, or degraded/expired drug** — a frequent, correctable problem in chronic disease.
- ▶ In **renal disease**, reduce dose of renally cleared drugs (digoxin, dofetilide, sotalol) and consider free phenytoin; in **hepatic disease/cirrhosis**, oral bioavailability of high first-pass drugs (morphine, midazolam, nifedipine) roughly doubles — start low.

High-yield exam pointers

- ▶ **TDM indications mnemonic:** narrow therapeutic index + good concentration–effect correlation + no clinical surrogate + wide PK variability + toxicity mimicking disease + saturable kinetics.
- ▶ **Sample at steady state** = ~4–5 half-lives; trough = just before the next dose; aminoglycoside **peak** 30 min post-infusion.
- ▶ **Specimen:** serum (plain red-top) for most; **whole blood EDTA** for ciclosporin and tacrolimus.
- ▶ **Free-drug monitoring** for highly protein-bound **phenytoin/valproate** in uraemia/hypoalbuminaemia.
- ▶ **Phenytoin** = classic zero-order drug → small dose change, large level change.
- ▶ **Digoxin:** target 0.5–0.9 ng/mL in HF; don't sample <6 h after oral dose; **hypokalaemia potentiates toxicity**.
- ▶ Drugs monitored by **surrogate, not level:** warfarin (INR), heparin (aPTT), insulin (glucose/HbA1c), antihypertensives (BP), levothyroxine (TSH).
- ▶ **QT interval at 1–2 h post-dose** for sotalol/dofetilide; **vancomycin trough** for efficacy/nephrotoxicity.

- **Pre-emptive pharmacogenomics:** TPMT/NUDT15 (thiopurines), HLA-B*1502 (carbamazepine), HLA-B*5701 (abacavir), HLA-B*5801 (allopurinol), G6PD (rasburicase/primaquine), DPYD (5-FU).

SOURCE & COVERAGE

- Harrison's *Principles of Internal Medicine*, 22e — "Principles of Clinical Pharmacology" (therapeutic index/window, pharmacokinetic timing, trough vs peak, QT and vancomycin monitoring, free vs total drug, zero-order kinetics, effects of renal/hepatic disease) and "Pharmacogenomics" (variant responders).
- CMDT 2026 — Appendix e5: "Therapeutic Drug Monitoring" (Table e5-1 target concentrations, half-lives, sampling specimens/timing) and "Selected Pharmacogenetic Tests: Clinical Relevance" (Table e5-2 — TPMT/NUDT15, HLA-B*1502/5701/5801, G6PD, CYP2C19, CYP2C9/VKORC1, DPYD, UGT1A1, SLCO1B1).
- *Coverage note:* INR target ~2–3 and heparin aPTT ~1.5–2.5× are stated as universally accepted standard internal medicine; the corpus confirms these drugs are monitored by INR/aPTT but does not quote the numeric targets in the chapters used.



X-linked disorders

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

Definition / Introduction — X-linked disorders are monogenic diseases caused by mutations in genes residing on the **X chromosome**, so their transmission and expression are governed by sex. Because males carry only a single X (they are **hemizygous**), a mutant allele is fully expressed in them regardless of whether it is dominant or recessive, whereas heterozygous females show variable expression that depends on the degree of **X-inactivation** and the function of the gene. X-linked conditions account for roughly 5% of **human monogenic disorders** (about 65% are autosomal dominant and 25% autosomal recessive). The two hallmark pedigree features are **absence of father-to-son (male-to-male) transmission** and the fact that **all daughters of an affected male are obligate carriers**.

Genetic basis and terminology

- **Sex-chromosome transmission:** A daughter *always* inherits her father's single X plus one of her mother's two X chromosomes; a son inherits the Y from his father and one **maternal X**. Hence an affected father can never pass an X-linked allele to a son.
- **Hemizygosity:** Males have one X, so a single mutant allele produces the phenotype. Females may be **heterozygous** or **homozygous**; the qualifiers *X-linked dominant* and *X-linked recessive* therefore strictly describe expression of the mutant phenotype **in women**.
- **X-inactivation (functional mosaicism, "Lyonization"):** In every somatic cell of a female, most genes on one of the two X chromosomes are silenced. Random inactivation gives a ~50:50 mix of cells expressing each X; **skewed (non-random) inactivation** can unmask disease in a carrier ("manifesting carrier").

- **Carrier expression is gene-dependent:** Most heterozygous carriers of **factor VIII deficiency (haemophilia A)** are asymptomatic because enough factor VIII is made; in contrast, females heterozygous for **α-galactosidase A deficiency (Fabry's disease)** may develop mild painful neuropathy and other features.

X-linked recessive vs X-linked dominant — characteristic features

Feature	X-linked recessive (XLR)	X-linked dominant (XLD)
Males (hemizygous)	Affected by a single mutant allele	Affected; often severe, may be lethal in utero
Heterozygous females	Usually unaffected carriers (may manifest if X-inactivation skewed)	Affected (variable, generally milder than males)
Father → son transmission	Absent	Absent
Affected father's daughters	All obligate carriers	All affected
Pedigree pattern	"Criss-cross"; chiefly males affected, skipped generations	Affected in successive generations; ~2:1 female:male excess
Examples	Haemophilia A/B, G6PD deficiency, Duchenne/Becker MD, Fabry, Fragile X	Rett syndrome (MECP2)

Pedigree and segregation patterns

- **Affected male × normal female:** all daughters are **obligate carriers**, all sons unaffected (no male-to-male spread).
- **Carrier female × normal male (XLR):** each son has a **50% chance of being affected**; each daughter has a **50% chance of being a carrier** (standard Mendelian extension).
- **Skipped generations** with predominantly affected males are typical of XLR — the disease appears to "jump" through unaffected carrier females (criss-cross inheritance).
- XLD pedigrees resemble autosomal dominant transmission but show **no father-to-son transmission** and an **excess of affected females**.

Important X-linked disorders (grounded in Harrison 22e)

Disorder	Gene / product	Pattern	Key point / management
Haemophilia A	F8 / factor VIII	XLR	Factor VIII replacement; carrier females usually asymptomatic
Haemophilia B	F9 / factor IX	XLR	Factor IX replacement
G6PD deficiency	G6PD	XLR	Avoidance of oxidant drugs and certain foods
Fabry's disease	α-galactosidase A (GLA)	XLR	Lipid-storage defect; heterozygous females may have mild neuropathy

Disorder	Gene / product	Pattern	Key point / management
Duchenne / Becker MD	DMD / dystrophin	XLR	Commonest muscular dystrophy; corticosteroids, physiotherapy, antisense-oligonucleotide exon skipping, stop-codon read-through
Nephrogenic diabetes insipidus	AVPR2 (AQP2 is AR)	XL	Vasopressin-resistant; thiazide/low-solute measures
Fragile X (FRAXA / FRAXE)	FMR1 / FMR2 protein	XLR	CGG / GCC repeat expansion; intellectual disability
Spinobulbar muscular atrophy (Kennedy)	Androgen receptor (CAG)	XLR	Trinucleotide-repeat disease, Xq12
Androgen insensitivity	Androgen receptor	XL recessive (missense)	Complete/partial; 46,XY with female phenotype
Rett syndrome	MECP2 (methyl-binding protein)	XLD	Developmental regression + stereotypic hand movements in girls

- **Duchenne muscular dystrophy** is the **commonest cause of muscular dystrophy**, reflecting the very large DMD gene (2.3 Mb, 79 exons); the phenotype is expressed in hemizygous males who have only one X. Dystrophin is part of a large complex linking the cytoskeleton to the muscle membrane. DMD mutations cause severe **Duchenne** or milder **Becker** disease depending on the severity of the protein defect (allelic heterogeneity).

X-linked dominant and X-linked trinucleotide-repeat disorders

- **X-linked dominant:** mutant allele expressed in heterozygous females and hemizygous males; many are **lethal or very severe in males** (e.g., **Rett syndrome** (MECP2), which predominantly affects girls). *Standard additional examples:* X-linked (vitamin D-resistant) hypophosphataemic rickets and incontinentia pigmenti.
- **X-linked trinucleotide-repeat (dynamic-mutation) disorders** (Harrison Table 479-5):
 - **Fragile X (FRAXA):** CGG repeat, Xq27.3; normal 6–50 → disease 200–300 (full mutation), FMR-1 protein.
 - **Fragile X (FRAXE):** GCC repeat, Xq28; FMR-2 protein.
 - **Spinobulbar muscular atrophy (Kennedy):** CAG repeat, Xq12; normal 11–34 → disease 40–62; androgen receptor.
- **Anticipation:** when repeat length increases across generations, disease becomes more severe or presents earlier — a key feature of these dynamic-mutation X-linked diseases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **X-linked recessive pedigree (3 generations):** labels — *Affected male* (filled square), *Carrier female* (circle with central dot), *Unaffected male/female* (open symbols), "*No male-to-male transmission*", "*All daughters of affected male = obligate carriers*", "*Skipped generation / criss-cross inheritance*".
- ▶ **Punnett square — carrier mother ($X^A X$) × normal father ($X Y$):** label gametes X^A , X (mother) and X , Y (father); offspring boxes — *Unaffected daughter (XX)*, *Carrier daughter ($X^A X$)*, *Unaffected son (XY)*, *Affected son ($X^A Y$)*; annotate "*50% sons affected, 50% daughters carriers.*"

Clinical / Diagnostic significance

- ▶ **Carrier detection and counselling:** identifying obligate/possible carrier females (daughters of affected men, mothers of an affected son) allows **genetic counselling, prenatal diagnosis and recurrence-risk estimation**; molecular testing is now routine for monogenic disorders.
- ▶ **Manifesting carriers:** skewed X-inactivation explains why some carrier women (e.g., Fabry, occasionally DMD) show clinical features — do not assume all female carriers are asymptomatic.
- ▶ **Genotype–phenotype and management:** DMD mutation type predicts Duchenne vs Becker severity; targeted therapies include **exon-skipping antisense oligonucleotides** and **stop-codon read-through**. G6PD carriers/patients must **avoid oxidant drugs and fava beans**; haemophilia is managed with the **specific deficient factor**.
- ▶ **Sex-reversal correlate (Y-linked):** SRY/testis-determining factor and AZF deletions are male-specific — useful contrast in disorders-of-sex-development work-up.

High-yield exam pointers

- ▶ **No male-to-male transmission** is the single most discriminating feature of X-linked inheritance.
- ▶ **All daughters of an affected male are obligate carriers**; affected sons inherit the mutant X from a carrier mother.
- ▶ Males are **hemizygous** → express both X-linked recessive and dominant alleles fully.
- ▶ *X-linked dominant / recessive* terminology applies to **expression in females**, modulated by X-inactivation.
- ▶ **Haemophilia A (factor VIII), haemophilia B (factor IX), G6PD deficiency, Fabry, DMD/Becker, Fragile X, Kennedy disease** = classic XLR; **Rett syndrome (MECP2)** = classic XLD.
- ▶ **DMD (dystrophin, 2.3 Mb, 79 exons)** is the commonest muscular dystrophy; allelic severity → Duchenne vs Becker.
- ▶ **Fragile X, Kennedy disease** are X-linked **trinucleotide-repeat** disorders showing **anticipation**.
- ▶ Carrier females may be symptomatic ("manifesting carriers") through **skewed X-inactivation**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 479 "Principles of Human Genetics" (X-linked & Y-linked inheritance, X-inactivation, genotype–phenotype correlation, Tables 479-2/479-5) and Ch 480 "The Integration of Inherited Genetics into Clinical Practice" (monogenic disorders with genetics-based interventions — haemophilia A/B, G6PD deficiency, nephrogenic DI, DMD; genetic counselling/carrier testing). **Coverage note:** The eponym "*Lyonization/Lyon hypothesis*" for X-inactivation, the gene symbol *GLA* for Fabry's α -galactosidase A, the carrier-cross segregation ratios (50% affected sons / 50% carrier daughters), the female:male excess in XLD, and the additional XLD examples (X-linked hypophosphataemic rickets, incontinentia pigmenti) are universally accepted standard genetics added for completeness and are not stated verbatim in Ch 479/480; the X-inactivation mechanism, hemizyosity, transmission rules and all listed disorders/genes are grounded in the provided text.

